Breast MRI for High-risk Screening

Francesco Sardanelli
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Editors

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This book is dedicated to all women worldwide.

The efforts for those of them who are at high risk for breast cancer are only a part of the global fight against this disease.

F.S. and F.P.

Foreword

I willingly accepted to write a foreword for this book focused on *breast MRI for high-risk screening* for many reasons.

My connections with the two editors represent the first reason. Francesco Sardanelli is a Professor of Radiology at the Milan University, where I served as a Professor of Radiation Oncology up until less than 2 years ago. Franca Podo, former Research Director of the Molecular and Cellular Imaging Unit at the Istituto Superiore di Sanità in Rome, has been also involved in the development of clinical MRI in Italy from the viewpoint of regulatory health authorities since the early 1980s. At the end of the 1990s, they launched the Italian multicenter study (HIBCRIT) that contributed to build the evidence in favor of MRI for screening women at high risk of breast cancer.

The second reason is related to the general evolution of breast cancer management in the last decades, which I had the fortune to witness and cooperate to from my position of Head of the Radiation Oncology Department at the European Institute of Oncology in Milan, under the scientific direction of Umberto Veronesi. This evolution followed the pathway of a progressive de-escalation of the aggressiveness of treatment: from mastectomy to breast conserving surgery and whole breast irradiation, from routine axillary dissection to sentinel node biopsy, from whole breast to partial breast irradiation. On the other side, chemotherapy, hormonal, and biological target therapies also evolved, increasing effectiveness while reducing side effects. What was clear in Veronesi's view was that all these efforts could be most effective in the case of small breast cancers. Smaller the tumors at diagnosis, less aggressive and more effective the treatment.

Early diagnosis is only possible through breast imaging performed as a screening tool. Women at high risk for breast cancer, especially those who are carriers of *BRCA* or *TP53* deleterious mutations, experienced the low diagnostic power of mammography and breast ultrasound in contrast to the higher incidence, earlier onset, and faster growth of breast tumors that affect these women, compared to the average female population. Breast MRI surveillance opened a new option, alternative to prophylactic mastectomy, for these women. Thus, MRI clearly works in the same general direction outlined above, i.e., to allow for early breast cancer diagnosis in this particular subgroup of women.

The third reason comes from another of Veronesi's views: *breast care is a multidisciplinary science*. This sentence is also mentioned by the editors at

the end of their Preface. Indeed, the panel of chapters' authors of this book is not only international, from New York to Sydney, but it also shows how the perspective of breast imaging, also when considering its most powerful tool, i.e., MRI, must be put in the general epidemiological, clinical, and also psychological context.

Finally, managing a high risk of breast cancer is only one aspect of a more general trend toward the use of risk stratification for personalized and precision medicine in oncology, which is one of the main challenges for the next future.

For all these reasons, I wish this book a great success in the whole world of breast cancer specialists.

European Institute of Oncology, Milan Roberto Orecchia
September 2019

Preface

The idea of this book came up as an effect of a long collaboration between the two editors, a radiologist (F.S.) working in Genoa until 2000 and then in Milan and a physicist (F.P.) working in Rome.

We met in person during a series of conferences on magnetic resonance imaging (MRI) in Italy in the late 1980s and in the 1990s. On the occasion of an international meeting in 1997, while attending a Poster Section on breast MRI, we started to envision an Italian study to investigate the role of contrast-enhanced MRI of the breast for screening women at high risk of breast cancer (BC).

To combine our efforts was a strategic decision. On one side, there was a more than 10-year clinical experience with breast MRI at the San Martino Hospital in cooperation with the National Institute for Cancer Research in Genoa. On the other side, there was a 10-year expertise on regulatory issues on the safety of clinical MRI systems and an over 15-year experience in basic research on preclinical cancer models using nuclear magnetic resonance (NMR) approaches at the Istituto Superiore di Sanità in Rome (Fig. 1).

Importantly, we were just in the first few years after the discovery of the oncosuppressor *BRCA* genes. In 1994, Y. Miki and coworkers [1] had identified the role of the *BRCA1* gene in breast and ovarian cancer susceptibility. In 1995, R. Wooster and coworkers [2] had identified a second BC susceptibility gene, *BRCA2*. In addition, in the first years of its clinical history, breast MRI had already substantially evolved with the introduction of breast-dedicated bilateral radiofrequency coils [3], with the use of gadopentetate dimeglumine (Gd-DTPA) [4] as the first gadolinium-based contrast agent to be injected intravenously, which was soon adopted for MRI of the breast [5], and with the development of fast gradient-echo sequences for dynamic studies, which allowed sufficient levels of both spatial and temporal resolution to be achieved [6].

For those researchers who were strongly interested in innovations in BC care, these advances in knowledge and technology had opened a special way to:

1. Verify the diagnostic performance of MRI in a screening setting with a higher BC incidence than that in the general female population.
2. Offer to women with hereditary predisposition to BC a possibility of getting a diagnosis earlier than that offered by mammography.

Fig. 1 The front of the main building of the Istituto Superiore di Sanità (Viale Regina Elena 299, Rome), scientific and technical organ of the Italian National Health Service, where the central coordination of the HIBCRIT-1 study was carried out from 1999 to 2013. At the left upper corner, the logo of this Italian governmental institution

Fortunately, in those years the Italian Society of Medical Radiology (SIRM)[1] had established a network of breast MRI centers thanks to a research grant provided by the Bracco company [7]. Thereafter, this project resulted in two papers, still frequently quoted in the literature, one on preoperative MRI [8], the other on MRI for characterizing mammographic microcalcifications [9]. Thus, in the late 1990s, a number of Italian centers with experience in breast MRI were available for participating in multicenter projects.

In this scenario, under the umbrella of the Istituto Superiore di Sanità, we started to plan the *High Breast Cancer Risk Italian 1* (HIBCRIT-1) study. F.P. got a series of grants that supported the study[2] and centrally coordinated all the organizational aspects, including contacts with each center and data management. F.S. provided the radiological coordination in terms of MRI protocol and interpretation. However, practically all the phases of the project, from the study design to the enrollment of centers as well as data clearing and interpretation, were managed by both of us in strict interaction and cooperation. We can say that for each of the many issues that investigators can encounter during a long study involving 18 hospitals or cancer centers, enrolling 500 patients and totaling more than 1,500 multimodality screening rounds, we could always find a solution working together. In the phase of data management for the final report, we had an important support from Filippo Santoro, a fellow of F.P. at the Istituto Superiore di Sanità.

[1] In particular, this project was led by the two SIRM sections of MRI (under the presidency of Alessandro Del Maschio, San Raffaele Hospital, Milan) and of Breast Imaging (under the presidency of Vincenzo Lattanzio, Azienda Ospedaliera Policlinico, Bari).

[2] The HIBCRIT-1 study was supported by the following: Italian Ministry of Health, Ricerca Finalizzata 1% 98/JT/T; Istituto Superiore di Sanità, Ricerca Corrente C3A3/2004; Italian Ministry of Health, Research Project on Cancer Screening, Law No. 138/2004; Special Project in Oncology 2006—Art. 3 "Rete Solidale e Collaborazioni Internazionali (ISS per ACC)," Project ACC2-InTEF.

Many experts[3] contributed to the results of this study that were published in three papers from 2002 to 2011 as preliminary [10], interim [11], and final [12] reports. We are grateful to the researchers of all participating centers. Only their cooperative efforts could allow an Italian network to be one of the few multicenter groups to provide the evidence making breast MRI accepted worldwide for screening high-risk women. Our preliminary report [10] was included in the initial evidence on which the American Cancer Society based the first recommendations [13] in favor of MRI for high-risk screening. More recently, we reported on survival analysis of the HIBCRIT-1 study [14], providing the first evidence that the combination of screening MRI with modern therapies can allow an equivalent good patient outcome in terms of survival for both triple-negative and non-triple-negative BCs in high-risk women.

The results of the HIBCRIT-1 study favored both of us in reinforcing already existing international relationships and in establishing new ones with many groups working on the application of breast MRI to high-risk women, including radiologists, physicists, geneticists, oncologists, surgeons, epidemiologists. This integrated network of experts has been the true author of this book.

Each chapter is independent from the others and can be read independently, but the reader will find a logic order in the sequence of individual subjects.

In Chap. 1, we have tried to summarize the evolution of MRI, explaining how breast tumor detection was one of the first purposes of those researchers who worked for transforming a physical phenomenon, NMR, into a medical imaging modality, MRI. In Chap. 2, Pascal Baltzer (Vienna) and F.S. give an extended explanation of the reasons for the *mantra* about the low specificity of breast MRI, which somehow delayed the clinical application of the technique. Jacopo Azzollini, Laura Fontana, and Siranoush Manoukian (Milan) offer in Chap. 3 an updated synthesis of the knowledge available on *BRCA* and other susceptibility genes. In Chap. 4, Ritse M. Mann and Suzan Vreemann (Nijmegen) illustrate the MRI technical protocols for screening, with emphasis on minimal requirements, type of sequences, and specific screening protocols, including the contrast-enhanced abbreviated and ultrafast protocols as well as the perspectives of non-contrast breast MRI. In Chap. 5, F.S., Simone Schiaffino, Andrea Cozzi, and Luca A. Carbonaro (Milan) give an overview on Gd-based contrast agents for breast MRI, including the issue of Gd retention in the brain, which resulted in the suspension from the market of linear agents by the European Medicines Agency. The Chap. 6 by Paola Clauser (Vienna) and Chiara Zuiani (Udine) is dedicated to the applica-

[3]We wish to thank here those researchers who mostly contributed to the HIBCRIT-1 study. Without them, this study and also the present book, as a consequence of our experience in coordinating the study, would not have been possible. You find here the list of these researchers, in alphabetic order: Paolo Belli, Silvana Bergonzi, Bernardo Bonanni, Massimo Calabrese, Luca A. Carbonaro, Anna Cilotti, Alma Contegiacomo, Stefano Corcione, Laura Cortesi, Marcello Crecco, Giuliano D'Agnolo, Alessandro Del Maschio, Ernesto Di Cesare, Cosimo Di Maggio, Massimo Federico, Siranoush Manoukian, Laura Martincich, Sandro Morassut, Pietro Panizza, Lorenzo Preda, Filippo Santoro, Antonella Savarese, Maura Tonutti, Giovanna Trecate, Daniela Turchetti, Daniele Vergnaghi, Chiara Zuiani. Many other experts collaborated to the HIBCRIT-1 study. Their list is available in the paper published in 2011 [12].

tion of the Breast Imaging Reporting and Data System to a high-risk population, while the Chap. 7 by Anne L. Martel (Toronto) illustrates potentials and limitations of computer-aided detection, diagnosis, and evaluation systems.

In Chap. 8, Katja Pinker (New York), Anke Meyer-Baese (Tallahassee, FL, USA), and Elizabeth Morris (New York) discuss the background of radiogenomics of breast MRI and summarize its potential, with a special focus on high-risk women. In Chap. 9, we present the primary evidence, i.e., the original studies, on breast MRI for high-risk screening, while in Chap. 10 Maria A. Marino (Vienna-Messina), Paola Clauser (Vienna), and Thomas Helbich (Vienna) specifically point out the evidence in favor of *MRI alone* for screening high-risk women. In Chap. 11, F.S., Giovanni Di Leo (Milan) and Nehmat Houssami (Sidney) summarize the secondary evidence, i.e., the results of meta-analyses and cost-effective analyses, regarding breast MRI screening of high-risk women. Catherine Colin (Lyon), Nicolas Foray (Lyon), and Michel Bourguignon (Fontenay aux Roses, France) illustrate in Chap. 12 what radioprotection issues are specifically relevant for *BRCA* mutation carriers and in general for women with hereditary BC predisposition. In Chap. 13, F.P., Ellen Warner (Toronto), Filippo Santoro (Rome), and F.S. describe the evidence about the impact of MRI screening on high-risk patient outcome.

Rubina M. Trimboli (Milan) and Giovanna Mariscotti (Turin) describe in Chap. 14 the special case of women who had previous chest radiation therapy, typically lymphoma survivors, who have lifetime risk similar to that of *BRCA* mutation carriers (where MRI has suboptimal sensitivity and mammography should be used as an adjunct to MRI). Giovanni Di Leo (Milan), Daniela Sacchetto (Turin), and Filippo Santoro (Rome) explain in Chap. 15 the role of electronic data capture systems for BC imaging research, with reference to breast MRI studies.

In Chap. 16, Ayla Selamoglu and Fiona J. Gilbert (Cambridge) illustrate the content of guidelines and recommendations on high-risk screening worldwide. Bernardo Bonanni, Massimiliano Cazzaniga, and Matteo Lazzeroni (Milan) give an overview on drugs and agents for primary prevention of BC in Chap. 17, while James O. Murphy (Waterford, Ireland) and Virgilio S. Sacchini (New York) illustrate the role of prophylactic mastectomy and oophorectomy in Chap. 18. In Chap. 19, Nadia Crotti and Valentina Broglia (Genoa) define the multiple psychological aspects of high BC risk, from the effect of family history to the decision to perform genetic tests or to ask for prophylactic mastectomy.

Chapter 20 by Adam R. Brentnall and Stephen W. Duffy (London) is dedicated to models for individual BC risk estimates. Chapter 21 by Manisha Bahl (Boston), Giovanni Di Leo (Milan), and Constance D. Lehman (Boston) summarizes the available evidence for using MRI for screening women with a personal BC history, while Chap. 22 by Sylvia H. Heywang-Köbrunner and Astrid Hacker (Munich) discusses the available evidence for using MRI for screening the other women at intermediate BC risk.

Finally, in Chap. 23, we try to draw some conclusions from this huge amount of knowledge: annual MRI is by far the best option for screening high-risk women unless they opt for prophylactic mastectomy, but its usage is conditioned by access to MRI and coverage of cost. In addition, we also

illustrate how artificial intelligence, especially deep learning algorithms, could impact on breast MRI screening in the next future.

Overall, to work as editors and authors of this book has been an exciting experience. We learned a lot from all the authors and we thank each of them sincerely.

Special thanks have to be given to Professor Roberto Orecchia for accepting to write the Foreword for this book. When we started to plan the book more than 4 years ago, our intention was to ask Professor Umberto Veronesi for this task. His historical role in breast cancer care was the best way to refer this book to the general message that *breast care is a multidisciplinary science*, as Umberto Veronesi stated on several occasions. Breast MRI for high-risk screening is part of this, being a matter of interest for the entire breast cancer team, not only for radiologists. Unfortunately, Umberto Veronesi passed away on November 8, 2016, when our book was still in preparation. Once all chapters had been completed and updated, we submitted the book to the consideration of Roberto Orecchia, asking him to write the Foreword. He is head of the Department of Radiation Oncology at the European Institute of Oncology in Milan since 1995 and succeeded Umberto Veronesi in the position of Scientific Director of the same institution. His leading role in the field of integrated therapies for breast cancer is an outstanding example of synergy between multidisciplinary science and clinical care.

Furthermore, we would like to express here our deepest thanks to Dr. Antonella Cerri. She has not only believed in this book but has also endured the long delays we have accumulated over time. Finally, we want to acknowledge the untiring work of Dr. Andrea Cozzi, who was absolute protagonist of the arduous but indispensable proofreading of all chapters.

Milan, Italy — Francesco Sardanelli
Rome, Italy — Franca Podo

References

1. Miki Y, Swensen J, Shattuck-Eidens D et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71
2. Wooster R, Bignell G, Lancaster J et al (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792
3. Wolfman NT, Moran R, Moran PR, Karstaedt N (1985) Simultaneous MR imaging of both breasts using a dedicated receiver coil. Radiology 155:241–243
4. Laniado M, Weinmann HJ, Schörner W, Felix R, Speck U (1984) First use of GdDTPA/dimeglumine in man. Physiol Chem Phys Med NMR 16:157–165
5. Heywang SH, Hahn D, Schmidt H et al (1986) MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr 10:199–204

6. Kaiser WA, Zeitler E (1989) MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 170:681–686
7. Del Maschio A, Bazzocchi M, Giuseppetti GM et al (2002) Breast MRI: report on a multicentric national trial by the Study Section of Magnetic Resonance and Breast Imaging. Radiol Med 104:262–272
8. Sardanelli F, Giuseppetti GM, Panizza P et al (2004) Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 183:1149–1157
9. Bazzocchi M, Zuiani C, Panizza P et al (2006) Contrast-enhanced breast MRI in patients with suspicious microcalcifications on mammography: results of a multicenter trial. AJR Am J Roentgenol 186:1723–1732
10. Podo F, Sardanelli F, Canese R et al (2002) The Italian multi-centre project on evaluation of MRI and other imaging modalities in early detection of breast cancer in subjects at high genetic risk. J Exp Clin Cancer Res 21:115–124
11. Sardanelli F, Podo F, D'Agnolo G et al (2007) Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 242:698–715
12. Sardanelli F, Podo F, Santoro F et al; High Breast Cancer Risk Italian 1 (HIBCRIT-1) Study (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol. 2011 Feb;46(2):94–105
13. Saslow D, Boetes C, Burke W et al; American Cancer Society Breast Cancer Advisory Group (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
14. Podo F, Santoro F, Di Leo G et al (2016) Triple-negative versus non-triple-negative breast cancers in high-risk women: phenotype features and survival from the HIBCRIT-1 MRI-including screening study. Clin Cancer Res 22:895–904

Contents

Abbreviations

BC	Breast cancer
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance

From NMR to Clinical Breast MRI

1

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Abbreviations

CE-MRI	Contrast-enhanced magnetic resonance imaging
Gd-DTPA	Gadopentetate dimeglumine
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance
RF	Radio frequency
US	Ultrasonography, ultrasound

1.1 Nuclear Magnetic Resonance

Although nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) are based on the same basic physical principles, the adjective "nuclear" has been dropped from the acronym used for the medical diagnostic modality, i.e., MRI, since its first introduction into the clinical use in the United Kingdom (Nottingham and Aberdeen) in 1980s [1]. In the early 1980s, the new imaging modality began to be clinically used in the United States (1981) and in many other countries. The choice of MRI as the acronym was mainly suggested by the need of avoiding possible confusions with nuclear medicine technologies, implying the use of radioactive tracers. However, for at least two decades, the original acronym of the physical phenomenon, NMR, from which the magnetic imaging modality was derived, continued to be occasionally used in clinical practice and is still used by some senior physicians.

Technically speaking, a huge difference does exist between NMR and MRI. In fact, from the discovery of the NMR phenomenon (1946) and the first magnetic resonance images of the human body (1977), there were more than 30 years during which several Nobel Prizes were assigned, followed by additional Nobel Prizes assigned for NMR/MRI matters up to 2003. The physical principles of NMR were established when Wolfgang E. Pauli (1900–1958) introduced the quantum concept of *spin*, a physical property firstly applied to electrons (1925) and then also to single and composite nuclear particles possessing a magnetic moment, protons being among them (1940). For his quantum mechanical *exclusion principle*, which underpins the whole modern theory of the structure of matter, including the NMR phenomenon, Pauli was awarded with the Nobel Prize in Physics in 1945 [2].

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In 1938, Isidor Isaac Rabi (1898–1988), Nobel laureate in physics in 1944 [2], firstly described the resonance method for recording the magnetic properties of atomic nuclei. Two years later (1946), Felix Bloch (1905–1983) and Edward M. Purcell (1912–1997) independently demonstrated the NMR phenomenon in liquids and solids and shared the Nobel Prize in Physics in 1952 [2]. During World War II, Purcell pioneered studies on the production, absorption, and detection of radio frequency (RF) waves at the Massachusetts Institute of Technology, Boston, MA, in the context of the development of radar. This Purcell's work had been one of the bases for the Rabi's discovery [3].

The discovery of NMR consisted of the reproducible observation of the following phenomenon: Atomic nuclei possessing a magnetic moment, such as those of ^{1}H and ^{31}P, when placed in a static magnetic field can absorb energy in the form of RF waves under the condition that the frequency of these waves is *tuned* to a value (Larmor[1] frequency) dependent upon the specific nature of the nucleus. In that case, we can say that the frequency is *in resonance*. The specificity of this resonance is so high that, for example, at the same magnetic field strength, ^{1}H nuclei within a water molecule resonate at a different frequency when compared to ^{1}H nuclei within a lipid molecule, and even nonequivalent chemical groups of a lipid molecule resonate at slightly different frequencies [4].

In other words, about 50 years after the discovery of x-rays (1895) by Wilhelm C. Roentgen and the Guglielmo Marconi's patent for the wireless telegraphy (1896), another possibility of interrogating the matter became possible, notably on the low-energy nonionizing side of the electromagnetic spectrum, i.e., in the RF range, with a great potential for the distinction among different molecules and chemical groups, clearly better than that of x-ray-based imaging techniques, and without the hazards of ionizing radiation exposure. However, while for x-rays the application to medical imaging was immediately open, from the first image of Bertha Roentgen's hand to the diagnosis of bone fractures by Marie Curie during the World War I [5], the potential of NMR to be used for medical imaging remained unexplored for the next three decades.

In this short sketch of the NMR history, which interplays with the history of physics, chemistry, and engineering from the end of the nineteenth until the first half of the twentieth century, we cannot ignore the role of Nikola Tesla (1856–1943), a Serbian[2] engineer who contributed to the development of the alternating current electrical system used worldwide today and discovered the applications of a rotating magnetic field. He obtained 700 patents in the United States and in Europe which covered every aspect of science and technology [6]. He probably also preceded Roentgen in discovering x-rays, but he did not publish this, as well as many other inventions he made in physics and engineering. In 1915, the New York Times announced that Thomas A. Edison and Nikola Tesla would become Nobel laureates for physics, but the Prize was given to two other scientists. The Nobel Committee did not negate that Tesla and Edison were their first choice but never explained the reasons for the change (possibly due to a refusal of sharing the award by both scientists) [7]. Anyway, the name of Tesla entered the everyday life of NMR and MRI due to adoption of *tesla* (T) as the measurement unit for magnetic induction or magnetic flux density in the meter-kilogram-second system decided by the International Electrotechnical Commission Committee of Action on June 27, 1956 [6].

For decades, NMR was *mainly* used as a technique for analytical chemistry and biochemistry, with a relevant role in the understanding of the structure of the matter, including biological tissues. Not surprisingly, two other NMR-related Nobel awards, both of them in chemistry, were

[1] Sir Joseph Larmor (1857–1942) was an Irish physicist and mathematician, Lucasian Professor of Mathematics in Cambridge from 1903 to 1932. He improved the understanding of physics of electricity, dynamics, and thermodynamics and contributed to the electron theory of matter.

[2] Nikola Tesla was born on 1856 in Smiljan, now in Croatia (https://www.biography.com/people/nikola-tesla-9504443. Accessed June 30, 2020).

assigned: in 1991, to the Swiss chemist Richard R. Ernst (born in 1933) for the development of high-resolution NMR spectroscopy [8], and in 2002, to the Swiss chemist Kurt Wüthrich (born in 1938) for his NMR spectroscopy investigations on the three-dimensional structure of biological macromolecules in solution [2].

At any rate, up to the seventies, no horizon for translating NMR to clinical imaging was visible.

1.2 Damadian's Translational Work on NMR Relaxometry

The potential of NMR in tumor analysis was firstly explored by Raymond V. Damadian. This physician, born in 1936 in New York to an Armenian family, was the first who tried to use NMR for cancer analysis. Between 1971 and 1974, he proposed spin-lattice (T1) and spin-spin (T2) NMR relaxometry for biological tissue characterization, in particular for discriminating between benign and malignant surgical specimens [9, 10], declaring that the technique was ready for use by pathologists [10]. In 1978, his group specifically applied the new technique to breast tumors [11], showing a highly significant difference between relaxation times of benign and malignant breast tissue, with an accuracy superior to 95%.

Thus, the project of using NMR in oncology, in particular for breast cancer detection, was proposed several years before the introduction of clinical MRI scanners. This pioneering work strongly pushed forward the technical improvement of NMR machines, revealing a potential huge impact on clinical research and practice. In those years, in fact, the use of ultrasound and of computed tomography in oncologic imaging became common practice, but radiologists early started to understand the limitations of these methods for tissue characterization [12, 13].

NMR relaxometry of cancer tissues was a turning point. Using a modern language, we could say that Damadian's work represented the translational jump from physics and chemistry to medicine. Radiology and not pathology was the discipline that gained the driving seat for this jump. This was properly related to the transformation of NMR into MRI, i.e., to the production of clinical images. A process measuring relaxation times became a way for looking inside the human body. Damadian's role in the origination of medical MRI was acknowledged by the US Supreme Court in its 1997 decision, when the court enforced Damadian's original patent [14] on the discovery of magnetic relaxation differences in tissues and their use in scanning.

1.3 Making Images Using MRI: P. Mansfield and P. C. Lauterbur

Having in mind the invention of computed tomography, introduced in clinical use for cranial scan in 1971 and for body scan a few years later, key issues to obtain clinical images from an NMR imaging equipment were:

1. To have large magnets where patients could be introduced horizontally, providing magnetic fields sufficiently high, stable, and homogenous.
2. To spatially localize the origin of the NMR signals received from the body of a subject introduced in the magnet.

While the first point could be considered *only* a matter of engineering suitable magnets, the second issue required a higher level of innovation. Spatial localization was not an issue when performing relaxometry or high-resolution spectroscopy experiments on biological samples, typically introduced inside cylindrical tubes to be vertically inserted into small-bore powerful magnets. However, spatial localization was a crucial step for imaging. The physicist Peter Mansfield (1933–2017), born in London and working at the University of Illinois, and the chemist Paul C. Lauterbur (1929–2007), born in Sidney and working at the New York Stony Brook State University, gave a fundamental contribution for solving the problem [15, 16].

The invention was to add to the principal static magnetic field $\mathbf{B_0}$, used for a classic NMR experiment, local modifications of the field intensity precisely controlled in space and time by *gradients* of magnetic field ($\mathbf{B_1}$) so that at each point of the space inside the magnet, a local magnetic field is generated, given by the vector sum of $\mathbf{B_0} + \mathbf{B_1}$. By rapidly switching on and off three orthogonal gradients oriented in a planned order during the NMR imaging experiment, a slice is firstly selected within the studied object. Then, the spatial localization of individual pixels within the slice is encoded using phase and frequency of the RF signals. The overall *free induction decay* signal received by the RF coil of a pulsed NMR equipment is the sum of thousands of different NMR signals generated by nuclear spins differently located in the space. The NMR experiment performed in the presence of magnetic field gradients is repeated many times, and the received RF signals are recorded into a mathematical matrix named *k-space*. The image, composed by the signal intensity values obtained for the individual pixels composing the slice, is obtained using a mathematical process, the two-dimensional Fourier transform (one dimension corresponding to the signal phase and the other to the signal frequency) [17].

For this ingenious idea and its subsequent implementations, Paul C. Lauterbur and Peter Mansfield shared in 2003 the Nobel Prize in Physiology and Medicine [2].

1.4 The Pre-Gadolinium Era: Unenhanced Breast MRI

During the first half of the 1980s, researchers explored the potential of breast MRI performed using the unenhanced standard sequences available in those days. Searching on the PubMed for breast MRI studies before the introduction of gadolinium-based contrast agent (August 1986; see below), we found 37 papers, only 11 of them regarding in vivo applications on humans.

The first clinical paper was published by R. J. Ross and coworkers (Cleveland, OH, USA) in 1982 [18]. They studied 128 breasts in 65 patients, describing the signal behavior of different lesions:

> *Normal breasts and breasts with extensive fatty replacement were found to have the lowest T1 values, whereas T1 values of malignant tissue were elevated. T1 values for mammary dysplasia extended over a wide range, and NMR images exhibited lower proton density than normal tissue. In several patients with severely dysplastic breasts, T1 values overlapped those from patients with documented breast neoplasms. Markedly elevated T1 values were obtained from fluid-filled cysts that were well beyond the range of malignancy.*

Five papers came from the same group of authors, S. J. el Yousef and coworkers (Cleveland, OH, USA), between 1983 and 1985 using a FONAR unit equipped with a vertical magnet. The last one [19] summarized their experience on 100 patients. Their conclusions were the following:

> *The precise role of MRI in the workup of breast lesions is not yet defined. Specificity and sensitivity of MRI are yet to be established in future prospective double-blind analysis with mammography and sonography. Our preliminary experience suggests that MRI has an adjunctive role to mammography and could be a valuable method for the diagnosis of breast lesions.*

In 1985, one paper described the first experience with radio frequency coils allowing simultaneous bilateral breast MRI [20], one paper investigated the variation of normal breast tissues during the menstrual cycle [21], and a third paper reported a first limited experience with a surface solenoid radio frequency coil [22].

Of note, in August 1985, Sylvia Heywang and coworkers (Munich, Germany) [23] reported on 50 breast masses in 41 consecutive patients evaluated by MRI and mammography (some of them also studied by US): 32 carcinomas, 1 secondary malignant lymphoma, 4 fibroadenomas, 2 papillomas, 3 cysts, 1 hamartoma, and 5 dysplastic nodules. The conclusion was very cautious: *Possible future indications are suggested for selected cases* (an elegant way for saying that unenhanced breast MRI showed few possibilities to enter clinical breast imaging practice). In addition, the same group of authors also published in the same year a case report on a breast cancer behind an implant [24].

Practically, translating NMR relaxometry into standard T1-, T2-, and proton density-weighted images allowed a very limited tissue discrimination, with the exception of normal fat and cysts.

However, the discrimination between liquid and solid lesions was a task that, even when problematic at mammography, had already become simple and cheap with breast ultrasonography (US) several years before [25].

1.5 Contrast-Enhanced Breast MRI

In 1986, Sylvia Heywang and coworkers from Munich, Germany, few months after the publication of their aforementioned paper on unenhanced breast MRI [24], reported the first experience with contrast-enhanced MRI (CE-MRI) of the breast [26], using the first available paramagnetic contrast agent (gadopentetate dimeglumine, Gd-DTPA). Notwithstanding the paucity of the case series, this study opened a completely new perspective. The short abstract was:

> *In a preliminary study 20 patients underwent breast examinations by magnetic resonance (MR) imaging without and with Gd-DTPA as contrast medium. All carcinomas enhanced, whereas dysplastic tissue enhanced slightly or not at all. Significant additional diagnostic information was available on the Gd-DTPA examinations in at least four of 20 cases compared with MR without contrast medium and X-ray mammography. Our preliminary results indicate that MR imaging of breast using Gd-DTPA may be helpful for the evaluation of dense breasts and the differentiation of dysplasia and scar tissue from carcinoma.*

At the beginning, even after the introduction of intravenous contrast injection, radiologists who pioneered the use of this technology faced difficulties and distrusts from the established medical community working on breast cancer. Even breast radiologists, who were in those days highly confident with the so-called triple assessment composed by mammography, US, and needle sampling, were not so favorable to MRI. Although mammography was still in the era of screen-film, US B-mode images were distant from the today quality, and needle sampling was mainly only fine needle aspiration (with its inherent uncertainties), surprisingly breast MRI did not receive a wide acceptance.

Breast MRI investigators highlighted that the new method allowed breast cancer identification, thanks to its ability to visualize *neoangiogenesis* associated with tumor progression, a completely new functional imaging approach intrinsically different from the only morphologic evaluation provided by mammography and US. Physically speaking, two completely different pieces of theory were involved: differences in photon attenuation as an effect of *electron density* on the x-ray side and differences in nuclear magnetic relaxation times due to the local uptake of the paramagnetic contrast material on the MRI side. Unfortunately, the reference to tumor-associated neoangiogenesis was reminiscent of the old thermography, an approach leading to a false hope for breast cancer diagnosis as it was burdened by a high rate of false negatives and false positives,[3] although it is still sometimes represented again as a new method [27].

The main criticisms against breast MRI were based on high cost, need of intravenous contrast injection, and, above all, an alleged high rate of false positives. A *mantra* arose very soon: *Breast MRI has a high sensitivity but a low specificity*. This was due to some papers reporting results of CE-MRI of the breast when descriptors and methods for interpreting breast MRI were still in their infancy. In fact, MRI was firstly considered in the Breast Imaging Reporting and Data System by the American College of Radiology only in 2003 [28]. Thus, every contrast-enhancing breast finding could at that early stage be considered as suspicious, with the result that small studies often reported low specificity values. Unfortunately, those small studies became the reference against breast MRI.

A clear example of this misleading use of published data is given by the comparison of two papers published in 1993 and 1994, a comparison firstly reported in Amsterdam by Pascal Baltzer from Vienna during the ceremony for the attribution of the European Society of Breast Imaging 2014 Gold Medal to the memory of the chemist and radiologist Werner A. Kaiser (1949–2013),

[3] Notably, some new currently emerging technologies such as *optical imaging* and *opto-acoustic imaging* should not be confused with the old *thermographic* methods. Interesting research on these new approaches is ongoing, and good results may be possible. See Di Leo G, Trimboli RM, Sella T, Sardanelli F (2017) Optical imaging of the breast: basic principles and clinical applications. AJR Am J Roentgenol 209:230–238.

one of the most prominent pioneers of breast MRI. Professor Kaiser firstly demonstrated the value of dynamic scan for CE-MRI of the breast [29] and was the author of a famous book entitled *Signs in MR Mammography* [30], where a total of 147 different signs for interpreting both T1- and T2-weighted unenhanced and T1-weighted dynamic contrast-enhanced images were described. On that occasion, Pascal Baltzer noted and commented the following two facts:

1. In 1993, a breast MRI study from Steven Harms and coworkers (Dallas, TX, USA) [31], conducted on 30 breasts with 47 malignant and 27 benign lesions, reported a 94% sensitivity and a 37% specificity.
2. In 1994, a group guided by Werner A. Kaiser (Jena, Germany) [32] reported a 98% sensitivity and a 97% specificity on the basis of 2,053 cases, with histopathological verification within 2 weeks (n = 766) or follow-up controls up to 7 years.

The reader will find an in-depth discussion about the *mantra* of low specificity of breast MRI in Chap. 2, where the reasons for this myth are explained from an historical and theoretical viewpoint, properly discussing the meaning of the results of these two papers.

To note, 1993 was also the year of the first report on a tumor suppressor gene (*BRCA1*) conferring a high breast cancer risk to women carriers of a deleterious mutation [33], and the identification of a similar role for another gene, *BRCA2*, followed very soon [34]. This relevant new knowledge created the possibility to identify populations of women having a risk of developing breast cancer during their lifetime clearly higher than that of the general female population. This opened the way to studies planned to compare the diagnostic performance of MRI with that of conventional imaging (mammography and/or US) for screening high-risk populations, which is the topic of this book.

High-risk screening was not the only field of application for breast MRI. Considerable efforts were also dedicated to other clinical topics. Taking into account the relevance of a multicenter study in providing high level of evidence not only in terms of *efficacy* but also in terms of *effectiveness* [35], an idea about the efforts devoted to breast MRI clinical research can be obtained looking at Table 1.1. Up to December 2017, overall, 62 studies were carried out, enrolling over 34,000 women who underwent over 51,000 breast MRI examinations in 739 centers. Eighty-five papers were published; interestingly, the majority of them, 54%, appeared in non-imaging, i.e., clinical journals; over 70% of these studies came from Europe. High-risk screening was the most popular research topic, with more than 8,000 women involved in 162 centers, about 20,000 MRI examinations performed, and 30 papers published from 12 different studies, mainly from Europe.

Of course, this is only a partial picture, first of all because also many single-center studies (and meta-analyses) contributed to build the body of evidence for the clinical use of breast MRI. However, the large experience of high-risk screening studies strongly contributed to make breast MRI a credible tool to non-radiologists and also to breast radiologists not yet practicing breast MRI.

Another way to appreciate the increasing role of breast MRI is to evaluate its relative weight among all the methods for breast cancer diagnosing. The results of a search on PubMed is shown in Fig. 1.1. While the total number of papers per year went up from tens in the 1960s to near 3,500 between 2011 and 2017, the relative weight of mammography dropped from over 90% to about 40%, both US and MRI progressively increased to over 20%, and in the last period, MRI (24%) slightly surpassed US (22%).

This increasing role of MRI in breast research, as testified by the PubMed citations, provided the evidence which prompted its use in clinical practice. To result the winner in the screening setting in comparison with mammography and US by far in terms of sensitivity, with good specificity and positive predictive value was the winning card for MRI.

Table 1.1 Multicenter breast MRI studies up to December 2017

Study type	Number of studies	Patients		MRI exams		Centers		Papers			Papers per countries of centers involved			
		Total	Min Max	Total	Min Max	Total	Min Max	Total	Imaging journals	Non-imaging journals	Europe	Europe and America	America	Asia
1. High-risk screening	**12** *19%*	**8,152** *24%*	93 2,500	**19,649** *38%*	171 7,500	**162** *22%*	4 30	**30** *35%*	**10**	**20**	**27**	**2**	**1**	**0**
2. Intermediate or average risk screening	**3** *5%*	**5,869** *17%*	754 2,995	**7,196** *14%*	754 4,322	**17** *2%*	2 9	**3** *4%*	**1**	**2**	**2**	**0**	**0**	**1**
3. Diagnostic performance/ contrast agents	**16** *26%*	**5,550** *16%*	63 1,537	**6,587** *13%*	24 1,652	**183** *25%*	3 25	**20** *24%*	**17**	**3**	**11**	**4**	**5**	**0**
4. Preoperative	**10** *16%*	**5,536** *16%*	90 1,787	**4,782** *9%*	90 1,878	**240** *32%*	2 45	**10** *12%*	**3**	**7**	**8**	**1**	**0**	**1**
5. MRI-guided interventions	**9** *15%*	**3,838** *11%*	63 1,509	**3,838** *7%*	63 1,509	**66** *9%*	2 20	**9** *11%*	**5**	**4**	**6**	**1**	**2**	**0**
6. Background parenchymal enhancement	**1** *2%*	**2,958** *9%*	–	**3,770** *7%*	–	**6** *1%*	–	**1** *1%*	**1**	**0**	**0**	**0**	**1**	**0**
7. NAT setting	**11** *18%*	**2,214** *6%*	39 759	**5,723** *11%*	46 1,518	**65** *9%*	3 15	**12** *14%*	**2**	**10**	**8**	**1**	**3**	**0**
Total	**62** *100%*	**34,117** *100%*	63 2,995	**51,545** *100%*	24 7,500	**739** *100%*	2 45	**85** *100%*	**39** *46%*	**46** *54%*	**62** *73%*	**9** *11%*	**12** *14%*	**2** *2%*

NAT Neoadjuvant therapy. Data from PubMed/Medline for "breast MR AND multicenter", accessed on January 22, 2018. The research was limited to multicenter studies published in English. One international study on preoperative breast MRI was classified as involving centers from Europe and United States but also some Asian centers were involved. Studies on screening of women with personal breast cancer history were included in group 6

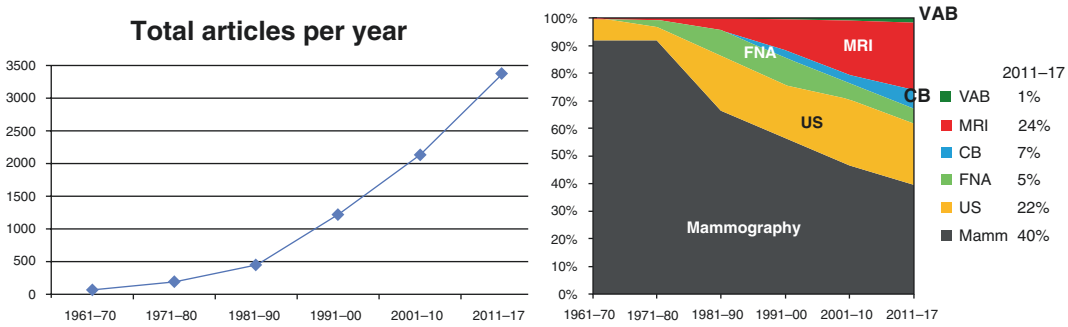

Fig. 1.1 Results of a research on PubMed, performed on June 1, 2018. The search was done for "breast" AND each of the following: "mammography," "ultrasound," "magnetic resonance imaging," "fine needle aspiration," "core biopsy," and "vacuum-assisted biopsy" (Mamm, US, MRI, FNA, CB, and VAB, respectively)

References

1. Grover VP, Tognarelli JM, Crossey MM, Cox IJ, Taylor-Robinson SD, McPhail MJ (2015) Magnetic resonance imaging: principles and techniques: lessons for clinicians. J Clin Exp Hepatol 5:246–255
2. The Nobel Prize website. https://www.nobelprize.org/. Accessed 30 Jun 2020
3. The New York Times (1997) Dr. Edward Purcell, 84, dies; shared Nobel prize in physics. https://www.nytimes.com/1997/03/10/us/dr-edward-purcell-84-dies-shared-nobel-prize-in-physics.html. Accessed 30 Jun 2020
4. Bottomley PA (1984) NMR in medicine. Comput Radiol 8:57–77
5. Babic RR, Stankovic Babic G, Babic SR, Babic NR (2016) 120 years since the discovery of x-rays. Med Pregl 69:323–330
6. Roguin A (2004 Mar) Nikola tesla: the man behind the magnetic field unit. J Magn Reson Imaging 19(3):369–374
7. Cheney, Margaret (2001) Tesla: Man Out of Time. Simon & Schuster, New York City
8. Shampo MA, Kyle RA, Steensma DP (2012) Richard Ernst—Nobel Prize for nuclear magnetic resonance spectroscopy. Mayo Clin Proc 87:e109
9. Damadian R (1971 Mar 19) Tumor detection by nuclear magnetic resonance. Science 171(3976):1151–1153
10. Damadian R, Zaner K, Hor D, DiMaio T (1974 Apr) Human tumors detected by nuclear magnetic resonance. Proc Natl Acad Sci U S A 71(4):1471–1473
11. Goldsmith M, Koutcher JA, Damadian R (1978 Oct) NMR in cancer, XIII: application of the NMR malignancy index to human mammary tumours. Br J Cancer 38(4):547–554
12. Roub LW, Drayer BP (1979 Aug) Spinal computed tomography: limitations and applications. AJR Am J Roentgenol 133(2):267–273
13. Bruneton JN, Philippe JC, Balu C, Drouillard J, Caramella E, Roux P (1983) Echography in tumor pathology of the spleen: limitations and perspectives. Nouv Rev Fr Hematol 25(6):355–361
14. U.S. Patent #3,789,832. https://patents.google.com/patent/US3789832A/en. Accessed 30 Jun 2020
15. Mansfield P, Maudsley AA (1977) Medical imaging by NMR. Br J Radiol 50:188–194
16. Lauterbur PC (1980) Progress in n.m.r. zeugmatography imaging. Philos Trans R Soc Lond Ser B Biol Sci 289:483–487
17. Elster AD. Questions and answers in MRI. https://www.mriquestions.com/from-signals-to-images.html. Accessed 30 Jun 2020
18. Ross RJ, Thompson JS, Kim K, Bailey RA (1982) Nuclear magnetic resonance imaging and evaluation of human breast tissue: preliminary clinical trials. Radiology 143:195–205
19. el Yousef SJ, O'Connell DM, Duchesneau RH et al (1985) Benign and malignant breast disease: magnetic resonance and radiofrequency pulse sequences. AJR Am J Roentgenol 145:1–8
20. Wolfman NT, Moran R, Moran PR, Karstaedt N (1985) Simultaneous MR imaging of both breasts using a dedicated receiver coil. Radiology 155:241–243
21. Nelson TR, Pretorius DH, Schiffer LM (1985) Menstrual variation of normal breast NMR relaxation parameters. J Comput Assist Tomogr 9:875–879
22. Kaiser W (1985) MRI of the female breast. First clinical results. Arch Int Physiol Biochim 93:67–76
23. Heywang SH, Fenzl G, Edmaier M, Eiermann W, Bassermann R, Krischke I (1985) Nuclear spin tomography in breast diagnosis. Röfö 143:207–212
24. Heywang SH, Eiermann W, Bassermann R, Fenzl G (1985) Carcinoma of the breast behind a prosthesis—comparison of US, mammography and MRI (case report). Comput Radiol 9:283–286
25. Cole-Beuglet C, Beique RA (1975) Continuous ultrasound B-scanning of palpable breast masses. Radiology 117:123–128
26. Heywang SH, Hahn D, Schmidt H et al (1986) MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr 10:199–204

27. Brkljacić B, Miletić D, Sardanelli F (2013) Thermography is not a feasible method for breast cancer screening. Coll Antropol 37: 589–593
28. American College of Radiology (2003) Breast Imaging Reporting and Data System® (BI-RADS®). 4th edition. American College of Radiology, Reston, VA, USA
29. Kaiser WA, Zeitler E (1989) MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 170:681–686
30. Kaiser WA (2008) Signs in MR-mammography. Springer-Verlag, Berlin
31. Harms SE, Flamig DP, Hesley KL et al (1993) MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. Radiology 187:493–501
32. Kaiser WA (1994) False-positive results in dynamic MR mammography. Causes, frequency, and methods to avoid. Magn Reson Imaging Clin N Am 2:539–555
33. Casey G, Plummer S, Hoeltge G, Scanlon D, Fasching C, Stanbridge EJ (1993) Functional evidence for a breast cancer growth suppressor gene on chromosome 17. Hum Mol Genet 2(11):1921–1927
34. Schutte MI, Rozenblum E, Moskaluk CA et al (1995) An integrated high-resolution physical map of the DPC/BRCA2 region at chromosome 13q12. Cancer Res 55(20):4570–4574
35. Oxford Centre for Evidence-based Medicine (2009) Levels of evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 30 Jun 2020

The *Mantra* about Low Specificity of Breast MRI

2

Pascal A. T. Baltzer and Francesco Sardanelli

Abbreviations

BI-RADS	Breast Imaging Reporting and Data System
DWI	Diffusion-weighted imaging
MRI	Magnetic resonance imaging
US	Ultrasonography, ultrasound

2.1 Introduction

Dynamic contrast-enhanced magnetic resonance imaging of the breast (referred to as *breast MRI* throughout this chapter, with few logic exceptions) is the most sensitive test for detection of breast cancer. This is due to the functional information given by breast MRI as the result of differences in tissue vascularization, microvascular permeability, and volume of the interstitial space. An increased contrast medium uptake due to changes of these parameters can be appreciated as bright areas of contrast enhancement on T1-weighted images, better visualized when temporal subtraction (contrast-enhanced minus unenhanced images) and/or spectral fat saturation are applied. As biologically active breast cancer is characterized by its vascularization due to neoangiogenesis, a process starting from about 3 mm in size, *breast MRI can depict most cancers*. Non-enhancing cancers are extremely rare and are a matter of case reports. Thus, false-negative diagnoses in breast MRI are mainly due to either technical problems or reader mistakes, for a variety of reasons, ranging from atypical localizations to motion and breathing artifacts. Finally, a malignant enhancement may be mistaken for a benign lesion or simple background enhancement.

The tissue changes demonstrated by breast MRI are not specific for malignant lesions. *A variety of other conditions lead to an increased contrast enhancement, including hormonally stimulated breast tissue, benign proliferative fibrocystic disease, benign tumors such as fibroadenoma, and lesions with uncertain malignant potential* (so-called B3 lesions at pathological examination of needle biopsy specimen). The safest diagnostic criterion to rule out malignancy in a technically adequate breast MRI examination is the absence of any contrast enhancement. However, this condition is not regularly fulfilled

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as most healthy women show at least some degree of background parenchymal enhancement and may also show one or several benign contrast enhancements. To distinguish benign from malignant enhancing lesions requires diagnostic criteria, none of which can absolutely rule in or rule out breast cancer. As the aim of breast imaging is to detect all biologically relevant cancers, the reader will in case of doubt decide for the more suspicious diagnosis and order a biopsy.

The high sensitivity of breast MRI can thus be considered its greatest challenge. This challenge has been described in a highly repetitive form by variations of the following sentence: "Breast MRI has a high sensitivity but low specificity." On multiple occasions, this sentence has been referred to as a "mantra" by Werner A. Kaiser [1], one of the earliest pioneers of this method and gold medalist of the European Society of Breast Imaging, attributed to his memory in 2014. The term "mantra" stems from Sanskrit and is typically defined as a group of words or a sentence that is believed to have psychological and spiritual powers. These transcendent powers are believed to influence the immanent usually by repetitive recitation [2]. Dr. Kaiser chose this term as he considered this statement as both *not backed up by scientific evidence* and *detrimental for the propagation of breast MRI*. In fact, it was used to discredit rather than embrace the new method [3]. A majority of both research and review articles on breast MRI have used this mantra. We invite our readers to explore this issue in more detail.

2.2 The Origin of the Mantra on *Low Specificity of Breast MRI*

When (dynamic contrast-enhanced) breast MRI was developed and introduced around 1990 [4, 5], screening mammography had already been established and found broad international application followed by quality assurance initiatives in 1992 in both Europe [6] and the United States [7, 8]. A generation of radiologists had previously established techniques to improve mammography workflow, reduce costs, and provide methods to establish diagnoses and guide surgery [9].

The proposal of breast MRI as a new and probably better diagnostic test could barely fall on fertile grounds in a time when decades of scientific, clinical, and commercial work were only beginning to show results. MRI was much less developed and available than it is today. In addition, not to consider important differences in costs, a problem that still persists today is related to organizational issues. On the one hand, breast radiologists have to compete with other colleagues to define suitable slots dedicated to breast imaging at MRI facilities. On the other hand, differently from brain/spine, musculoskeletal, and body MRI playing a mainly purely diagnostic job, breast MRI is much more interacting with other diagnostic imaging methods and also linked to imaging-guided biopsy and presurgical localization. This special role of MRI poses a serious workflow challenge in the breast clinic.

Additional findings on breast MRI must be further worked up, either by targeted (also named second-look) ultrasonography (US), biopsy, surgery, or follow-up. Sending a patient to breast MRI for a specific purpose (e.g., to clarify whether a mammographic density is due to a scar or cancer recurrence) and getting back one or multiple additional ipsilateral and/or contralateral findings could be frustrating, even more so in past times when the MRI guidance for biopsy and localization was not available and the experience in targeted US procedures after MRI was only in an early phase. These additional findings, which require more effort in terms of time and personnel, were and currently are considered more difficult to manage than mammographic or US findings. *This has led to the widespread believe that breast MRI is rather a problem maker than a problem solver*.

2.3 Is the Specificity of Breast MRI Indeed Low? The Scientific Evidence

As said, articles quoting variations of the sentence "Breast MRI has a high sensitivity but low specificity" in a mantra-like fashion are abundant. Exploring cross-references between these articles should thus lead to the original evidence.

However, this is not fully true in this case: Either the authors cite overview articles containing the same statement or do not reference their claim at all, contributing to the mantra-like impression of the statement. Despite that the reader will identify several articles connected to the claim of breast MRI having a low specificity, the most important one in terms of referencing is arguably an early work by Steven E. Harms and coworkers published in *Radiology* in 1993 [10]. We will compare this work to that published in the following year (1994) by Werner A. Kaiser in *Magnetic Resonance Imaging Clinics of North America* [11], in order to illustrate some important aspects about the assertion of a low specificity linked to breast MRI.

The Harms' study [10], conducted on 30 breasts with 47 malignant and 27 benign lesions, reported a 94% sensitivity and a 37% specificity. The Kaiser' study [11] conducted on 2,053 breast MRI examinations, 766 of them with histopathological verification within 2 weeks, the remaining having a follow-up up to 7 years, reported a 98% sensitivity and a 97% specificity. While the results obtained by Harms were reported in the abstract, those by Kaiser were not, probably contributing to a lower impact of the latter on the medical community. However, the difference in the reported specificity between the two articles deserves an in-depth analysis and discussion, beyond the simple notice of the huge difference in sample size, which could immediately close the discussion in terms of confidence intervals of any performance indices.

A potential pitfall in the interpretation of diagnostic performance is the assumption that parameters such as sensitivity and specificity reflect the intrinsic accuracy of the test. This is not the case. A reported diagnostic performance is linked to multiple factors besides the inherent diagnostic ability of the test itself, such as readers' experience, examination protocol, and, probably most important, the setting the test is applied in. We should also distinguish screening from assessment, that is, when asymptomatic subjects or symptomatic subjects are studied, respectively. However, a screening population can vary by age, individual risk for breast cancer, and individual breast tissue composition. Assessment is a vast field of quite substantially different indications for breast imaging, such as nipple discharge or retraction, palpable findings, or screening-detected mammographic abnormalities. Evaluating the diagnostic performance of a diagnostic test in these different indications will likely find highly variable results, as the utilized test may be more suited to one setting than to another. Finally, when evaluating the diagnostic performance of a diagnostic test in empirical research, the choice of the reference standard has a dramatic influence on the results.

2.4 Impact of the Reference Standard on MRI Specificity

In case of a diagnostic test with high sensitivity (such as MRI) that practically rules out breast cancer in a substantial number of women, patients receiving a negative result will be returned to screening or to a long-term follow-up. When follow-up examinations are used as a reference standard, the following principle is applied: The absence of any malignant lesions detected at follow-up examinations within a suitable time frame (at least 1 year, more often 2 years) can be considered a demonstration of the true negative result of the test. In this context, however, we use also the assumption that unchanged findings in the considered time frame are an indicator of negativity (absence of malignant lesions).

Traditionally, histopathology is considered the most accurate reference standard for radiological examinations. The rationale behind this is that by choosing follow-up examinations as a reference standard, malignant lesions may be wrongly considered benign if they do not show a progression in the evaluated time frame. This holds particularly true for less aggressive breast lesions as happens in the case of microcalcifications associated with ductal carcinoma in situ that may not show a progression in several years, thus leading to a potential (although *minor*) overestimation of sensitivity. On the other hand, the selection bias by choosing only histopathology as the reference standard will lead to an underestimation of specificity as all true negative cases that do not undergo histopathological sampling (and therefore also all

normal breast tissues) will not enter the equation for specificity, that is, true negative cases/(true negative cases + false-positive cases).

Notably, the use of histopathology as a reference standard in the absence of any imaging sign of pathology cannot be applied in the clinical practice on humans with the only exception of particular circumstances. This is the case when patients with unifocal tumors are treated with mastectomy, and the negative predictive value of MRI for additional lesions is evaluated using the pathology of the entirely excised breast as a reference standard [12]. In clinical practice, only nontrivial benign cases undergo histopathology. Simple cases (e.g., newly diagnosed fibroadenomas) undergo only needle biopsy, while complex cases (e.g., the abovementioned B3 lesions) undergo also surgical removal.

As a consequence, *those clinical studies that use histopathology as a reference standard* (even though including histopathology from imaging-guided needle sampling) are burdened by a selection bias that mostly includes nontrivial benign cases. Thus, *the specificity is underestimated and the false-positive rate is overestimated*. The only way to avoid this bias is a prospective application of the test under investigation without further case selection despite the focus on a specific clinical indication and ensuring an appropriate reference standard for all cases. Most studies on breast MRI, however, are retrospective and audit the performance of breast MRI in clinical practice, missing a large fraction of true negative findings. On the other hand, studies on the diagnostic performance of mammography have relied on follow-up reference standard as well, thus naturally reporting higher specificities. *Although the described biases are considered textbook knowledge by epidemiologists and statisticians, most clinicians, including radiologists, are not completely aware of the scale of these biases.*

For illustration reasons, we took data from a theoretical scenario [13] that is shown in Table 2.1 (raw data) and Fig. 2.1 (test results). This scenario includes 1,000 women undergoing a diagnostic test. Ninety-five breast cancer patients are correctly diagnosed, and five are missed. Fifty of 900 healthy individuals are biopsied due to a positive test result, while 50 are biopsied due to other reasons (e.g., complex cases with discrepant findings between different tests). The remaining 800 women are controlled by follow-up examinations. These examinations identify all five patients in which breast cancer was missed and prove stability in the remaining 795 women (see Table 2.1). The resulting diagnostic parameters (sensitivity = true positives/(true positives + false negatives); specificity = true negatives/(true negatives + false positives)) are given in Fig. 2.1 and illustrate the *minor overestimation of sensitivity* coupled with a *major underestimation of specificity* when using only histopathology as the reference standard (referred to as *reference standard 1*) compared to a combined reference standard composed of both histopathology and follow-up examinations (referred to as *reference standard 2*).

The example and its illustration of the potential biases allow for a better understanding of the differences between the results of sensitivity and specificity reported by Harms and coworkers [10] versus those reported by Kaiser [11]: In fact, Harms and coworkers used reference standard 1, while Kaiser used reference standard 2 (Table 2.2). The results are conceivable keeping in mind the theoretical example: a much higher specificity obtained by Kaiser as compared to Harms. Though the first impression may be an exaggerated diagnostic performance reported by Kaiser, the comparison with the theoretical dataset demonstrates that the results of both reports fall well within the expected values. For further illustration, we have "zero-filled" the true nega-

Table 2.1 Contingency tables of theoretical test results compared with two reference standards

	Only histopathology+	Only histopathology−	All cases+	All cases−
Test+	95	50	95	50
Test−	0	50	5	850

All cases, reference standard composed of histopathology when available and negative follow-up for patients who did not undergo any needle biopsy or surgery

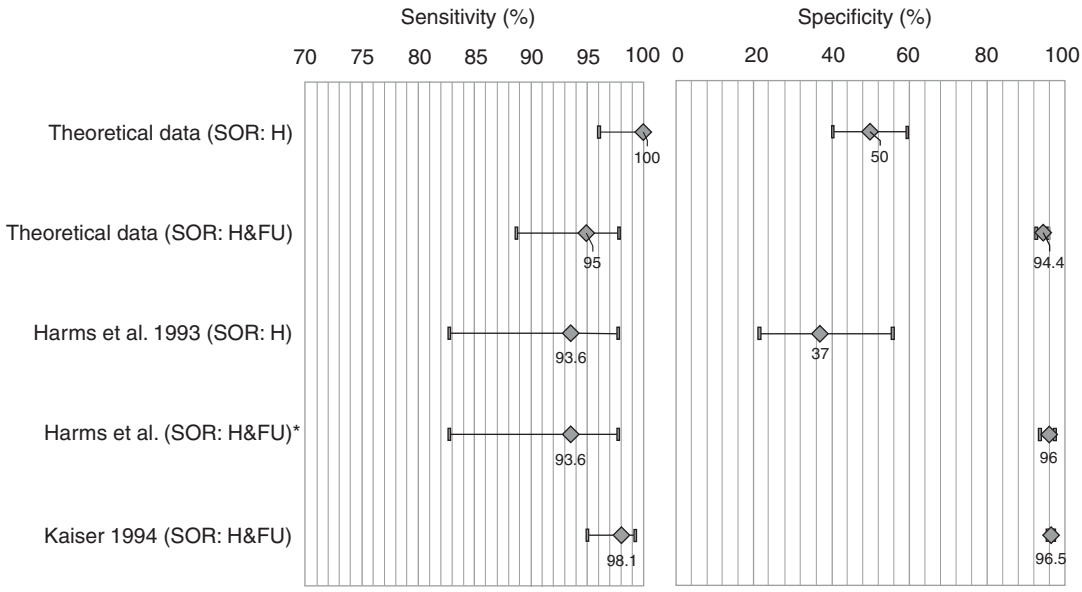

Fig. 2.1 Forest plot of test results (rhombus) taken from Tables 2.1 and 2.2 with the respective 95% confidence intervals (error bars). *Results from Harms et al. [10] extrapolated to simulate results if also follow-up examinations would be considered (see Table 2.2). *SOR*, standard of reference; *H*, histopathology; *FU*, follow-up

Table 2.2 Contingency tables of actual test results as given in references [10, 11]

	Harms et al. [10]		Kaiser [11]	
	Histopathology+	Histopathology−	All cases+	All cases−
Test+	44	17	203	47
Test−	3	10[a]	4	1,799

All cases, reference standard composed of histopathology when available and negative follow-up for patients who did not undergo any needle biopsy or surgery.
[a]To simulate a similar population as found in Kaiser [11], this number is raised to 404 for calculation of diagnostic parameters as indicated by the asterisk (∗) in Fig. 2.1

tive cases in the Harms' data to simulate the conditions of a reference standard 2 applied to their population. As expected, the results would fall well within the range of Kaiser under these conditions (see Fig. 2.1).

In addition, any given diagnostic parameter put outside a proper context cannot be properly interpreted. In other words, reporting the specificity of a test such as breast MRI without demonstrating its superiority or inferiority to alternative tests (in this case, typically, mammography) is meaningless due to a lack of data for comparison. Intraindividual comparison studies both in the high-risk screening and assessment setting employing reference standard 2 have shown significantly higher sensitivities and comparably similar specificities for breast MRI as matched to conventional imaging [14, 15].

2.5 Indications for Breast MRI and Diagnostic Performance

As stated above, the accuracy of a diagnostic test may vary according to its appropriateness to resolve a given clinical question. This may have two reasons: First, the underlying prevalence of malignancy may vary according to the indication, and second, the general ability of the diagnostic test selected to diagnose disease may be preferred under specific conditions. In general, the comparative evidence regarding this topic is sparse, and this sparse data distribution has been considered to explain the variability of results among different breast MRI studies [16]. For breast MRI, it has been shown that its diagnostic performance depends on whether lesions are associated with mammographically visible microcalcifica-

tions or not. Breast MRI performs better under the latter condition and may not be suited to diagnose breast cancer in BI-RADS 3 microcalcifications [16, 17].

2.6 Technical Equipment and Examination Protocols

It is conceivable that improvements in technical equipment, leading to better contrasted images with a higher spatial resolution, will lead to better diagnostic results. Since the introduction of dynamic contrast-enhanced breast MRI, several improvements such as dedicated multichannel coils and higher field strengths have been introduced. While per se advocated as improvements in diagnostic performance, the clear majority of research papers did not investigate a diagnostic benefit compared to standard procedures applying an intraindividual approach. Thus, a meta-analysis investigating the relation between variation of the diagnostic performance of breast MRI and technical characteristics of MRI examination performed did not find any significant associations but hinted at insufficient reporting quality on technical factors in the investigated primary literature, precluding any in-depth analysis [18]. More recent meta-analyses investigating the publication date as a proxy of technical progress were also unable to demonstrate any significant effect on either sensitivity or specificity [16, 17]. Thus, although modern equipment provides superior image quality (Fig. 2.2), a positive influence on specificity has not been proven yet.

There is one exception. Since the introduction of MRI sequences allowing for diffusion-weighted imaging (DWI), this technique has found widespread application as an adjunct to standard breast MRI protocols. A number of research studies consistently demonstrated that the addition of quantitative diffusivity data obtained by DWI can improve the specificity of breast MRI [16–22]. Although not yet officially recommended as an integral part of standard pro-

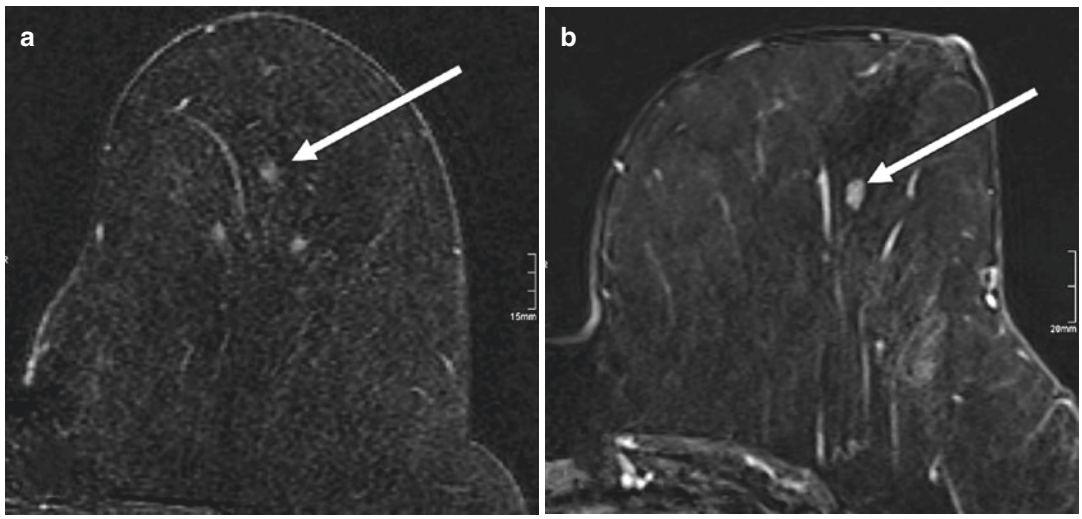

Fig. 2.2 Example of two subsequent breast MRI examinations in a 57-year-old woman 6 months apart. The first examination was performed at 1.5 T using a four-channel coil and a 2D dynamic gradient echo sequence (**a**). A slow and persistent enhancing incidental lesion of 6 mm with indistinct morphology (white arrow) was identified by the reader and rated BI-RADS 3. Follow-up MRI was initiated. The follow-up examination (**b**) was performed on the same 1.5 T scanner but using a newer 16-channel coil and a 3D gradient echo sequence. Albeit some differences in positioning, the lesion (white arrow) and the nearby vessel can be easily recognized. The higher signal-to-noise and spatial resolution are evident, allowing to characterize the lesion as a circumscribed oval mass lesion with persistent enhancement. It was downgraded to BI-RADS 2, identified by second-look US, and demonstrated US and MRI stability over the next 4 years

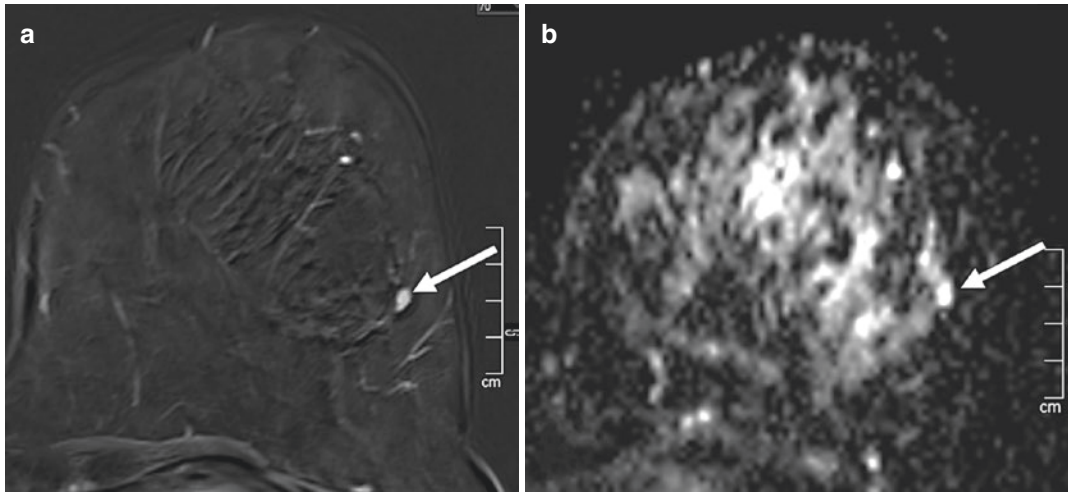

Fig. 2.3 Example of an incidental lesion in a 44-year-old woman. A 7 mm mass lesion with plateau enhancement curve-type and rather circumscribed margins was identified on early contrast-enhanced T1-weighted subtracted images (**a**). The apparent diffusion coefficient (ADC) map obtained by DWI clearly showed a highly hyperintense correlate. Quantitative ADC was measured as 2.3×10^{-3} mm²/s, corresponding to a benign finding (**b**). Consequently, the lesion was rated BI-RADS 2 and demonstrated long-term stability over 5 years

tocols [23, 24], DWI can clearly be suggested to reduce the number of false-positive findings (Fig. 2.3). It remains unclear, however, to which extent the selection bias of histologically verified patient groups (reference standard 1) has led to an overestimation of the impact of DWI on breast MRI specificity.

Finally, we should consider that also the type and dose of contrast material utilized for breast MRI can impact on the diagnostic performance. This topic will be treated in the Chap. 5 of this book.

2.7 Reading of Breast MRI and Reader Experience

Besides the technical adequacy and quality of imaging protocols, the person interpreting the test result is a variable factor influencing diagnostic performance. As explained in the Introduction to this chapter, breast MRI enables the visualization of increased tissue vascularization, microvascular permeability, and volume of the interstitial space. Depending on the population under investigation, the proportion of positive examinations and the ratio between benign and malignant lesions can be highly different. In particular, the number of benign lesions can range from substantial to overwhelming in the reader's perception.

Many diagnostic criteria to distinguish benign from malignant lesions have been described in breast MRI, the largest collection of which was published in a dedicated book by Werner A. Kaiser [1]. The challenge to apply these criteria lies in the semantic nature of the majority of diagnostic features. A precise and comprehensible definition of each criterion needs to be provided. This was tried by the BI-RADS committee, and the resulting lexicon is a great help for communication of clinical and research findings between international institutions [25]. It is therefore not surprising that the BI-RADS lexicon found widespread acceptance and subsequent worldwide application. However, early limitations that were even present in the initial assessment of the BI-RADS lexicon by its creators included high inter-reader variation and a redundancy of diagnostic information contained within the features used to describe enhancing lesions [26, 27]. While the BI-RADS lexicon allowed the identification of problematic subgroups by distinguishing benign from malignant enhancing

lesions, namely, *non-mass enhancements*, researchers demonstrated that the lower diagnostic performance was mainly due to the limited diagnostic information defined for these lesions within the BI-RADS features [28–30].

In this context, we can understand how the reader experience affects both sensitivity and specificity of breast MRI [31]. Of note, readers with intermediate and high experience levels showed comparable performance, a finding that stresses that breast MRI is not a tool restricted only to highly experienced readers due to its complexity [31]. One approach to reduce the inter-reader variability is to enforce clinical decision rules. Such algorithms lead to a diagnostic category by incorporating several criteria [32]. Several clinical decision rules have been proposed by researchers, some based on empirical reasoning and some on data-mining approaches [21, 33–36]. One of these algorithms demonstrated improved inter-reader agreement in a multiple reader validation study as compared to BI-RADS interpretation and was able to increase reader specificity to that of a highly experienced reader [37]. In addition, the same algorithm was shown to possibly decrease unnecessary biopsies of lesions detected by MRI only, thanks to applicable rule-out thresholds corresponding to diagnostic feature combinations that exclude malignancy [38]. Currently, however, no clinical decision rule has been fully adopted into standard reporting of breast MRI in clinical practice, and this still remains a research area of great interest. As already happened in the last decades for interpreting mammography and breast US, the majority of breast radiologists will base improvements of breast MRI interpretation on refinements contained in future editions of the BI-RADS.

2.8 Political Aspects in Interpreting Empirical Evidence

A well-known phenomenon in scientific research is publication bias. It is usually connected to outcome or content of a study influencing its probability to get published or referenced [39]. This bias usually affects studies presenting statistically significant results as compared to those without significant results. One of the risks for such bias to occur is prejudice, for instance, due to financial interests [40]. Here, we refer in particular to the probability to get referenced.

The two studies compared in detail above [10, 11] were published more than 20 years ago (in 1993 and in 1994). On the one hand, the highly positive results by Kaiser who had at that time an exceptionally high case number and breast MRI experience have been cited 79 times till today. On the other hand, the small study by Harms and coworkers, practically reporting on their very first steps in a new method resulting in a specificity well below 50% in a more than tenfold smaller patient population, has hence been cited 883 times [41]. Even considering a superior distribution of the journal *Radiology*, this discrepancy in the number of citations is disproportionately high.

We can see here a publication bias (in terms of probability to get referenced). Many factors could have contributed to this. First is the above-mentioned context of evolving screening programs based on mammography and the efforts for establishing quality assurance program for this widespread technology. The community of breast radiologists did not have comparable access to (and thus experience in) breast MRI as compared to both mammography and US. This is still an issue today. The breast radiologists community has more quickly embraced techniques that easily fit in with any mammography department such as digital mammography and digital breast tomosynthesis as compared to breast MRI [42]. Also, contrast-enhanced mammography will probably exploit this competitive advantage in the next future. Second, the high sensitivity of MRI gave radiologists a potential relevant role in the preoperative setting for treatment planning. This trend was counteracted, more or less consciously, by balancing the high sensitivity with the mantra highlighting the assumed low specificity of MRI. In fact, the logical consequence of MRI preoperative false positives (especially before the introduction of devices for MRI-

guided breast interventions) was unnecessary surgery, that is, overtreatment. The 37% specificity has been used frequently to show that results of breast MRI in terms of specificity were highly variable, *from 37% to over 90%*. What remained from this message was that breast MRI could have a specificity as low as 37%. But this was only an extremely low value, of which we have explained the reasons.

2.9 Reduction of False-Positive Findings

As explained in previous sections, the assumption of breast MRI being associated with a low specificity is not correct. Is this also true for the statement of "MRI being rather a problem maker than a problem solver"? Although the specificity of MRI may be equal to that of conventional mammography, the inherent higher sensitivity of breast MRI will lead to the detection of additional lesions. However, breast MRI may rule out malignancy in the majority of mammography-detected lesions, as highlighted by the literature [16]. Anyway, the application of an additional test can lead to false-positive results caused by this test. False-positive findings ultimately result in unnecessary biopsies that are cost intensive if MRI-guided biopsies are performed. Approaches to reduce MRI-guided biopsies include clinical decision rules [38], improved and new MRI techniques such as increased spatial and temporal resolution dynamic contrast-enhanced MRI, computer-aided diagnosis [43], DWI [19–22], and targeted (second-look) US [44].

2.10 Conclusions and Perspectives

The specificity of breast MRI is not low. We have analyzed reasons for this false assumption and demonstrated a variety of methodological, psychological, and political reasons that have led to the mantra affirming a low specificity of breast MRI. Although breast MRI may downgrade some or most false-positive findings caused by conventional imaging, it will also cause additional false-positive findings.

Strategies to improve the classification of MRI-detected lesions into benign and malignant include clinical decision rules and improved and new MRI techniques, as explained above. In particular, DWI is the most promising approach, although not specifically tested in the high-risk screening setting, a research topic to be explored by future projects. Targeted US allows for fast and cheap procedures. At the end, if a suspicious lesion is only visible on MRI, MRI-guided vacuum-assisted biopsy remains the method of choice.

All in all, the mantra of low specificity of breast MRI is progressively fading. The breast cancer medical community has learned and is still learning about the real diagnostic performance of breast MRI. However, radiologists should not give up to teach their colleagues what is true and what is false.

References

1. Kaiser WA (2008) Signs in MR-mammography. Springer, Berlin
2. Jan Gonda (1975) The Indian mantra. Selected studies, vol IV. E.J. Brill, Leiden
3. Kaiser WA (2008) Personal communication to Baltzer PA
4. Heywang SH, Hilbertz T, Pruss E et al (1988) Dynamic contrast medium studies with flash sequences in nuclear magnetic resonance tomography of the breast. Digitale Bilddiagn 8:7–13
5. Kaiser WA, Zeitler E (1989) MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 170:681–686
6. Tubiana M (2006) Preface. In: Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L (eds) European guidelines for quality assurance in breast cancer screening and diagnosis, 4th edition, pp VII–VIII.
7. Hendrick RE (1992) Quality assurance in mammography. Accreditation, legislation, and compliance with quality assurance standards. Radiol Clin N Am 30:243–255
8. Sickles EA (1992) Quality assurance. How to audit your own mammography practice. Radiol Clin N Am 30:265–275
9. Gold RH (1992) The evolution of mammography. Radiol Clin N Am 30:1–19

10. Harms SE, Flamig DP, Hesley KL et al (1993) MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. Radiology 187:493–501
11. Kaiser WA (1994) False-positive results in dynamic MR mammography. Causes, frequency, and methods to avoid. Magn Reson Imaging Clin N Am 2:539–555
12. Sardanelli F, Giuseppetti GM, Panizza P et al (2004) Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 183:1149–1157
13. Baltzer PA, Schelhorn J, Dietzel M, Kaiser WA (2010) Breast screening programs using MRI: is there a role for computer-aided diagnosis? Imaging Med 2:659–673
14. Benndorf M, Baltzer PA, Vag T, Gajda M, Runnebaum IB, Kaiser WA (2010) Breast MRI as an adjunct to mammography: does it really suffer from low specificity? A retrospective analysis stratified by mammographic BI-RADS classes. Acta Radiol 51:715–721
15. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 148:671–679
16. Bennani-Baiti B, Bennani-Baiti N, Baltzer PA (2016) Diagnostic performance of breast magnetic resonance imaging in non-calcified equivocal breast findings: results from a systematic review and meta-analysis. PLoS One 11:e0160346
17. Bennani-Baiti B, Baltzer PA (2017) MR imaging for diagnosis of malignancy in mammographic microcalcifications: a systematic review and meta-analysis. Radiology 283:692–701
18. Warren R, Ciatto S, Macaskill P, Black R, Houssami N (2009) Technical aspects of breast MRI—do they affect outcomes? Eur Radiol 19:1629–1638
19. Partridge SC, DeMartini WB, Kurland BF, Eby PR, White SW, Lehman CD (2009) Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value. AJR Am J Roentgenol 193:1716–1722
20. Pinker K, Bickel H, Helbich TH et al (2013) Combined contrast-enhanced magnetic resonance and diffusion-weighted imaging reading adapted to the "Breast Imaging Reporting and Data System" for multiparametric 3-T imaging of breast lesions. Eur Radiol 23:1791–1802
21. Baltzer A, Dietzel M, Kaiser CG, Baltzer PA (2016) Combined reading of contrast-enhanced and diffusion weighted magnetic resonance imaging by using a simple sum score. Eur Radiol 26:884–891
22. Spick C, Pinker-Domenig K, Rudas M, Helbich TH, Baltzer PA (2014) MRI-only lesions: application of diffusion-weighted imaging obviates unnecessary MR-guided breast biopsies. Eur Radiol 24:1204–1210
23. Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 18:1307–1318
24. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
25. American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
26. Ikeda DM, Hylton NM, Kinkel K et al (2001) Development, standardization, and testing of a lexicon for reporting contrast-enhanced breast magnetic resonance imaging studies. J Magn Reson Imaging 13:889–895
27. Benndorf M, Baltzer PAT, Kaiser WA (2011) Assessing the degree of collinearity among the lesion features of the MRI BI-RADS lexicon. Eur J Radiol 80:e322–e324
28. Gutierrez RL, DeMartini WB, Eby PR, Kurland BF, Peacock S, Lehman CD (2009) BI-RADS lesion characteristics predict likelihood of malignancy in breast MRI for masses but not for nonmasslike enhancement. AJR Am J Roentgenol 193:994–1000
29. Baltzer PAT, Benndorf M, Dietzel M, Gajda M, Runnebaum IB, Kaiser WA (2010) False-positive findings at contrast-enhanced breast MRI: a BI-RADS descriptor study. AJR Am J Roentgenol 194:1658–1663
30. Jansen SA, Shimauchi A, Zak L, Fan X, Karczmar GS, Newstead GM (2011) The diverse pathology and kinetics of mass, nonmass, and focus enhancement on MR imaging of the breast. J Magn Reson Imaging 33:1382–1389
31. Baltzer PAT, Kaiser WA, Dietzel M (2015) Lesion type and reader experience affect the diagnostic accuracy of breast MRI: a multiple reader ROC study. Eur J Radiol 84:86–91
32. Oxford Centre for Evidence-based Medicine (2009) Levels of Evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 30 Jun 2020
33. Baum F, Fischer U, Vosshenrich R, Grabbe E (2002) Classification of hypervascularized lesions in CE MR imaging of the breast. Eur Radiol 12:1087–1092
34. Schnall MD, Blume J, Bluemke DA et al (2006) Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 238:42–53
35. Demartini WB, Kurland BF, Gutierrez RL, Blackmore CC, Peacock S, Lehman CD (2011) Probability of malignancy for lesions detected on breast MRI: a predictive model incorporating BI-RADS imaging features and patient characteristics. Eur Radiol 21:1609–1617
36. Baltzer PAT, Dietzel M, Kaiser WA (2013) A simple and robust classification tree for differentiation between benign and malignant lesions in MR-mammography. Eur Radiol 23:2051–2060
37. Marino MA, Clauser P, Woitek R et al (2016) A simple scoring system for breast MRI interpretation:

does it compensate for reader experience? Eur Radiol 26:2529–2537
38. Woitek R, Spick C, Schernthaner M et al (2017) A simple classification system (the Tree flowchart) for breast MRI can reduce the number of unnecessary biopsies in MRI-only lesions. Eur Radiol 27:3799–3809
39. Song F, Parekh S, Hooper L et al (2010) Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess 14: iii, ix–xi, 1–193
40. Ioannidis JPA (2005) Why most published research findings are false. PLoS Med 2:e124
41. Google Scholar. https://scholar.google.com/. Accessed 30 Jun 2020
42. Sardanelli F, Aase HS, Álvarez M et al (2017) Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. Eur Radiol 27:2737–2743
43. Williams TC, DeMartini WB, Partridge SC, Peacock S, Lehman CD (2007) Breast MR imaging: computer-aided evaluation program for discriminating benign from malignant lesions. Radiology 244: 94–103
44. Spick C, Baltzer PAT (2014) Diagnostic utility of second-look US for breast lesions identified at MR imaging: systematic review and meta-analysis. Radiology 273:401–409

Hereditary Breast Cancer: BRCA and Other Susceptibility Genes

3

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Abbreviations

AT	Ataxia-telangiectasia
ATM	Ataxia-telangiectasia mutated
CHK2	Checkpoint kinase
CS	Cowden syndrome
DNA	Deoxyribonucleic acid
GWAS	Genome-wide association studies
LFS	Li-Fraumeni syndrome
NF1	Neurofibromatosis type 1
NGS	Next-generation sequencing
PARPi	Poly-ADP ribose inhibitors
PJS	Peutz-Jeghers syndrome
SNPs	Single nucleotide polymorphisms
TNBC	Triple negative breast cancer
VUS	Variants of uncertain clinical significance

3.1 Introduction: *Hereditary* and *Familial* Breast Cancer

Female breast cancer is the most common malignancy in most countries: over 450,000 new yearly diagnoses are registered in Europe and more than 1 million worldwide [1]. In developed countries, it is estimated that one in 9–12 women will develop breast cancer during the lifetime [2].

As for any type of cancer, breast cancer is considered a genetic disease, as it is initiated and driven by accumulation of acquired defects in a cell's deoxyribonucleic acid (DNA). These defects typically confer to the transformed cell the ability to divide uncontrollably by altering the function of genes involved in the maintenance of the physiological tissue homeostasis [3]. However, in the majority of cases, its development is mainly driven by the influence of environmental, lifestyle or stochastic factors, whereas only in a minor subset of women inherited constitutional genetic defects represent the main determinant of the disease.

Nevertheless, a positive family history for breast cancer is observed in a considerable proportion of affected women, and studies on twin siblings estimated that a genetic component underlies about 25–30% of cases [1, 4–6].

Owing to the growing number of studies, which demonstrated an increased breast cancer risk among close relatives of affected individuals, family history is now considered the most important risk-modifying factor [5, 7, 8]. In recent years, it was observed that, on average, the risk of developing the disease is nearly doubled by the presence of breast cancer in first-degree

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relatives, with a further increase determined by additional affected relatives with earlier age at diagnosis [8, 9].

The molecular basis of this genetic predisposition in most cases is not yet characterised, though it has become clear that this type of susceptibility is extremely complex, with the cancer risk determined by rare variants in high-penetrance genes (conferring a high probability of cancer development), but also variants in moderate-/variable-penetrance genes and common variants which have a slight and less estimable effect.

Since genetic factors are recognised as major determinants of increased breast cancer risk, extensive searches for genes underlying this susceptibility have been undertaken. According to the level of breast cancer risk conferred and the prevalence of each disease-causing variant in the population, all susceptibility genes identified to date have been divided into three main risk classes: high-, moderate- and low-penetrance genes. The level of penetrance describes the likelihood that a carrier of a particular genetic variant will develop the disease as a result of the presence of the variant. Pathogenic variants (commonly referred to as mutations) in high-penetrance genes, such as *BRCA1* and *BRCA2*, confer a risk increase of more than fourfold and up to 10- to 20-fold compared with non-carriers, corresponding to a 40–80% lifetime risk. Moderate-penetrance genes confer a two- to threefold increased risk, which corresponds to a lifetime risk of 20–36%, whereas all the low-penetrance variants identified to date are associated with a relative risk of less than 1.3-fold [10].

Breast cancers with a genetic susceptibility component are traditionally classified as either *hereditary* or *familial*, overall comprising 25–30% of cases (Fig. 3.1). The *high-risk class*, which includes known cancer hereditary predisposition syndromes, accounts for 5–10% of breast cancers. It is usually characterised by pathogenic variants in high-penetrance genes with a dominant inheritance pattern (i.e., vertical transmission through a parent), earlier age of onset, bilateral/multifocal

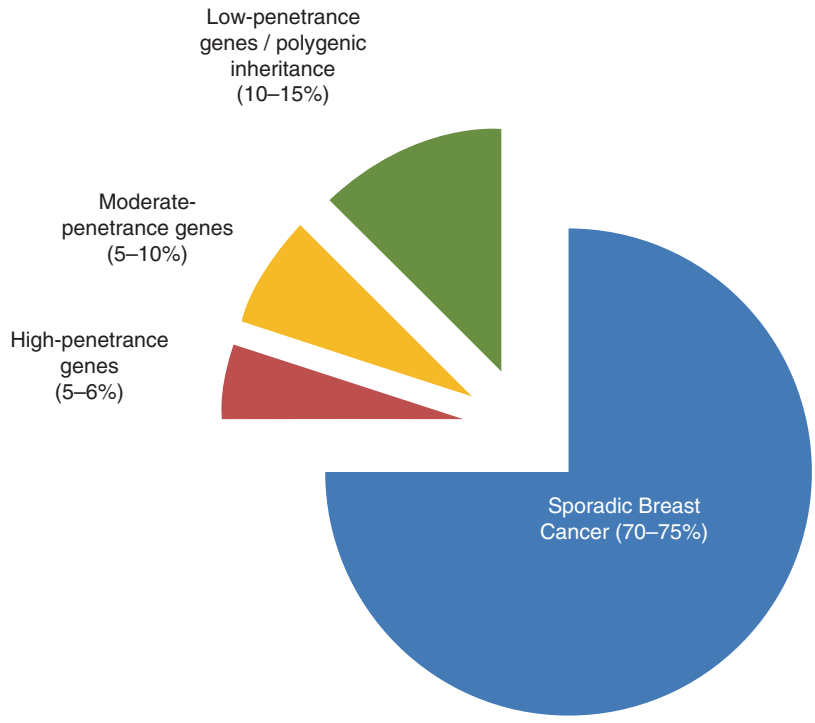

Fig. 3.1 Overall distribution of breast cancer cases according to genetic susceptibility. Cases with a relevant genetic component are characterised by the involvement of genes conferring high, moderate or above average risk of developing the disease. The percentages shown are approximated, as these categories might partly overlap, and several susceptibility genes and variants are yet to be characterised. Moreover, the frequency of hereditary breast cancer cases may differ in specific ethnic groups

cancers or multiple primary cancers in a single individual and increased risk for other types of tumours [7, 11, 12].

Conversely, *familial* breast cancer is a less defined type, characterised by a recurrence of the same tumour in multiple relatives, with variable age of onset in the absence of other typical features of hereditary cancer syndromes. Familial breast cancer, accounting for 20–25% of cases, albeit being more common than hereditary cancers, has a much less characterised molecular basis. In most of these families, the increased susceptibility might be explained by rare variants in lower-penetrance genes, on which available information is still limited, or multiple common variants each slightly increasing the risk (common genetic background). In some families, familial aggregation of breast cancers may also be due to common environmental and/or lifestyle factors or even to chance clustering of sporadic cases.

The aim of this chapter is to provide an overview of the known and emerging genetic factors driving breast cancer development, along with current evidence on how they modify the risk for breast cancer and guide the access to additional screening/surveillance and preventative strategies.

3.2 High-Penetrance Genes

Mutations in high-penetrance genes are generally rare but confer a risk higher than fourfold of developing breast cancer. Most of these genes take part in ubiquitous DNA repair pathways and, if altered, may also increase the risk of other types of cancer. A summary of high-penetrance genes and the respective risk estimates is provided in Table 3.1.

Variants associated with breast cancer risk are typically mono-allelic and inherited in an autosomal dominant fashion. Bi-allelic mutations in *BRCA1*, *BRCA2* and *PALB2* cause a recessive syndrome in the spectrum of the *Fanconi anaemia* (OMIM #610832), characterised by chromosomal instability and variable clinical features including bone marrow failure, congenital malformations, predisposition to acute myeloid leukaemia and other solid tumours [52].

3.2.1 *BRCA1* and *BRCA2*

BRCA1 and *BRCA2* were the first genes to be associated with hereditary breast and ovarian cancer [53, 54]. These early studies, which exploited linkage analysis and positional cloning, finally uncovered the pathogenetic cause underlying a relevant fraction of families with hereditary breast and ovarian cancers, thus making predictive genetic testing feasible.

The proteins encoded by these genes are involved in the double-strand breaks repair and homologous recombination mechanisms, even if with distinct roles. BRCA1 is a nuclear phosphoprotein that combines with other DNA damage sensors and signal transducers to form a multiprotein complex known as the BRCA1-associated genome surveillance complex (BASC), involved in several mechanisms safeguarding genome stability [55]. BRCA2 binds and recruits RAD51 onto single-strand DNA breaks where it takes part to the homologous recombination repair mechanism [56]. The link between BRCA1 and BRCA2 pathways is provided by PALB2, that directly binds to BRCA1 and is recruited to damaged DNA, where it stabilises the BRCA2-RAD51 complex [57]. BRCA1 may thus function as a regulatory platform for sensing DNA breaks and defining the repair pathway to be activated, while BRCA2 actively participates in homologous recombination repair.

Mutations in *BRCA1* and *BRCA2* account for about 3% of all breast cancers [58]. The frequency of pathogenic mutations is variable among different populations: founder variants have been mainly reported in Ashkenazi Jews but are also described in other ethnic groups [59–69]. *BRCA1* and *BRCA2* mutations are typically observed in families with clustering of breast and/or ovarian cancers with early onset of the diseases, though in most of these families (~70%), pathogenic variants in the *BRCA* genes are not observed [70–72].

Table 3.1 Genes with high- or moderate-penetrance for breast cancer and their respective cumulative lifetime risks. Information on other associated tumours is also provided

Gene	Magnitude of risk (high/moderate)	Lifetime breast cancer risk	Other associated cancers	References
BRCA1	High	40–90%	Ovarian, fallopian tubal, primary peritoneal	Antoniou et al. [13] King et al. [14] Lee et al. [15] Chen and Parmigiani [16] Mavaddat et al. [17] Berrino et al. [18]
BRCA2	High	40–90%	Ovarian, fallopian tubal, primary peritoneal	Antoniou et al. [13] King et al. [14] Lee et al. [15] Chen and Parmigiani [16] Mavaddat et al. [17] Berrino et al. [18]
TP53	High	50–80%[a]	Soft tissue sarcomas, brain tumours, osteosarcomas, leukaemias, adrenocortical carcinomas	Hisada et al. [19] Hwang et al. [20] Lustbader et al. [21] Wu et al. [22] Li et al. [23] Bougeard et al. [24]
PTEN	High	25–85%[b]	Thyroid, renal, endometrial	Bubien et al. [25] Tan et al. [26] Pilarski et al. [27] Nieuwenhuis et al. [28] Nelen et al. [29] Ngeow et al. [30]
STK11	High	32–54%[c]	Gastrointestinal, pancreatic, endometrial, ovarian sex cord-stromal tumours	Hearle et al. [31] Tchekmedyian et al. [32]
CDH1	High	42–53%	Diffuse gastric cancer	Pharoah et al. [33] Hansford et al. [34]
PALB2	Probably high	35–58%	NA	Antoniou et al. [35] Heikkinen et al. [36] Rahman et al. [37] Erkko et al. [38] Easton et al. [39]
CHEK2	Moderate	29–37%[d]	NA	Meijers-Heijboer et al. [40] Weischer et al. [41] Cybulski et al. [42]
NF1	Moderate	[d]	Malignant tumours of the peripheral nerve sheath, central nervous system	Sharif et al. [43] Madanikia et al. [44] Seminog and Goldacre [45] Da Silva et al. [46]
ATM	Moderate	[d]	NA	Renwick et al. [47] Pylkas et al. [48] Bogdanova et al. [49] van OS et al. [50]
NBN	Moderate	[d]	NA	Zhang et al. [51]

NA not available

[a]Most published estimates are subject to ascertainment bias

[b]Risk estimates reported by studies based on selected families with Cowden or other *PTEN*-related syndromes, possibly resulting in overestimation of risk

[c]Possible overestimation of risk in families at high risk for breast cancer; these data include also Peutz-Jeghers syndrome families with no *STK11* variants identified

[d]Available data suggest a relative risk (RR) for breast cancer between two and three for genetic variants in *CHEK2*, *NF1*, *ATM* and *NBN* [39], although reliable risk estimates for moderate-penetrance genes are currently limited

In *BRCA1* and *BRCA2* mutation carriers, the average cumulative lifetime risk for breast cancer is estimated to be about 60%, but might be as low as 40% in consecutive breast cancer series or as high as 80–90% in families selected for highly significant family history, with the greatest incidence recorded between 30 and 60 years of age [13–18]. Moreover, a difference in cancer risks was reported according to the birth cohort, with the risk being higher in carriers born after 1940 compared with those born before [13, 14, 18].

The risk of contralateral breast cancer, which appears to be influenced by several factors, including the age of onset of primary breast cancer and the use of adjuvant therapies, is estimated at about 35–60% at 20 years following the first diagnosis, equivalent to 2–3% cumulative risk per year [73].

The most common cancer morphology observed in carriers is the ductal type (~80%), though lobular, medullary and other types may be observed [74]. Several studies on the histopathological features of breast tumours in *BRCA* mutation carriers highlighted an association between triple negative breast cancers (TNBCs) and *BRCA1* mutations. Notably, over 60% of *BRCA1*-related breast cancers display a TNBC phenotype, and *BRCA1* pathogenic variants have been identified in about 10% of unselected TNBC [74–77]. Conversely, the breast tumour phenotype of *BRCA2* mutation carriers is less distinctive than *BRCA1*, with most cases being hormone receptor positive [76].

Due to the altered homologous recombination machinery in BRCA-deficient cancer cells, several phase II trials of novel therapies targeting homologous recombination defects, such as poly-ADP ribose inhibitors (PARPi), have been conducted in breast cancer patients that harbour *BRCA* mutations [78–80]. Although a response was observed in *BRCA*-mutated cancers, these therapies have not shown to be active in sporadic TNBC, and definite data from ongoing phase III clinical trials are required to determine the actual benefits of PARPi in the adjuvant and neoadjuvant treatment of *BRCA*-related breast cancers [81].

The risk of adnexal tumours, in *BRCA* mutation carriers, typically increases starting from 35 to 40 years of age, being estimated to be about 40–60% for *BRCA1* and 10–20% for *BRCA2* by the age of 70 years [13, 16–18]. The spectrum of gynaecological tumours associated with *BRCA* mutations includes ovarian, fallopian tube and primary peritoneal cancers. Ovarian tumours are usually high-grade serous epithelial carcinomas but may also display an endometrioid or clear-cell histology. Conversely, mucinous and borderline tumours are usually not observed [74, 82, 83].

In families with *BRCA1* and *BRCA2* pathogenic variants, an increased risk for breast cancer is also observed in males, particularly in *BRCA2* mutation carriers, for whom a 5–10% lifetime risk has been recorded [84].

Several studies highlighted a potential increased risk of cancer other than breast and ovarian in *BRCA1* and *BRCA2* mutation carriers, in particular colorectal, pancreatic and prostate cancers. These findings have not been confirmed in all the examined cohorts of carriers, and the extent of such risks is yet to be defined [85–89]. Thus, with respect to non-breast or ovarian cancers, family history is currently regarded as the main driver to offer specific surveillance to these individuals.

BRCA1 and *BRCA2* high-risk variants, which include point mutations but also large rearrangements (6–10% of all mutations) [71], are typically truncating, although missense variants have also been identified in crucial functional domains. Of note, not all truncating mutations confer the same cancer risk. Particular mutations in *BRCA1* and *BRCA2* are associated with a relative risk of breast cancer substantially lower (about 1.4) than other truncating mutations, suggesting that, even if *BRCA1* and *BRCA2* are considered high-penetrance genes, cancer risk is variant-specific [90, 91].

3.2.2 *TP53*

TP53 is one of the major caretakers of the genome by controlling gene transcription to induce cell cycle arrest, DNA repair, apoptosis and senescence in response to DNA damage [92]. Germline missense and truncating mutations in *TP53* have

been associated to the autosomal dominant *Li-Fraumeni syndrome* (LFS; OMIM #151623) [93]. Although disrupting variants of this gene were considered to be very rare, recent data suggest an actual prevalence as high as 1:5,000–1:20,000 [94, 95]. The LFS is characterised by genome instability and tumour predisposition, including breast cancer, soft tissue sarcomas, brain tumours, osteosarcomas, leukaemias and adrenocortical carcinomas, typically developing before the age of 45 years [23, 24]. Carriers of *TP53* mutations display a risk of cancer of about 50% by the age of 30 years and about 90% by the age of 60 years, although males have significantly lower lifetime risks than females [21, 22]. In fact, female breast cancer represents the most frequent tumour observed in LFS, affecting up to 80% of all female carriers [24]. The early age at diagnosis is an important indicator of *TP53* mutations, as about 3–8% women diagnosed with sporadic breast cancer before the age of 31 years have been found to be *TP53* mutation carriers [24, 96–98].

With respect to the tumour characteristics, breast cancers in LFS patients are usually oestrogen receptor (ER) negative, progesterone receptor (PgR) negative, and/or HER-2-positive ductal carcinomas [99–101].

Concerns about the increased risk of radiation-induced second primary breast cancers in these patients have elicited recommendations for complete mastectomy instead of lumpectomy followed by radiotherapy [24, 102, 103]. Nevertheless, most experts recommend that a careful evaluation of risks and benefits should be undertaken, and the treatment efficacy should be prioritised above the risk of potential late effects.

3.2.3 *PTEN*

The *PTEN* gene encodes for a phosphatase that antagonises the PI3K-AKT/PKB signalling pathway by dephosphorylating phosphoinositides and thereby modulating cell cycle progression and cell survival. Heterozygous germline mutations in *PTEN* are associated to the *Cowden syndrome* (CS; OMIM #158350), a rare autosomal dominant condition (prevalence ~1:200,000) characterised by macrocephaly; thyroid abnormalities; dermatological lesions, in particular hamartomas, papillomas and trichilemmomas; presence of *Lhermitte-Duclos disease*; and an increased risk of developing cancers, including breast, thyroid, renal and endometrial [29, 30]. More than 90% of individuals show some clinical manifestation by the age of 20–30 years [104–106].

Reliable estimates of breast cancer risk are lacking, but the lifetime risk for CS-affected women is estimated to be at least 25–50% with an average age at diagnosis of 38–50 years [27]. However, other studies reported a higher lifetime risk, estimated at 67–85% [26, 28].

3.2.4 *STK11*

STK11 (also known as LKB1) is a serine-threonine kinase that takes part in cell metabolism, polarity, apoptosis and DNA damage response by promoting the activity of AMP-activated protein kinases. As a caretaker of the genome, STK11 is involved in the TP53-dependent apoptosis pathway and in the UV radiation-induced DNA damage response mediated by CDKN1A. Mutations in *STK11* result in the *Peutz-Jeghers syndrome* (PJS; OMIM #175200), a rare autosomal dominant condition (prevalence between 1:25,000 and 1:280,000) characterised by hamartomatous gastrointestinal polyps, mucocutaneous pigmentation and multiple cancers predisposition, including colorectal, gastric, pancreatic, breast, uterus and ovarian cancers [32, 107]. The lifetime risk for breast cancer, which is mainly of the ductal type, is of about 32–54%, with only few cases diagnosed before the age of 50 [31]. With respect to ovarian cancer, unlike *BRCA* mutation carriers, females with PJS are at increased risk for ovarian sex cord tumours with annular tubules (SCTATs) and mucinous tumours of the ovaries and fallopian tubes. Males occasionally develop large cell calcifying Sertoli cell tumours (LCST) of the testes derived from sperm cord cells [108].

3.2.5 *CDH1*

CDH1 belongs to the cadherin family, a well-known group of calcium-dependent cell adhesion proteins. CDH1 is involved in cell-cell adhesion, motility and proliferation of epithelial cells, and thus CDH1 loss of function is believed to contribute to cancer progression by increasing proliferation, invasion and metastasis [109]. Germline *CDH1* mutations are associated with the *autosomal dominant hereditary diffuse gastric cancer syndrome* (HDGC; OMIM #137215), characterised by the development of diffuse gastric cancer (also called signet ring cell gastric cancer), and lobular breast cancer. The estimated risk for gastric cancer by the age of 80 years is estimated at 67% for men and at 83% for women [33]. The lifetime risk of developing lobular breast cancer, in *CDH1*-mutated women, ranges between 42% and 53%, with an average age at diagnosis of 53 years [34].

3.2.6 *PALB2*

PALB2 is the essential partner and localiser of *BRCA2* and acts as a bridging factor between *BRCA1* and *BRCA2*, synergising their genome caretaker activities [110]. Mono-allelic mutations in *PALB2* have been associated to a high-to-moderate risk of cancer, but the extent of such risk is only partially defined. A large family-based study has recently estimated that *PALB2* mutation carriers have sixfold (and up to ninefold) higher risk of breast cancer compared to non-carriers, and the risk is influenced by birth cohort and other factors, as observed also in *BRCA* families [35]. In particular, breast cancer risk was shown to be eight- to ninefold higher among women younger than 40 years, six- to eightfold among women aged 40–60 years and five times higher for those older than 60 years [35]. The observed cumulative risk was 14% by the age of 50 years and 35% by the age of 70 years. Family history appeared to be an important risk modifier as the absolute lifetime risk for women without family history was 33%, while in families with two or more affected relatives, it was estimated at 58% [35]. Based on the current available data, although *PALB2* mutations may confer a high risk for female breast cancer, the confidence intervals are still too wide to be certain [39].

Several studies reported *PALB2* mutations in males affected with breast cancer, providing initial evidences of an increased breast cancer risk also in male carriers [35, 111–113].

3.3 Moderate-/Intermediate-Penetrance Genes

Mutations in moderate-penetrance genes have been demonstrated to be associated to a two- to fourfold breast cancer risk. These genes are currently included in most next-generation sequencing (NGS) gene-panel analyses for high-risk individuals (NGS technologies allow a faster and less expensive parallel analysis of large genomic portions within a single DNA sample). A summary of moderate-penetrance genes and the respective risk estimates is provided in Table 3.1.

3.3.1 *CHEK2, NF1, ATM* and *NBN*

The *CHEK2* gene encodes for the checkpoint kinase 2 (CHK2), that controls the activity of several downstream effectors including BRCA1 and p53, in response to DNA damage [114, 115]. *CHEK2* mutations have been initially hypothesised to underlie LFS or LF-like syndrome, although subsequent studies confirmed a moderate risk for breast cancer but ruled out its role as a LFS gene [116–123].

The *CHEK2* truncating variant c.1100delC has been associated to a two- to threefold higher risk of breast cancer in women negative for *BRCA1* and *BRCA2* mutations [40, 124, 125]. The cumulative risk for carriers ranges between 29% and 37%, with a 3.5-fold risk of developing a contralateral cancer [41, 119]. Moreover, c.1100delC-associated breast cancers are typically of the luminal subtype and ER-negative and PgR-positive, suggesting a different impact on tumour aetiology compared to *BRCA1* mutations

[126, 127]. Two further truncating mutations (c.444 + 1G>A and del5567), conferring a comparable breast cancer risk, have been identified in Eastern Europe, while a breast cancer-associated missense mutation (p.(I157T)) showed a lower penetrance [128–130].

The neurofibromatosis type 1 (NF1; OMIM #162200) is an autosomal dominant multisystemic disease characterised by a predisposition to both benign and malign tumours [131]. Mutations in the *neurofibromin* gene (*NF1*) were found to be causative of NF1 [131], but a link between *NF1* and breast cancer has been only recently evidenced. In particular, *NF1* mutations were found to confer a 2.5- to 3.5-fold increased risk of female breast cancer, which becomes particularly significant starting from the age of 30 and should be taken into account when planning screening programs in individuals affected with NF1 [43–46].

Another master player of the DNA double-strand breaks repair pathway is *ATM*, which encodes for a protein kinase that controls the activity of several proteins involved in cell cycle progression, apoptosis and DNA damage response, comprising BRCA1, BRCA2, TP53 and CHEK2 [132]. Bi-allelic loss-of-function mutations of *ATM* result in ataxia-telangiectasia (AT; OMIM #208900), a condition characterised by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctivae and immunodeficiency. Heterozygous *ATM* mutations were found in 0.5–1% of the general populations, and carriers of monallelic truncating mutations were shown to exhibit increased sensitivity to ionising radiation and an average breast cancer risk about threefold higher than non-carriers [47–50]. Moreover, some missense variants are reported to act in a dominant negative manner and confer a higher risk of breast cancer even if in the homozygous state, it leads to a milder AT phenotype [133].

The NBN protein is a member of the MRE11-RAD50-NBS1 (MRN) complex that assembles on DNA double-strand breaks favouring ATM activation [134]. Homozygous mutations in the *NBN* gene cause the Nijmegen breakage syndrome (NBS; OMIM #251260) featured by microcephaly, immunodeficiency, growth retardation and cancer predisposition. A unique truncating mutation, c.657_661del, is commonly found in Eastern Europe populations: in a meta-analysis of ten different studies it was clearly demonstrated to be associated with a 2.7-fold increased risk of breast cancer [51].

3.3.2 Other Genes

Several studies have focussed on the impact of genetic variants in other genes, possibly involved in breast cancer predisposition. These genes include other components of the MRN complex, such as *RAD50*, the BCDX2 complex (*RAD51B*, *RAD51C*, *RAD51D* and *XRCC2*), involved in the homologous recombination repair; the RecQ-type helicase *RECQL*; and other *Fanconi anaemia* genes (*FANCM*, *FANCC* and *FANCA*) [77, 135–141]. Although these initial findings are promising, further studies are required to provide clear evidence on the association between variants in these genes and breast cancer.

Rare variants in high- and moderate-penetrance genes account only for a limited number of familial and hereditary breast cancer cases but do not elucidate the genetic contribution in a large fraction of familial and in sporadic breast cancer development. In the last years, sporadic breast cancer has, indeed, emerged as a polygenic disease, in which the susceptibility derives from the cumulative effect of several low-penetrance variants. In this regard, genome-wide association studies (GWAS) were exploited to uncover significant differences in the allelic frequency of single nucleotide polymorphisms (SNPs) between healthy controls and affected individuals. This strategy allowed the identification of over 150 genomic loci associated with breast cancer, shedding light on the pathogenetic mechanism of this tumour and uncovering variants with potential clinical utility [142].

3.4 Risk Assessment and Genetic Counselling

The incidence of breast cancer is continuously increasing, making it the most prevalent cancer in all countries with a Western lifestyle. Therefore, the development of risk evaluation tools has been a compelling need in order to predict which women are at higher risk and should be offered additional primary and secondary preventive options.

Several international scientific societies have drawn guidelines in order to identify individuals who may benefit from cancer risk assessment and genetic counselling, and to guide decisions related to genetic testing. The criteria outlined by most guidelines derive from a combination of features that are considered associated with hereditary breast cancers, including:

- Early age at onset
- Multiple affected relatives on the same side of the family
- Degree of relationship of affected family members
- Other related early-onset tumours
- Bilateral disease
- Biological markers (e.g., TNBC)
- Number of individuals (large families are more informative)

Examples of widely used empirical criteria are provided in Table 3.2. All individuals/families who fulfil these criteria are considered eligible for a genetic assessment and should be referred to board-certified genetic counsellors.

As an additional tool to predict the risk class of an individual, a number of Bayesian models have been developed, providing two main types of risk assessment. Some models exclusively estimate the chances of breast cancer development over a given time span. Other models estimate the chances of carrying a pathogenic variant in known high-penetrance genes (i.e., *BRCA1* and *BRCA2*). The former will be further discussed in Chap. 22. The latter, usually referred to as *genetic risk prediction models*, are based on data from large epidemiological studies on the empirical cancer risks in both carriers and the general population and consider breast and ovarian cancer status, the age of onset, but also the current age of all healthy relatives.

Since the offer of genetic testing is usually based on a higher a priori probability of being a carrier, with a threshold conventionally set at 10% by the first guidelines by the American Society of Clinical Oncology (ASCO) [148], the use of these models has been widespread. Although the Bayesian models show a good predictive performance, they are not exempt from limitations, and their use in clinical practice should be approached with caution by trained healthcare professionals. Moreover, it has been underlined that *these models could not substitute for a proper genetic counselling* [146].

Genetic counselling is a complex process, involving several phases. The proband would undergo a formal risk assessment, including a detailed family history and collection of clinical records of each affected family member. The family history evaluation is crucial to assess the likelihood that a predisposing gene variant is present within a family, since most often no other peculiar phenotypic features allow to discriminate carriers, with the exception of rare cases such as *Cowden syndrome*, *Peutz-Jeghers syndrome* or *neurofibromatosis type 1*. The probands' medical and surgical history should also be assessed, and a focussed physical examination, in selected cases, should be performed in order to detect peculiar pathognomonic features. Moreover, a thorough genetic counselling should also evaluate the probands' personal needs and concerns.

If appropriate, a genetic testing may be offered to the family member most likely to be a carrier of pathogenic variants (i.e., the youngest affected individual), and women should be advised about the cancer risks in themselves and in other family members.

Upon the proband's informed consent to undergo a genetic analysis, the diagnostic test should be performed by laboratories with established and certified experience in oncogenetic molecular analyses [11, 143, 149, 150].

Table 3.2 Examples of referral criteria for genetic counselling and BRCA testing in six different countries

GC-HBOC (Kast et al.) [70] Germany	INT (Azzollini et al.) [72] Italy[a]	NCCN (guidelines 1.) [11] USA
1. Family history of BC/OC		
Single cases		
BC<36 years	BC <36 years	BC ≤45 years
BBC any age (first ≤50 years)	OC <46 years	BC ≤50 years with limited FH[c]
	BC + OC any age	BBC any age (first ≤50 years)
	BBC <50 years	OC any age
	Male BC any age	Male BC any age
Multiple affected relatives[b]		
1 BC ≤50 years + 1 BC any age	2 BCs <50 years	1 BC ≤50 years + 1 BC any age
1 BC any age + 1 OC cany age	1 BC <50 years + 1 BBC any age	3 BCs any age
2 OCs any age	1 BC <50 years + 1 OC any age	
1 male BC + 1 BC or OC any age	1 BC <50 years + 1 male BC any age	
3 BCs any age	1 BBC any age + 1 OC any age	
	1 BBC any age + 1 male BC any age	
	2 OCs any age	
	3 BCs any age	
2. Hormone receptor status (TNBC)		
–	1 TNBC ≤42 years	1 TNBC ≤60 years
3. Ethnicity		
BC and Ashkenazi ancestry	BC and Ashkenazi ancestry	BC and Ashkenazi ancestry
		Pancreatic cancer and Ashkenazi ancestry
4. Other tumours		
–	–	1 BC ≤50 years + 1 pancreatic cancer any age
		1 BC ≤50 years + 1 prostate cancer any age (Gleason score ≥7)
		1 BC any age + 2 pancreatic or prostate cancers (Gleason score ≥7) any age
		3 relatives with BC, prostate (Gleason score ≥7) or pancreatic cancer any age
NICE (2013 guidelines) [143] UK	**SEOM (Llort et al.) [144] Spain**	**AGO (Marth et al.) [145] Austria**
1. Family history of BC/OC		
Single cases		
BBC average age <50 years	BC <36 years (≤40 years in uninformative families)	BC <35 years
BC <50 + OC any age	BBC any age (first ≤40 years)	
BC risk >8% in the next 10 years or >30% lifetime	OC any age (high-grade epithelial non-mucinous)	
Carrier probability >10%	BC + OC any age	
Multiple affected relatives[b]		
2 BCs average age <50 years (1st degree)	2 BCs <50 years	2 BCs <50 years
3 BCs average age <60 years (at least 2 1st degree)	1 BC <50 years + 1 BBC any age	1 BC <50 years + 1 OC any age
4 BCs any age (at least 2 1st degree)	1 BC any age + 1 OC any age	2 OCs any age
1 BC <50 years + 1 OC any age (1st/2nd degree)	2 Male BCs	1 BC any age + 1 male BC any age

Table 3.2 (continued)

NICE (2013 guidelines) [143] UK	SEOM (Llort et al.) [144] Spain	AGO (Marth et al.) [145] Austria
2 BCs average age <60 years + 1 OC any age (1st/2nd degree)	3 BCs and/or OCs any age	3 BCs <60 years
2 OCs any age (1st/2nd degree?)		
1 BBC any age + 1 BC <60 years (1st/2nd degree)		
1 BC <50 years + 1 male BC any age (1st/2nd degree)		
2 BCs average age <60 years + 1 male BC any age (1st/2nd degree)		
2. Hormone receptor status (triple negative BC, TNBC)		
1 TNBC <40 years	1 TNBC ≤50 years	–
3. Ethnicity		
BC and Jewish ancestry	BC and Jewish ancestry	–
4. Other tumours		
–	–	–

BC breast cancer, *BBC* bilateral breast cancer, *OC* ovarian cancer, *FH* family history
[a]Reported criteria refer to those in use at the National Cancer Institute of Milan—Fondazione IRCCS Istituto Nazionale dei Tumori, which largely overlap the FONCaM and INTEF guidelines [146, 147].
[b]INT: 1st-degree relatives; 2nd degree is considered for the paternal side of the family. NCCN: 1st-, 2nd-, 3rd-degree relative. CG-HBOC, SEOM, AGO: degree of kinship not specified.
[c]Limited family history defined by <2 1st-/2nd-degree female relatives surviving beyond 45 years in either side of the family

Gene testing analyses of index cases provide three possible outcomes:

1. Identification of pathogenic variants, known to be responsible for an increased cancer susceptibility
2. Identification of variants of uncertain clinical significance (VUS)
3. Absence of any variant with an ascertained or suspected pathogenic effect

All the identified genetic variants must be categorised based on a pathogenicity likelihood estimate. This estimate is usually performed using a multifactorial likelihood model, as proposed by the International Agency for Research on Cancer (IARC), with variants being subsequently classified according to a five-tier scheme (pathogenic, likely pathogenic, uncertain, likely neutral or neutral) [151, 152]. In order to facilitate the classification of variants, several data-sharing initiatives have been developed, such as the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) and the BRCA Challenge (a joint initiative of the Global Alliance for Genomics and Health and the Human Variome Project) [153–155].

Due to the still limited knowledge on the molecular basis of hereditary breast cancers, *non-detection of definitely pathogenic variants in index cases (i.e., the aforementioned outcomes 2 and 3) does not rule out an underlying genetic susceptibility, possibly caused by other yet unidentified genes*. Therefore, test results need to be accurately interpreted, and the residual risks in probands testing negative, or carrying a VUS, should be carefully discussed. Moreover, benefits and pitfalls of current surveillance and preventative options have to be extensively explained, taking into account also post-test risk estimates. *The genetic testing is offered to relatives only if a pathogenic variant is identified in the proband, in order to discriminate between relatives at higher risk and those with the average population risk*. In order to address all these relevant issues and foster a multidisciplinary approach in the management of individuals at increased genetic risk, *counselling should be performed both before and after testing* [11, 143, 144, 149, 156].

In the recent years, NGS technologies have been extensively employed in order to identify putative disease-associated genes. Multigene testing with NGS techniques, which simultaneously analyse sets of selected genes, has begun to be used in the context of clinical practice in oncology. Several studies reported a variable increase in the detection rate of pathogenic variants in clinically actionable genes, leading to recommendations for further surveillance and highlighting the potential of this technology to influence clinical management [157–159].

Nevertheless, multigene testing presents several issues to be considered before its widespread use in diagnostic services. The major concern for the routine clinical use of multigene testing is that *gene panels often include moderate-penetrance genes, for which limited data on cancer risks are currently available and guidelines for an adequate clinical management are lacking* [11, 160–162]. *As a consequence, the communication of the risks and possible preventive options for carriers of such variants is extremely difficult, and results might be inconclusive and yet raise testing-related anxieties*. Moreover, not all genes included in multigene panels are necessarily clinically actionable, and the information from testing does not significantly change the risk management compared to that based on family history alone. Consistently, as demonstrated by a recent study on the clinical outcomes of NGS panels, the use of multiple-gene sequencing is not associated with an increased uptake of prophylactic mastectomy in the United States [163]. The study also highlighted that, although the detection rate of pathogenic variants compared with single-gene testing has improved, multigene panels dramatically increase the frequency of identified VUS, especially in minorities, adding further complexity to the interpretation of results.

In addition, due to their wide range of customisation, commercially available NGS gene panels present relevant differences in the selection of genes, experimental methods, variant classification and many other factors. It must be also considered that some variants, detected by conventional single-gene analyses, may be missed by NGS techniques [164]. International guidelines thus recommend that multigene tests, as well as the specific laboratory, should be chosen carefully, on the basis of the phenotype of the individuals/families to be tested, offered only by professionals with genetic expertise and in the context of a genetic counselling [11, 143].

In order to instruct the appropriate clinical management, concerning surveillance or other preventive options, cancer risks are estimated, taking into account the genetic testing results. It should be considered, though, that *even among families with pathogenic variants in the same gene, the risk of cancer is considerably variable*. A higher penetrance is usually observed in carriers with a positive family history, possibly due to an underlying polygenic predisposition, multifactorial predisposition or both.

In general, both affected and healthy women with pathogenic variants in high-penetrance genes are considered at high risk for breast cancer and are thus offered additional screening through breast MRI, usually starting from 25 to 30 years of age [165]. Depending on the age of the patient, risk-reducing surgery may be also discussed with high-risk women on a case-by-case basis, along with the extent of cancer risk reduction, the risks associated with surgeries and the available reconstructive options [166].

For women with pathogenic variants in *PALB2* or moderate-penetrance genes and without a relevant family history of breast cancer, consensus recommendations about the use of MRI and risk-reducing surgery are not currently available due to the lack of data on important end points, including mortality [166].[1]

Conversely, in families considered at high risk based on family history alone, irrespective of the identification of genetic variants, breast MRI may be indicated, in healthy and affected women, and risk-reducing surgery may be discussed with women who already developed breast cancer.

Moreover, as the initial risk estimate might be modified by additional cancer cases diagnosed in a family, re-evaluation of family history over time may be necessary.

[1] See also Chap. 16.

Chemopreventive strategies, such as the use of tamoxifen for primary prevention, are currently under evaluation.[2] Although an effect has been recorded in carriers of *BRCA2* pathogenic variants, who develop mostly hormone receptor-positive breast cancers, conclusive data supporting its use in high-risk women are lacking [166, 167].

3.5 Conclusions

Breast cancers with a clear genetic component represent the minority of all breast cancer cases. Nevertheless, the identification of *actionable* genes pointed out the clinical relevance of genetic testing in order to identify women at high risk. *The identification of hereditary breast cancers is a complex process, which should always be performed within a genetic counselling*.

Evidences on the efficacy of surveillance and other preventive options are still limited, and conclusive data are needed, not only for families testing negative but also for families with pathogenic variants in well-characterised high-penetrance genes. Moreover, as the efficacy of each preventive option is directly related to the individual cancer risk, more personalised risk estimates need to be achieved. Considering the actual complexities, *it is recommended that risk management strategies should be discussed for each woman with a multidisciplinary approach, in order to foster a tailored prevention program*.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374–1403
2. Lalloo F, Evans DG (2012) Familial breast cancer. Clin Genet 82:105–114
3. Stephens PJ, Tarpey PS, Davies H et al; Oslo Breast Cancer Consortium (OSBREAC) (2012) The landscape of cancer genes and mutational processes in breast cancer. Nature 486:400–404
4. Peto J, Mack TM (2000) High constant incidence in twins and other relatives of women with breast cancer. Nat Genet 26:411–414
5. Lichtenstein P, Holm NV, Verkasalo PK et al (2000) Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343:78–85
6. Mucci LA, Hjelmborg JB, Harris JR et al; Nordic Twin Study of Cancer (NorTwinCan) Collaboration (2016) Familial risk and heritability of cancer among twins in nordic countries. JAMA 315:68–76. Erratum in: JAMA 2016;315:822
7. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA (1997) Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 71:800–809
8. Møller P, Stormorken A, Holmen MM, Hagen AI, Vabø A, Mæhle L (2014) The clinical utility of genetic testing in breast cancer kindreds: a prospective study in families without a demonstrable BRCA mutation. Breast Cancer Res Treat 144:607–614
9. Claus EB, Risch N, Thompson WD (1991) Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 48:232–242
10. Evans DG, Astley S, Stavrinos P et al (2016) Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. Southampton (UK): NIHR Journals Library. PubMed PMID: 27559559
11. National Comprehensive Cancer Network (NCCN) (2017). Genetic/familial high-risk assessment: breast and Ovarian. Version 1. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed 30 Jun 2020.
12. Lynch HT, Watson P, Conway TA, Lynch JF (1990) Clinical/genetic features in hereditary breast cancer. Breast Cancer Res Treat 15:63–71
13. Antoniou A, Pharoah PD, Narod S et al (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130. Erratum in: Am J Hum Genet 2003;73:709
14. King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group (2003) Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302:643–646
15. Lee AJ, Cunningham AP, Kuchenbaecker KB, Mavaddat N, Easton DF, Antoniou AC; Consortium of Investigators of Modifiers of BRCA1/2; Breast Cancer Association Consortium (2014) BOADICEA breast cancer risk prediction model: updates to cancer incidences, tumour pathology and web interface. Br J Cancer 110:535–545
16. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329–1333

[2] See Chap. 17.

17. Mavaddat N, Peock S, Frost D et al; EMBRACE (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 105:812–822
18. Berrino J, Berrino F, Francisci S et al (2015) Estimate of the penetrance of BRCA mutation and the COS software for the assessment of BRCA mutation probability. Familial Cancer 14:117–128
19. Hisada M, Garber JE, Fung CY, Fraumeni JF Jr, Li FP (1998) Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 90:606–611
20. Hwang SJ, Lozano G, Amos CI, Strong LC (2003) Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet 72:975–983
21. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC (1992) Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet 51:344–356
22. Wu CC, Shete S, Amos CI, Strong LC (2006) Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res 66:8287–8292
23. Li FP, Fraumeni JF Jr, Mulvihill JJ et al (1988) A cancer family syndrome in twenty-four kindreds. Cancer Res 48:5358–5362
24. Bougeard G, Renaux-Petel M, Flaman JM et al (2015) Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 33:2345–2352
25. Bubien V, Bonnet F, Brouste V et al; French Cowden Disease Network (2013) High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet 50:255–263
26. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C (2012) Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 18:400–407
27. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E (2013) Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 105:1607–1616
28. Nieuwenhuis MH, Kets CM, Murphy-Ryan M et al (2014) Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. Familial Cancer 13:57–63
29. Nelen MR, Kremer H, Konings IB et al (1999) Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet 7:267–273
30. Ngeow J, Eng C (2015) PTEN hamartoma tumor syndrome: clinical risk assessment and management protocol. Methods 77–78:11–19
31. Hearle N, Schumacher V, Menko FH et al (2006) Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res 12:3209–3215
32. Tchekmedyian A, Amos CI, Bale SJ et al (2013) Findings from the Peutz-Jeghers syndrome registry of uruguay. PLoS One 8:e79639
33. Pharoah PD, Guilford P, Caldas C; International Gastric Cancer Linkage Consortium (2001) Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 121:1348–1353
34. Hansford S, Kaurah P, Li-Chang H et al (2015) Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol 1:23–32. Erratum in: JAMA Oncol 2015;1:110
35. Antoniou AC, Foulkes WD, Tischkowitz M (2014) Breast-cancer risk in families with mutations in PALB2. N Engl J Med 371:1651–1652
36. Heikkinen T, Kärkkäinen H, Aaltonen K et al (2009) The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res 15:3214–3222
37. Rahman N, Seal S, Thompson D et al; Breast Cancer Susceptibility Collaboration (UK) (2007) PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet 39:165–167
38. Erkko H, Xia B, Nikkilä J, Schleutker J et al (2007) A recurrent mutation in PALB2 in Finnish cancer families. Nature 446:316–319
39. Easton DF, Pharoah PD, Antoniou AC et al (2015) Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372:2243–2257
40. Meijers-Heijboer H, van den Ouweland A, Klijn J et al; CHEK2-Breast Cancer Consortium (2002) Low-penetrance susceptibility to breast cancer due to CHEK2(∗)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55–59
41. Weischer M, Nordestgaard BG, Pharoah P et al (2012) CHEK2∗1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol 30:4308–4316
42. Cybulski C, Wokołorczyk D, Jakubowska A et al (2011) Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol 29:3747–3752
43. Sharif S, Moran A, Huson SM et al (2007) Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening. J Med Genet 44:481–484
44. Madanikia SA, Bergner A, Ye X, Blakeley JO (2012) Increased risk of breast cancer in women with NF1. Am J Med Genet A 158A:3056–3060
45. Seminog OO, Goldacre MJ (2015) Age-specific risk of breast cancer in women with neurofibromatosis type 1. Br J Cancer 112:1546–1548
46. Da Silva AV, Rodrigues FR, Pureza M, Lopes VG, Cunha KS (2015) Breast cancer and neurofibromatosis type 1: a diagnostic challenge in patients with a high number of neurofibromas. BMC Cancer 15:183
47. Renwick A, Thompson D, Seal S et al; Breast Cancer Susceptibility Collaboration (UK) (2006) ATM

mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet 38:873–875
48. Pylkäs K, Tommiska J, Syrjäkoski K et al (2007) Evaluation of the role of Finnish ataxia-telangiectasia mutations in hereditary predisposition to breast cancer. Carcinogenesis 28:1040–1045
49. Bogdanova N, Cybulski C, Bermisheva M et al (2009) A nonsense mutation (E1978X) in the ATM gene is associated with breast cancer. Breast Cancer Res Treat 118:207–211
50. van Os NJ, Roeleveld N, Weemaes CM et al (2016) Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet 90:105–117
51. Zhang G, Zeng Y, Liu Z, Wei W (2013) Significant association between Nijmegen breakage syndrome 1 657del5 polymorphism and breast cancer risk. Tumour Biol 34:2753–2757
52. Tischkowitz M, Xia B (2010) PALB2/FANCN: recombining cancer and Fanconi anemia. Cancer Res 70:7353–7359
53. Miki Y, Swensen J, Shattuck-Eidens D et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71
54. Wooster R, Bignell G, Lancaster J et al (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792. Erratum in: Nature 1996 379:749
55. Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J (2000) BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes Dev 14:927–939
56. Thorslund T, McIlwraith MJ, Compton SA et al (2010) The breast cancer tumor suppressor BRCA2 promotes the specific targeting of RAD51 to single-stranded DNA. Nat Struct Mol Biol 17:1263–1265
57. Pauty J, Rodrigue A, Couturier A, Buisson R, Masson JY (2014) Exploring the roles of PALB2 at the crossroads of DNA repair and cancer. Biochem J 460:331–342
58. Kleibl Z, Kristensen VN (2016) Women at high risk of breast cancer: molecular characteristics, clinical presentation and management. Breast 28:136–144
59. Warner E, Foulkes W, Goodwin P (1999) Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst 91:1241–1247
60. Thorlacius S, Olafsdottir G, Tryggvadottir L et al (1996) A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 13:117–119
61. Struewing JP, Hartge P, Wacholder S et al (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401–1408
62. Rudkin TM, Hamel N, Galvez M et al (2006) The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations. BMC Med Genet 7:15
63. Salazar R, Cruz-Hernandez JJ, Sanchez-Valdivieso E et al (2006) BRCA1-2 mutations in breast cancer: identification of nine new variants of BRCA1-2 genes in a population from central Western Spain. Cancer Lett 233:172–177
64. Janavičius R (2010) Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control. EPMA J 1:397–412
65. Karami F, Mehdipour P (2013) A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013:928562
66. Krajc M, Zadnik V, Novaković S et al (2014) Geographical distribution of Slovenian BRCA1/2 families according to family origin: implications for genetic screening. Clin Genet 85:59–63
67. Caleca L, Putignano AL, Colombo M et al (2014) Characterization of an Italian founder mutation in the RING-finger domain of BRCA1. PLoS One 9:e86924
68. Cini G, Mezzavilla M, Della Puppa L et al (2016) Tracking of the origin of recurrent mutations of the BRCA1 and BRCA2 genes in the North-East of Italy and improved mutation analysis strategy. BMC Med Genet 17:11
69. Apostolou P, Pertesi M, Aleporou-Marinou V et al (2017) Haplotype analysis reveals that the recurrent BRCA1 deletion of exons 23 and 24 is a Greek founder mutation. Clin Genet 91:482–487
70. Kast K, Rhiem K, Wappenschmidt B et al; German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) (2016) Prevalence of BRCA1/2 germline mutations in 21 401 families with breast and ovarian cancer. J Med Genet 53:465–471
71. Judkins T, Rosenthal E, Arnell C et al (2012) Clinical significance of large rearrangements in BRCA1 and BRCA2. Cancer 118:5210–5216
72. Azzollini J, Scuvera G, Bruno E et al (2016) Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study. Eur J Intern Med 32:65–71
73. Basu NN, Ingham S, Hodson J et al (2015) Risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a 30-year semi-prospective analysis. Familial Cancer 14:531–538
74. Mavaddat N, Barrowdale D, Andrulis IL et al (2012) Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomark Prev 21:134–147
75. Hartman AR, Kaldate RR, Sailer LM et al (2012) Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer 118:2787–2795
76. Spurdle AB, Couch FJ, Parsons MT et al; ABCTB Investigators; EMBRACE Group; GENICA Network; HEBON Group; kConFab Investigators

(2014) Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Res 16:3419
77. Couch FJ, Hart SN, Sharma P et al (2015) Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol 33:304–311
78. Tutt A, Robson M, Garber JE et al (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 376:235–244
79. Gelmon KA, Tischkowitz M, Mackay H et al (2011) Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 12:852–861
80. Kaufman B, Shapira-Frommer R, Schmutzler RK et al (2015) Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 33:244–250
81. Lehmann BD, Pietenpol JA, Tan AR (2015) Triple-negative breast cancer: molecular subtypes and new targets for therapy. Am Soc Clin Oncol Educ Book 2015:e31–39
82. Evans DG, Young K, Bulman M, Shenton A, Wallace A, Lalloo F (2008) Probability of BRCA1/2 mutation varies with ovarian histology: results from screening 442 ovarian cancer families. Clin Genet 73:338–345
83. Candido-dos-Reis FJ, Song H, Goode EL et al; for EMBRACE, kConFab Investigators, Australian Ovarian Cancer Study Group (2015) Germline mutation in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer. Clin Cancer Res 21:652–657
84. Liede A, Karlan BY, Narod SA (2004) Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 22:735–742
85. Moran A, O'Hara C, Khan S et al (2012) Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Familial Cancer 11:235–242
86. Phelan CM, Iqbal J, Lynch HT et al; Hereditary Breast Cancer Study Group (2014) Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: results from a follow-up study. Br J Cancer 110:530–534
87. Sopik V, Phelan C, Cybulski C, Narod SA (2015) BRCA1 and BRCA2 mutations and the risk for colorectal cancer. Clin Genet 87:411–418
88. Salo-Mullen EE, O'Reilly EM, Kelsen DP et al (2015) Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 121:4382–4388
89. Holter S, Borgida A, Dodd A et al (2015) Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol 33:3124–3129
90. Spurdle AB, Whiley PJ, Thompson B et al; kConFab; Dutch Belgium UV Consortium; German Consortium of Hereditary Breast and Ovarian Cancer; French COVAR group collaborators; ENIGMA Consortium (2012) BRCA1 R1699Q variant displaying ambiguous functional abrogation confers intermediate breast and ovarian cancer risk. J Med Genet 49:525–532
91. Meeks HD, Song H, Michailidou K et al; EMBRACE; kConFab Investigators; Australia Ovarian Cancer Study Group; HEBON; GEMO Study Collaborators; OCGN; PRostate cancer AssoCiation group To Investigate Cancer Associated aLterations in the genome (2015) BRCA2 polymorphic stop codon K3326X and the risk of breast, prostate, and ovarian cancers. J Natl Cancer Inst 108:djv315
92. Reinhardt HC, Schumacher B (2012) The p53 network: cellular and systemic DNA damage responses in aging and cancer. Trends Genet 28:128–136
93. Malkin D, Li FP, Strong LC, Fraumeni JF Jr et al (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233–1238. Erratum in: Science 1993;259:878
94. Lalloo F, Varley J, Ellis D et al; Early Onset Breast Cancer Study Group (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361:1101–1102
95. Gonzalez KD, Noltner KA, Buzin CH et al (2009) Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27:1250–1256
96. Lalloo F, Varley J, Moran A et al (2006) BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. Eur J Cancer 42:1143–1150
97. Mouchawar J, Korch C, Byers T et al (2010) Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. Cancer Res 70:4795–4800
98. McCuaig JM, Armel SR, Novokmet A et al (2012) Routine TP53 testing for breast cancer under age 30: ready for prime time? Familial Cancer 11:607–613
99. Melhem-Bertrandt A, Bojadzieva J, Ready KJ et al (2012) Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer 118:908–913. Erratum in: Cancer 2012;118:2561
100. Giacomazzi J, Koehler-Santos P, Palmero EI et al (2013) A TP53 founder mutation, p.R337H, is associated with phyllodes breast tumors in Brazil. Virchows Arch 463:17–22
101. Masciari S, Dillon DA, Rath M et al (2012) Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat 133:1125–1130

102. Heymann S, Delaloge S, Rahal A et al (2010) Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol 5:104
103. Limacher JM, Frebourg T, Natarajan-Ame S, Bergerat JP (2001) Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome. Int J Cancer 96:238–242
104. Nelen MR, Padberg GW, Peeters EA et al (1996) Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet 13:114–116
105. Eng C (2000) Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 37:828–830
106. Zbuk KM, Eng C (2007) Cancer phenomics: RET and PTEN as illustrative models. Nat Rev Cancer 7:35–45
107. Beggs AD, Latchford AR, Vasen HF et al (2010) Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 59:975–986
108. Young RH (2005) Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. Mod Pathol 18(Suppl. 2):S81–S98
109. Berx G, Van Roy F (2001) The E-cadherin/catenin complex: an important gatekeeper in breast cancer tumorigenesis and malignant progression. Breast Cancer Res 3:289–2893
110. Sy SM, Huen MS, Chen J (2009) PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci USA 106:7155–7160
111. Ding YC, Steele L, Kuan CJ, Greilac S, Neuhausen SL (2011) Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. Breast Cancer Res Treat 126:771–778
112. Blanco A, de la Hoya M, Balmaña J et al (2012) Detection of a large rearrangement in PALB2 in Spanish breast cancer families with male breast cancer. Breast Cancer Res Treat 132:307–315
113. Silvestri V, Zelli V, Valentini V et al (2017) Whole-exome sequencing and targeted gene sequencing provide insights into the role of PALB2 as a male breast cancer susceptibility gene. Cancer 123:210–218
114. Antoni L, Sodha N, Collins I, Garrett MD (2007) CHK2 kinase: cancer susceptibility and cancer therapy—two sides of the same coin? Nat Rev Cancer 7:925–936
115. Jackson SP, Bartek J (2009) The DNA-damage response in human biology and disease. Nature 461:1071–1078
116. Bell DW, Varley JM, Szydlo TE et al (1999) Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science 286:2528–2531
117. Cybulski C, Górski B, Huzarski T et al (2004) CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet 75:1131–1155
118. Evans DG, Birch JM, Narod SA (2008) Is CHEK2 a cause of the Li-Fraumeni syndrome? J Med Genet 45:63–64
119. Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG (2008) CHEK2∗1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol 26:542–548
120. Gronwald J, Cybulski C, Piesiak W et al (2009) Cancer risks in first-degree relatives of CHEK2 mutation carriers: effects of mutation type and cancer site in proband. Br J Cancer 100:1508–1512
121. Narod SA (2010) Testing for CHEK2 in the cancer genetics clinic: ready for prime time? Clin Genet 78:1–7
122. Robson M (2010) CHEK2, breast cancer, and the understanding of clinical utility. Clin Genet 78:8–10
123. Manoukian S, Peissel B, Frigerio S et al (2011) Two new CHEK2 germ-line variants detected in breast cancer/sarcoma families negative for BRCA1, BRCA2, and TP53 gene mutations. Breast Cancer Res Treat 130:207–215
124. Vahteristo P, Bartkova J, Eerola H et al (2002) A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. Am J Hum Genet 71:432–438
125. CHEK2 Breast Cancer Case-Control Consortium (2004) CHEK2∗1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 74:1175–1182
126. Kriege M, Hollestelle A, Jager A et al (2014) Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy. Br J Cancer 111:1004–1013
127. Nagel JH, Peeters JK, Smid M et al (2012) Gene expression profiling assigns CHEK2 1100delC breast cancers to the luminal intrinsic subtypes. Breast Cancer Res Treat 132:439–448
128. Górski B, Cybulski C, Huzarski T et al (2005) Breast cancer predisposing alleles in Poland. Breast Cancer Res Treat 92:19–24
129. Cybulski C, Wokołorczyk D, Huzarski T et al (2007) A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland. Breast Cancer Res Treat 102:119–122
130. Bogdanova N, Enssen-Dubrowinskaja N, Feshchenko S et al (2005) Association of two mutations in the CHEK2 gene with breast cancer. Int J Cancer 116:263–266
131. Shen MH, Harper PS, Upadhyaya M (1996) Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet 33:2–17
132. Shiloh Y, Ziv Y (2013) The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat Rev Mol Cell Biol 14:197–210
133. Goldgar DE, Healey S, Dowty JG et al (2011) Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res13:R73
134. Assenmacher N, Hopfner KP (2004) MRE11/RAD50/NBS1: complex activities. Chromosoma 113:157–166

135. Heikkinen K, Rapakko K, Karppinen SM (2006) RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. Carcinogenesis 27:1593–1599
136. Antoniou AC, Sinilnikova OM, Simard J et al; Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers Study (GEMO); Epidemiological Study of BRCA1 and BRCA2 Mutation Carriers (EMBRACE); German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC); Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab); Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) (2007) RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet 81:1186–1200
137. Bartkova J, Tommiska J, Oplustilova L et al (2008) Aberrations of the MRE11-RAD50-NBS1 DNA damage sensor complex in human breast cancer: MRE11 as a candidate familial cancer-predisposing gene. Mol Oncol 2:296–316
138. Cybulski C, Carrot-Zhang J, Kluźniak W et al (2015) Germline RECQL mutations are associated with breast cancer susceptibility. Nat Genet 47:643–646
139. Kiiski JI, Pelttari LM, Khan S et al (2014) Exome sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer. Proc Natl Acad Sci USA 111:15172–15177
140. Litim N, Labrie Y, Desjardins S et al; INHERIT BRCAs (2013) Polymorphic variations in the FANCA gene in high-risk non-BRCA1/2 breast cancer individuals from the French Canadian population. Mol Oncol 7:85–100
141. Peterlongo P, Catucci I, Colombo M et al; GENESIS; kConFab; SWE-BRCA (2015) FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor. Hum Mol Genet 24:5345–5355
142. Michailidou K, Lindström S, Dennis J, et al; NBCS Collaborators; ABCTB Investigators; ConFab/AOCS Investigators (2017) Association analysis identifies 65 new breast cancer risk loci. Nature 551:92–94
143. National Collaborating Centre for Cancer (UK) (2013). Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (NICE Clinical Guidelines, No. 164). http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0068971/. Accessed 30 Jun 2020
144. Llort G, Chirivella I, Morales R et al (2015) SEOM clinical guidelines in Hereditary Breast and ovarian cancer. Clin Transl Oncol 17:956–961
145. Marth C, Hubalek M, Petru E (2015) AGO Austria recommendations for genetic testing of patients with ovarian cancer. Wien Klin Wochenschr 127:652–654
146. Varesco L, Viassolo V, Viel A et al (2013) Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting BRCA mutation carrier probabilities: a retrospective study in a sample of Italian cancer genetics clinics. Breast 22:1130–1135
147. FONCAM. Linee guida carcinoma eredo-familiare: Donne ad alto rischio per carcinoma mammario familiare: sorveglianza e trattamento. http://www.senologia.it/images/pdf/carcinoma%20eredo-familiare.pdf. Accessed 30 Jun 2020
148. American Society of Clinical Oncology (1966) Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility. J Clin Oncol 14:1730–1736
149. Daly MB, Pilarski R, Axilbund JE et al (2016) Genetic/familial high-risk assessment: breast and ovarian, version 2.2015. J Natl Compr Cancer Netw 14:153–162
150. Robson ME, Bradbury AR, Arun B et al (2015) American society of clinical oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660–3667
151. Plon SE, Eccles DM, Easton D et al; IARC Unclassified Genetic Variants Working Group (2008) Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 29:1282–1291
152. Tavtigian SV, Greenblatt MS, Goldgar DE, Boffetta P; IARC Unclassified Genetic Variants Working Group (2008) Assessing pathogenicity: overview of results from the IARC Unclassified Genetic Variants Working Group. Hum Mutat 29:1261–1264
153. ENIGMA Consortium. Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA). http://enigmaconsortium.org/. Accessed 30 Jun 2020
154. Spurdle AB, Healey S, Devereau A et al (2012) ENIGMA—evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Hum Mutat 33:2–7
155. BRCA Challenge. The Human Variome Project. http://www.humanvariomeproject.org/brca-challenge.html. Accessed 30 Jun 2020
156. U.S. Preventive Services Task Force (2015) Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: recommendation statement. Am Fam Physician 91
157. Walsh T, Casadei S, Coats KH et al (2006) Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 295:1379–1388
158. Kurian AW, Hare EE, Mills MA et al (2014) Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol 32:2001–2009

159. Desmond A, Kurian AW, Gabree M et al (2015) Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol 1:943–951
160. Rainville IR, Rana HQ (2014) Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. Curr Oncol Rep 16:371
161. Walsh T, Lee MK, Casadei S et al (2010) Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci USA 107:12629–12633
162. Bombard Y, Bach PB, Offit K (2013) Translating genomics in cancer care. J Natl Compr Cancer Netw 11:1343–1353
163. Kurian AW, Ward KC, Hamilton AS et al (2018) Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer. JAMA Oncol 4:1066–1072
164. Hall MJ, Forman AD, Pilarski R et al (2014) Gene panel testing for inherited cancer risk. J Natl Compr Cancer Netw 12:1339–1346
165. Madorsky-Feldman D, Sklair-Levy M, Perri T et al (2016) An international survey of surveillance schemes for unaffected BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 157:319–327
166. Hartmann LC, Lindor NM (2016) The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med 374:454–468
167. King MC, Wieand S, Hale K et al; National Surgical Adjuvant Breast and Bowel Project (2001) Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286:2251–2256

MRI Protocols for Breast Cancer Screening

4

Ritse M. Mann and Suzan Vreemann

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ADC	Apparent diffusion coefficient
ASL	Arterial spin labeling
BI-RADS	Breast Imaging Reporting and Data System
CEST	Chemical exchange saturation transfer
DCE	Dynamic contrast-enhanced
DCIS	Ductal carcinoma in situ
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
Gd-DTPA	Gadopentetate dimeglumine
GE, GRE	Gradient-echo
GRASP	Golden-angle radial sparse parallel
IVIM	Intravoxel incoherent motion
MIP	Maximum intensity projection
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
SE	Spin-echo
SNR	Signal-to-noise ratio
SWI	Susceptibility-weighted imaging
TE	Echo time
TR	Repetition time
TSE	Turbo spin-echo
TWIST	Time-resolved imaging with stochastic trajectories

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4.1 Introduction

Magnetic resonance imaging (MRI) is nowadays widely known as the most effective imaging modality for the early detection of breast cancer. Contrast-enhanced breast MRI has been increasingly used since the 1980s, when an excellent breast lesion conspicuity after intravenous injection of gadopentetate dimeglumine (Gd-DTPA) was firstly shown [1]. Thanks to the acquisition of multiple series of contrast-enhanced images, the method rapidly evolved into dynamic contrast-enhanced (DCE) breast MRI [2]. Initial evaluations showed not only that DCE-MRI was capable of showing most cancers but also yielded significant additional information over mammography and ultrasound. In subsequent studies, a sensitivity of over 90% was documented for breast malignancies.

The high sensitivity led to the rapid spread of applications and indications for breast MRI. It was thought to be an excellent screening tech-

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nique as it does not use any ionizing radiation and has a very high negative predictive value. A standard protocol for DCE-MRI was adopted, consisting of at least one T1-weighted acquisition before contrast injection and several acquisitions after contrast injection. Other contrast materials than the original Gd-DTPA were also used.

Multiple prospective trials investigated the value of DCE-MRI using variations of this protocol for breast cancer screening in women at various classes of increased risk and reported a sensitivity in the range from 71% to 91% (Table 4.1).

Using the results of early studies, skeptics pointed at the so-called low specificity of breast MRI as a flaw that prevented the use of MRI in screening. Since in screening most scans are normal, a high number of false positives would lead to a very high recall rate, and this would pose an unacceptable burden on healthy women and large logistic issues to health-care systems. This led to a wide range of additional acquisitions, including not only old and new T2-weighted sequences but also diffusion-weighted imaging (DWI), and even proton spectroscopy, each of which were shown to have a potential for reducing false positives of breast MRI. Therefore, the current state-of-the-art protocols in breast MRI are multiparametric in nature. Nonetheless, the so-called low specificity of breast MRI is a complex questionable phenomenon to which the readers' inexperience and the absence of prior screening MR studies also gave critical contributions. The *mantra* on the *low breast MRI specificity* has been extensively discussed in Chap. 2.

Even though the performance of MRI screening with multiparametric protocols seems excellent, the scan time required, as well as the time needed for evaluation, and thus the associated costs are high, and this currently contributes to the limited use of breast MRI as a screening tool in high-risk women.

Current research, therefore, focuses on the development of shorter imaging protocols to reduce scan times and to cut costs. In addition, imaging biomarkers are extracted focusing on the evaluation of aggressiveness of breast cancer, in order to open a way for characterizing those cancers that are biologically active. Finally, new techniques that aim at excluding contrast agent administration from the acquisition are under development. Updates on recent developments on these topics will be discussed in this chapter.

4.2 Indications for Breast MRI Screening

The risk level of women included in various MRI screening studies is highly heterogeneous. The MRISC trial [3] included all women with a lifetime risk of 15% or greater, whereas, for example, the Canadian trials [9] only included women with *BRCA* mutations and their first-degree relatives. In 2007, the American Cancer Society published a guideline [11] on screening with supplemental MRI. They concluded that *MRI as an adjunct to mammography* was indicated for all women with a lifetime risk ≥20–25% as assessed with BRCAPRO or similar tools that mainly focus on family history. In 2008, these guidelines were also adopted by the European Society of Breast Imaging (EUSOBI), as the recommendations were mainly based on European studies [12].

Table 4.1 Sensitivities and specificities for breast MRI screening of women at elevated breast cancer risk

First author [reference #]	Year	Screened women	Number of cancers	Sensitivity (%)	Specificity (%)
Kriege [3]	2004	1,909	45	71	90
Leach [4]	2005	649	35	77	81
Kuhl [5]	2005	529	43	91	97
Rijnsburger [6]	2010	2,157	75	71	90
Trop [7]	2010	184	12	83	94
Sardanelli [8]	2011	501	52	91	97
Passaperuma [9]	2012	496	57	86	90
Riedl [10]	2015	559	40	90	89

The group of high-risk women considered by these guidelines consists of women with either a proven *BRCA1* or *BRCA2* germline mutation, other genetic syndromes associated with a high incidence of breast cancer, or a ≥20–25% lifetime risk of developing breast cancer (see Chap. 3). Women with history of chest radiation therapy between the ages of 10 and 30 also have a similar risk and should be screened with supplemental MRI (see Chap. 14).

For women at intermediate risk (defined as 15–20% lifetime risk or a personal history of invasive or in situ carcinoma, lobular neoplasia, or atypical hyperplasia), the use of breast MRI for screening is still under investigation, and there has been no clear statement yet. It is agreed that breast MRI screening should not be currently used in women with a lifetime risk lower than 15% [13]. However, screening trials with MRI for women at average risk, but with very dense breast, are on their way, thus introducing risk factors for stratification that were not used in previous screening studies or risk models. *Whether or not screening guidelines should be expanded to also include these women will become evident in the coming years.*

Despite the abovementioned guidelines, national guidelines are often more conservative as they focus more on cost-effectiveness. While there is a clear increase in breast cancer detection in all risk groups, cost-effectiveness is only proven for women at the highest risk (e.g., those with a *BRCA* mutation and their first-degree relatives and those with a history of chest radiation therapy before 30), and hence several current national breast cancer screening guidelines only state that a yearly breast MRI is appropriate for women at very high risk for developing breast cancer (see Chap. 16).

4.3 Requirements for Breast MRI

The EUSOBI [12], the European Society of Breast Cancer Specialists (EUSOMA) [14], and the American College of Radiology [15] have specified requirements for the performance of breast MRI. *So far, these requirements are general and not specifically focused on breast MRI for screening.* In the light of the current diversion between MRI for screening and MRI for staging or other indications, these guidelines will likely be adapted in the near future to be more specific for the indication for which breast MRI is performed. However, *the minimal requirements as specified by these organizations remain vital as they are very liberal*. All breast MRI protocols should include T1-weighted pre- and post-contrast sequences to report on lesion morphology and enhancement features with sufficient spatial and temporal resolution. All other sequences are deemed supplemental; however, the use of additional T2-weighted acquisitions is generally endorsed.

Minimal requirements are as follows [12, 14]:

- *Field Strength*
  A 1.5-T magnet is considered a minimum technical requirement because of the relationship between field strength and resolution (the advantages and disadvantages of 3.0-T imaging will be discussed later in this chapter).
- *Spatial Resolution*
  Sufficiently high spatial and temporal resolutions are needed to detect and characterize small abnormalities. The EUSOBI guidelines state that the slice thickness should not be higher than 2.5 mm and the in-plane resolution should be 1 mm^2 or less, thus minimizing the problem of volume averaging effects. Other guidelines still accept up to a 3 mm slice thickness.
- *Scan Plane*
  No absolute preference for scan plane is recommended by guidelines. While in past times some technical issue favored the use of coronal planes with the aim of optimizing both temporal and spatial resolution, currently axial and sagittal planes are preferred, also for the evaluation of symmetry.
- *Fat Saturation and Temporal Subtraction*
  Spectral fat saturation can be used to reduce the fat signal while preserving the signal-to-noise ratio (SNR); however, it is not mandatory. The guidelines state that radiologists

must not solely rely on temporal subtraction images for the assessment of enhancement, since this may result in misregistration due to patient motion. When motion artifacts do appear, motion correction might be helpful in reducing artifacts encountered with image registration.

- *Radio Frequency Coils and Simultaneous Bilateral Imaging*
  Guidelines state that simultaneous bilateral high-resolution images should be acquired as breasts are symmetric organs and comparison between the two breasts can be performed. The use of a multichannel-dedicated bilateral breast coil is mandatory [5, 7, 16, 17]. These are commercially available and provide excellent spatial and temporal resolution for improved visualization of small lesions [18].
- *Contrast Agent*
  Breast MRI without contrast is not acceptable according to current standards, except for the evaluation of breast implants integrity. Therefore, all screening examinations should be contrast-enhanced studies. As a contrast agent, a two-compartment (vascular/interstitial) gadolinium chelate should be administered intravenously as a bolus with the standard dose of 0.1 mmol/kg with an injection rate of 2–3 ml/s, followed by saline flushing (20–30 ml at 2 ml/s), preferably using an automatic injector. Specific information on paramagnetic contrast agents available for breast MRI can be found in Chap. 5.
- *Temporal Resolution*
  The time interval between images series for dynamic contrast-enhanced (DCE) studies should be no longer than 120 s [14].
- *Volume of MRI Studies per Institution*
  The EUSOMA [14] recommends that a minimum number of 150 cases need to be performed per institution per year. Despite the lack of recommendations from the other societies, this seems a wise recommendation, especially when considering the screening setting. Even in very high-risk screening, the cancer detection rate is only in the order of 2–3%, and hence at a rate of 150 screening examinations, only three cancers are detected per year. Therefore, some degree of centralization and significantly larger volumes are recommended.

4.4 MRI Sequences

4.4.1 T1-Weighted Sequences

To understand the basics of sequences used for screening, some knowledge of MRI physics is desirable.

One of the most common MRI pulse sequences is the T1-weighted sequence, also referred to as the spin-lattice relaxation sequence. The images obtained from this sequence display the differences in T1 relaxation times among different tissues. This sequence relies upon the longitudinal relaxation of the tissue's net magnetization vector (T1 relaxation describes the spin relaxation in the *z*-direction). T1-weighting is achieved with short echo times and repetition times. As fat quickly realigns its longitudinal magnetization with B_0 (the main magnetic field), it appears bright on a T1-weighted image. Conversely, water has a much slower longitudinal magnetization realignment after a radio frequency pulse and, therefore, has less transverse magnetization. Thus, water has a low signal and appears dark on T1-weighted images. Figure 4.1 shows examples of the different images obtained using a T1-weighted sequence either with or without fat suppression. Gadolinium-based contrast agents have a paramagnetic effect on the tissue and hence reduce the T1 relaxation time (i.e., the time needed for longitudinal relaxation). This increases the signal of the tissue, and hence, a high signal (that appears bright on the image) is produced in areas of contrast agent uptake [19].

In breast MRI screening protocols, T1-weighted sequences are thus used for detection of areas where the contrast agent accumulates, such as malignant breast lesions [12, 15]. Several T1-weighted sequences are obtained in dynamic succession to visualize the course of tissue contrast enhancement.

In the early years of breast MRI, it was necessary to choose between temporal and spatial

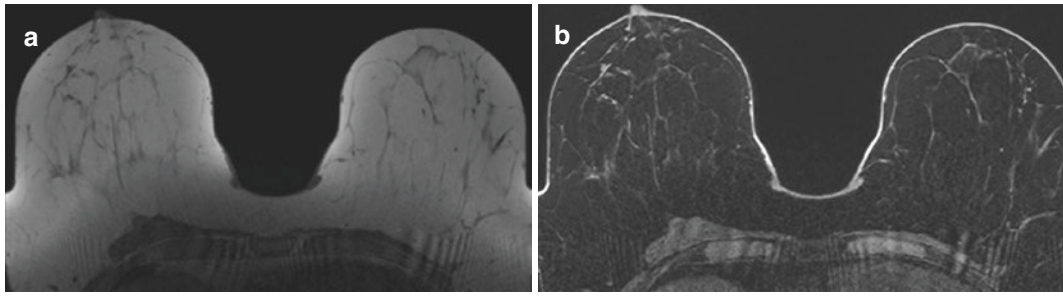

Fig. 4.1 Axial T1-weighted images in a 42-year-old *BRCA2* mutation carrier with relatively fatty breasts, using a sequence without fat suppression (**a**) or with fat suppression (**b**)

resolution. Two fundamentally different protocol designs evolved, the static design and the dynamic design. The *static design* was most popular in the United States and specifically evaluated the morphological features of enhancing lesions at high spatial resolution. The *dynamic design* was instead mostly favored in European countries with the aim of using dynamic enhancement characteristics to distinguish benign lesions from malignant lesions [20]. Nowadays, thanks to the technical progress that has been made, it is possible, to a certain extent, to integrate these two demands, and the final evaluation is virtually always based upon a combination of morphological and dynamic enhancement features [20].

The BI-RADS MRI lexicon [21] states the different enhancement patterns that have to be rated based on T1-weighted sequences. All findings should be viewed on both pre- and post-contrast scans, and both morphologic and kinetic characteristics should be evaluated. Malignant lesions tend to enhance rapidly, typically reaching 90% of peak enhancement within 60 s following injection, while fibroadenomas and other benign lesions tend to enhance at a lower rate. Strong early enhancement with a relative signal increase of over 140% and a peak of enhancement before 3 min together with an early washout (signal decrease of more than 10% following maximum enhancement) [16] is highly suggestive of malignancy.

Different T1-weighted sequences exist, as shown in Table 4.2. Spin-echo sequences are generally not recommended as these are too slow to achieve the spatial and temporal resolution required for breast MRI screening. The EUSOBI recommends at least a T1-weighted spoiled gradient-echo pulse sequence before the administration of contrast agent, one at peak enhancement approximately 90 s after contrast agent administration and one 5–7 min after contrast administration in order to investigate the morphology and the dynamics of enhancement. Most protocols that are currently in use include one pre-contrast T1 sequence and three to five post-contrast T1 sequences for the dynamic evaluation [12, 23–27].

In order to obtain a more reliable T1-weighting, gradient-echo (GE) sequences used for DCE breast imaging use the so-called *spoiler* (typically a radio frequency spoiler) that disrupts transverse coherences that may persist from cycle to cycle of the sequence. Thus, immediately before each radio frequency pulse, the steady-state magnetization has no transverse components, while the longitudinal magnetization reaches a steady state [28].

However, spoiled gradient-echo sequences exist in both two-dimensional (2D) and three-dimensional (3D) acquisition modes. It is still unknown which of the two is the best or most appropriate one for breast MRI, in particular for screening. Both methods have their own advantages and disadvantages. When comparing 2D to 3D sequences, 3D sequences are known for their higher T1-contrast and higher SNR, resulting from shorter repetition times and echo times. The higher SNR can be used to improve the spatial resolution, both in-plane (pixel size) and through-plane (partition thickness). However, 3D imaging

Table 4.2 T1-weighted sequences

Sequence	Characteristics
Spin-echo (SE)	• T1-weighting is maximized by setting repetition time (TR) to be similar to or slightly shorter than the T1 values of the tissue of interest while setting echo time (TE) as short as possible • It takes time to rephase the signal, thus increasing the scan time
Turbo spin-echo (TSE)	• Because of the long scan time of SE sequences, TSE meets the demand for faster imaging. Multiple echoes are formed and measured by adding several 180° pulses and measuring a spin-echo after each pulse rather than measuring a single echo after each 90°–180° combination
Fast advanced spin-echo (FASE)	• Half-Fourier imaging is used, which shortens scan time even more than TSE
Gradient-echo (GE, GRE)	• Similar to spin-echo sequences with two main differences: – Use of an initial 10–270° pulse rather than a 90° pulse – Use of a gradient reversal instead of a 180° pulse to form an echo, thus eliminating the need to wait to allow a regrowth of the longitudinal magnetization • T1-weighting is achieved by using a short TR, very short TE, and a moderate flip angle [22] • Due to a higher T1 contrast and shorter acquisition times, these sequences are generally preferred over spin-echo sequences and are therefore recommended by guidelines [12, 14]

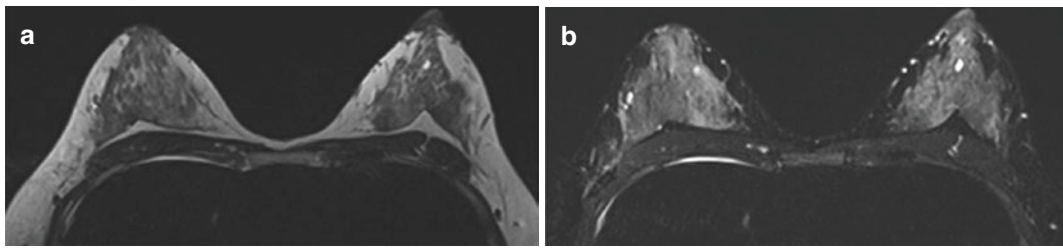

Fig. 4.2 Axial T2-weighted images in a 38-year-old woman at familial risk of breast cancer with dense breasts, using a sequence without fat suppression (**a**) or with fat suppression (**b**)

may suffer from image degradation (pulsation, susceptibility, and ghosting artifacts), and therefore, some authors prefer 2D imaging [28].

4.4.2 T2-Weighted Sequences

Most of the current breast MRI screening protocols include a T2-weighted sequence (examples are presented in Fig. 4.2). In the EUSOBI guidelines for breast MRI, it is stated that this sequence can be useful in the differentiation between benign and malignant lesions (and thus increasing specificity and positive predictive value), as in most cases cancer does not yield a high signal on turbo spin-echo T2-weighted images without fat suppression, whereas many benign lesions do. However, as most of these lesions can also be identified in T1-weighted images, the EUSOBI guidelines state that there is no clear evidence of the added value of T2-weighted sequences in screening yet [12].

In 1999, Christiane Kuhl and coworkers were the first investigators to evaluate the added value of T2-weighted imaging for breast MRI [29]. They investigated whether T2-weighted pulse sequences can help in the differential diagnosis of enhancing lesions on dynamic breast MRI. Fibroadenomas and well-circumscribed breast cancers may have a similar appearance, as both may present as a rapidly and strongly enhancing focal lesion. Fibroadenomas and breast cancers tend to demonstrate different signal intensities on T2-weighted imaging. In practice, if a well-circumscribed enhancing lesion is detected in breast MRI, high signal intensity in

the corresponding T2-weighted image can be used to support the diagnosis of a benign lesion. In the higher age groups (over 40), a low T2-weighted signal should arouse suspicion for malignancy, even though the lesion is well circumscribed. The authors concluded that T2-weighted turbo spin-echo sequences can be helpful as an adjunct to the dynamic breast MRI protocol, and it should not be used as a standalone approach but in conjunction with and secondary to criteria-like enhancement kinetics and morphological data. Laura Heacock and coworkers [26] came to similar conclusions. In their study, the addition of a T2-weighted sequence to the dynamic protocol resulted in a higher lesion conspicuity but had no effect on cancer detection. Unfortunately, the effect of the T2-weighted images on specificity was not evaluated.

The use of spectral fat saturation as added to T2-weighted sequences was specifically evaluated in the abovementioned work by Kuhl and coworkers [29]. They stated that the TSE pulse sequence without fat suppression is the only suitable sequence to assist in lesion characterization. If used cautiously, T2-weighted imaging should improve the diagnostic accuracy of diagnostic breast MRI by helping to avoid false-positive diagnoses, particularly in young women. Therefore, a T2-weighted turbo (also called fast) spin-echo sequence can be performed as a start of a breast MRI screening, before the dynamic protocol. In combination with fat saturation, this sequence can also be used to identify cysts, as cysts have extremely long T1 and T2 values relative to other breast tissues. Cysts typically have a few macromolecules to shorten T1 and lack of cellular structure to shorten T2. Thus, cysts appear darker on T1-weighted sequences while they appear much brighter than other tissues on T2-weighted sequences due to their longer T2 values and higher hydrogen densities. Hence, cysts are easily identifiable on fat-suppressed T2-weighted imaging [22]. However, the necessity to detect cysts in a screening protocol remains questionable, and this alone should not be used as an argument to perform a T2-weighted acquisition.

4.4.3 Diffusion-Weighted Imaging (DWI) and Other Additional Sequences

Diffusion-weighted imaging is sensitive to the mobility of water molecules in tissue. Water motion is most commonly quantified by means of an apparent diffusion coefficient (ADC), a model using the principle that tissue-confined water behaves similarly to free water, but with reduced diffusivity (Fig. 4.3). This is used as a marker of cellularity in oncologic imaging as it represents a decrease in extracellular space relative to the more viscous intracellular fluid of proliferating cells. Measurement of diffusivity does not require administration of contrast agents. Thus, DWI might be a suitable technique for non-contrast breast MRI, as we will discuss below.

Notably, the signal obtained by DWI sequences is based on a T2-weighted acquisition. Diffusivity is measured by applying a strong spoiler gradient to excited hydrogen protons. After a certain period of time, this spoiler gradient is reversed. Strength and duration of the spoiler gradient together determine the so-called *b-value*: the higher the b-value, the stronger the signal positive correlation with tissue diffusivity. In fact, protons that do not move regain their signal, whereas moving protons experience a different gradient at both instances and hence lose their signal [30]. Some studies [31, 32] focused on the choice of b-values for DWI of the breast. A b-value near to 0 s/mm^2 (or 50 s/mm^2) to reduce signal from vessels and a b-value around 800–850 s/mm^2 are sufficient for clinical imaging. However, for more elaborate DWI techniques such as diffusion tensor imaging (DTI) or intravoxel incoherent motion (IVIM) imaging, multiple and higher b-values are required.

Studies have shown the potential of DWI to increase breast MRI specificity. As discussed by Gurpreet S. Dhillon and coworkers [18], DWI has a higher specificity to differentiate benign from malignant lesions than CE-MRI. However, to not lose in terms of sensitivity, a feasible way to implement DWI in a multiparametric protocol appears to adapt BI-RADS scores based on ADC

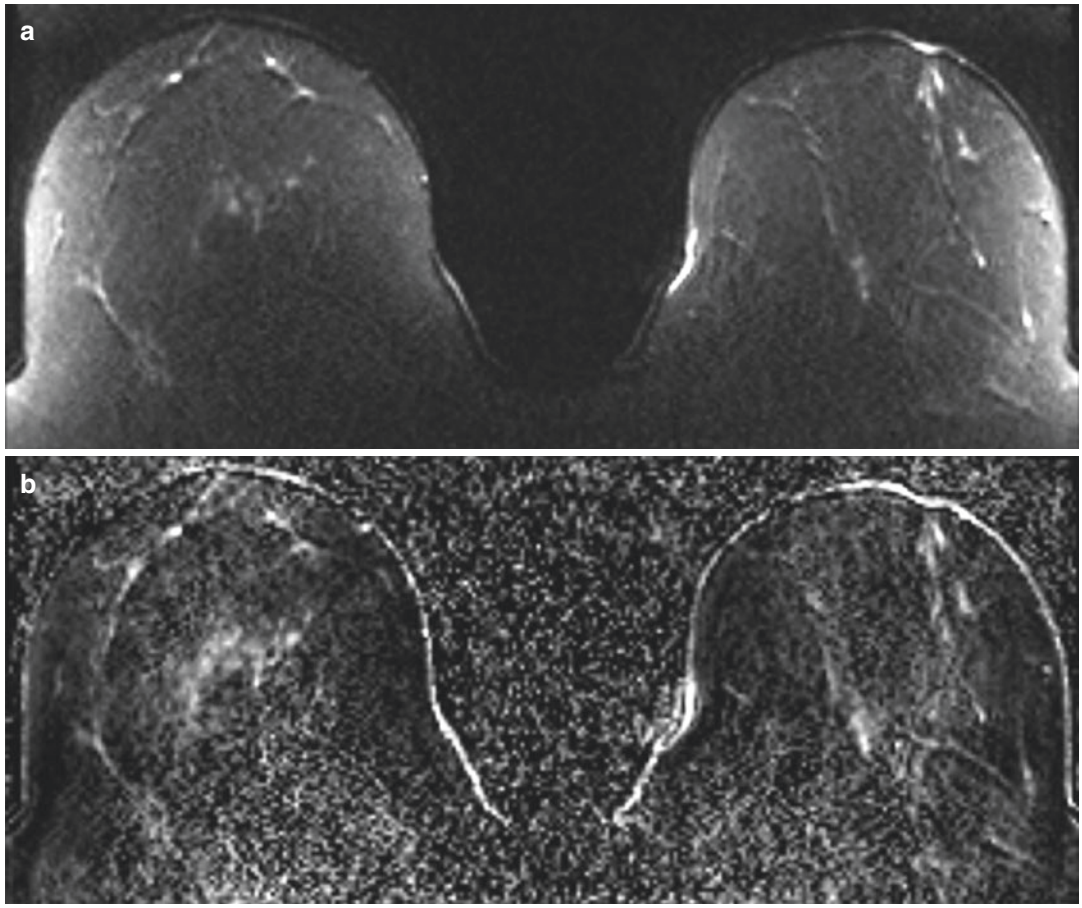

Fig. 4.3 Axial diffusion-weighed images in a 42-year-old *BRCA2* mutation carrier using DWI (b = 850 s/mm^2) (**a**) and the corresponding ADC map (**b**)

values as proposed by Katja Pinker and coworkers [33]. Differences in ADC values may be able to distinguish ductal carcinoma in situ (DCIS) from both normal tissue and invasive ductal carcinoma. The ADC value is lowered in DCIS compared to normal breast parenchyma but is still significantly higher than the ADC values seen in invasive ductal carcinoma. However, this intermediate ADC value is not specific to DCIS and might overlap with other benign and malignant lesions [34].

Several studies investigate the added value of DWI when DCE-MRI is available. Sibel Kul and coworkers [35] applied this strategy to 84 breast lesions, showing that the combination of DWI and DCE-MRI had the potential to increase the specificity of breast MRI, a result confirmed by Richa Bansal and coworkers [36] in a larger study including 232 lesions.

Other sequences have been proposed to further improve the specificity, including *dynamic susceptibility contrast* (DSC) *imaging*, which is a kind of perfusion imaging based on the T2* effect of contrast agent (contrast uptake reduces the T2* value, thus resulting in a lowered signal), and susceptibility-weighted imaging (SWI), which is based on the tissue inhomogeneities and calcifications (again resulting in a lowered signal on T2*-weighted images) [37, 38], as well as various types of mainly ^{1}H-based magnetic resonance spectroscopy (MRS) approaches [39–41]. Although each of the techniques has some merits, none of these approaches really made it into clinical practice. Especially for screening purposes,

they are currently obsolete. Faster approaches and techniques to increase the signal might, however, in the future render these techniques viable again.

A recent comparison between the evidence in favor of DWI and that in favor of spectroscopy found that DWI is certainly the winner [42]. As mentioned above, DWI, considering both the robustness and short acquisition times, entered breast MRI clinical protocols as the most used additional sequence.

4.5 Breast MRI at 3.0 T: Advantages and Disadvantages

As 3.0-T systems become more widely available throughout the world, many facilities may consider performing breast MRI, including screening protocols, at this higher field. In fact, it is widely known that a higher field strength results in a higher SNR. The improved SNR should, in theory, allow for a better visualization and characterization of enhancing lesions, which may improve the detection of breast cancers [15]. However, this higher field strength also causes an increased field inhomogeneity, which is a clear disadvantage. In the case of 3.0-T imaging, several artifacts can be categorized according to their main underlying mechanism, such as increased SNR, susceptibility variation, chemical shift, or decreased radio frequency wavelength [43, 44].

Increased SNR can result in more pronounced *Gibbs ringing artifacts* at 3.0 T compared to 1.5 T. These artifacts occur when Fourier transforms are used to reconstruct MRI signals into images. Any signal (and thus every image) can be represented as an infinite summation of sine waves of different amplitudes, phases, and frequencies. In MRI, we sample a finite number of frequencies, and we approximate the image by using relatively few sine waves in its Fourier representation. In other words, the Fourier series is cut short. Gibbs ringing artifacts are prominent at high-contrast interfaces, manifested by variable undershoot and overshoot oscillations. These artifacts can have a variety of forms, including false widening of edges, enhancement of the edges, or distortion of tissues.

Ghosting artifacts are associated with *parallel imaging* (commonly used in MRI with the aim to decrease acquisition times at both 1.5 and 3.0 T) and are usually more severe at 3.0 T. In fact, the increased SNR at 3.0 T, especially in combination with a high channel count (eight or more coils, which is currently standard of care in most clinical practices) used for parallel imaging, can worsen the problem.

Chemical shift artifacts are more often present at 3.0 T. At a fixed receiver bandwidth, the fat-water chemical shift will be twice as many pixels compared to 1.5 T.

Susceptibility variations due to the presence of implanted foreign bodies can also cause local nonuniformity of the main magnetic field resulting in several artifacts, including nonplanar 2D slices, in-plane image distortion, and local regions of hypointensity and hyperintensity. These artifacts are also stronger at 3.0 T. Sequences with long echo trains suffer the most from susceptibility variations. To decrease these artifacts, parallel imaging could be used, taking the comments on the abovementioned ghosting artifacts into account.

Because 3.0-T imaging is already well introduced in clinical imaging, most of these artifacts can be overcome by several already available methods [43]. *Clinical 3.0 T images are adequate in general, even though it remains uncertain whether these are better than 1.5 T images*.

There are only few comparisons between breast imaging at 1.5 and 3.0 T. Christiane Kuhl and coworkers [45] described intraindividual results in 37 women with 53 lesions. At 3.0 T, the image quality was slightly but significantly better, and the diagnostic confidence as measured at receiver operating characteristics analysis was significantly higher. No susceptibility effects were observed. Motion artifacts were observed at 3.0 and 1.5 T at the same rate and degree. The smaller pixel size in patients who were examined at 3.0 T with high in-plane imaging matrices could result in subtraction artifacts due to motion and, therefore, degraded the image quality. Nevertheless, the higher spatial resolution at

3.0 T helped to improve classification of 11 of 51 lesions (two were excluded because of insufficient enhancement).

Ana P. Lourenco and coworkers [17] reported on a comparison of 495 3.0 T versus 650 1.5 T breast MRI screening scans. They found a significant increase in both biopsy recommendation rate and the positive predictive value of biopsy at 3.0 T. Notably, cancer detection rate was significantly higher at 3.0 T (2.6%), compared with 1.5 T (0.9%). These results, even limited by the retrospective interindividual design, showed a potential for a greater efficacy of breast MRI screening at 3.0 T.

Thus, despite existing disadvantages from scanning at a higher field strength, 3.0 T breast MRI still seems to improve the diagnostic confidence and the cancer detection rate in a screening population. However, 1.5 T breast MRI remains adequate in most settings when updated protocols and breast coils are used.

4.6 Screening Sequence Protocols

Examples of breast MRI screening sequence protocols used at 1.0, 1.5, and 3.0 T are reported in Table 4.3. However, we should consider that a large variety of technical options were used, although all of them were mainly based on a 2D or 3D spoiled gradient-echo dynamic series.

Table 4.3 Examples of screening protocols

First author [ref. #]	Breast MRI protocol	Sequence parameters
Sardanelli [8][a]	1.0 or 1.5 T	
	1. 3D T1-weighted spoiled gradient-echo (1 pre-contrast and 5 post-contrast)	1. Transverse or coronal plane; TR 13 ms; flip angle 20°–30°; partition thickness, ≤3 mm; number of partitions 40–128; acquisition time up to 120 s; pixel size up to 1.4 × 1.4 mm
Kuhl [46]	1.5 T	
	1. 2D or 3D T1-weighted spoiled gradient-echo series (1 pre- and ≥4 post-contrast) 2. T2-weighted sequence	1. Spatial resolution ≤1 × 1 mm (in-plane), ≤3 mm (through-plane); acquisition time 120 s 2. Spatial resolution ≤1 × 1 mm (in-plane), ≤3 mm (through-plane) Total acquisition time 15 min
Emaus [47]	3.0 T	
	1. T2-weighted sequence (optional)	1. Acquisition VS ≤1.11 × ≤1.46 × ≤4.00 mm Reconstruction VS: ≤0.90 × ≤0.90 × ≤4.00 mm Acquisition time 147–248 s
	2. DWI sequence	2. Acquisition VS ≤2.25 × ≤2.51 × ≤5.00 mm Reconstruction VS: ≤1.55 × ≤1.70 × ≤4.00 mm Acquisition time 215–301 s b-values 0, 50 or 150, and 800 s/mm^2
	3. DCE data sets 3.1. High spatial resolution pre-contrast 3.2. High-temporal-resolution series before and during the first 90 s after contrast injection 3.3. High-spatial-resolution series post-contrast	3.1. Acquisition VS ≤1.00 × ≤1.00 × ≤2.00 mm Reconstruction VS ≤1.00 × ≤0.94 × 1.00 mm Acquisition time 80–152 s 3.2. Acquisition VS ≤2.58 × ≤2.82 × ≤6.00 mm Reconstruction VS ≤1.18 × ≤1.18 × ≤3.00 mm Pre-contrast acquisitions (n = 1) Post-contrast acquisitions (n = 15–19) 3.3. Acquisition VS ≤0.90 × ≤1.00 × ≤1.80 mm Reconstruction VS ≤1.00 × ≤0.80 × ≤1.00 mm Acquisitions (n = 5 or 6)

VS voxel size

[a]Although not considered in the final report [8] (the BI-RADS classification was mainly based on DCE imaging), a T2-weighted sequence was also included in the protocol

4.7 Abbreviated Screening Protocols

While breast MRI screening as currently implemented has shown great potential for early detection of cancer in women at increased risk of breast cancer, its wide implementation remains difficult. This is largely caused by the high costs of MRI itself. In addition, the huge amount of image series produced lengthens the reading time and makes actual mass screening very difficult.

Therefore, several research groups focused on reducing the time required for scanning and evaluating breast MRI. Evidence is mounting that shorter protocols in fact are just as good for screening as the much lengthier multiparametric protocols that are currently in use. This could potentially increase the access to breast MRI by significantly reducing the cost and time associated with the examination, both the acquisition time, and the radiologist's reading time.

Several abbreviated protocols were described by different groups of authors [23–26] (Table 4.4).

In 2014, Christiane Kuhl and coworkers [23] presented the first and simplest version of *abbreviated breast MRI.* The protocol is condensed into one pre-contrast and one post-contrast acquisition. The subsequent generation of subtraction images and maximum intensity projections (MIPs) also renders reading exceptionally fast. Reading time of the MIPs was reported to be below 2 s. In their study, it was evaluated whether this abbreviated protocol would be sufficient to identify breast cancer in a screening cohort. The full diagnostic protocol included a T1-weighted pre-contrast and five post-contrast scans followed by a T2-weighted sequence and a coronal T1-weighted sequence. While the full protocol needed about 17 min, the abbreviated protocol needed only 184 s. The overall sensitivity of the abbreviated protocol was 100.0% (negative predictive value 99.8%) with a specificity of 94.3%. However, only 11 cancers were detected overall. With the use of the full diagnostic protocol, the characterization of findings classified as possibly benign (BI-RADS 3) was improved, showing that the additional pulse sequences in the full protocol are mainly needed for lesion characterization.

In 2015, Victoria L. Mango and coworkers [24] looked into the sensitivities per sequence of the abbreviated protocol. They found a mean sensitivity of cancer detection of the first post-contrast sequence of 96%, equal to the first post-contrast subtracted sequence. Sensitivity using only the MIPs was significantly inferior (93%), which must be taken into account when deciding to screen using only MIPs.

In the same year, Lars J. Grimm and coworkers [25] tested two different abbreviated protocols in a specifically designed case series of 48 patients selected from high-risk screening. One protocol consisted of a T2-weighted sequence, as well as the pre-contrast and the first post-contrast T1-weighted sequences. In the other protocol, the second post-contrast T1-weighted sequence was added to the sequences of the first protocol. They found no significant differences in sensitivity and specificity between each of the two abbreviated protocols (86% and 89%, respectively) and the full protocol (95%).

Table 4.4 Abbreviated and full breast MRI protocols

First author [reference #]	Protocol	Dynamic pre-contrast	Dynamic first post-contrast	Dynamic second post-contrast	Dynamic third–fifth post-contrast	T1 TSE	T2	DWI
Kuhl [23]	Abbreviated	Yes	Yes					
	Full	Yes	Yes	Yes	Yes	Yes	Yes	
Mango [24]	Abbreviated	Yes	Yes					
	Full	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grimm [25]	Abbreviated1	Yes	Yes				Yes	
	Abbreviated2	Yes	Yes	Yes			Yes	
	Full	Yes	Yes	Yes	Yes	Yes	Yes	
Heacock [26]	Abbreviated	Yes	Yes				Yes	
	Full	Yes	Yes	Yes	Yes		Yes	Yes

However, the case series was relatively statistically underpowered while the enriched series (especially the proportion of malignant lesions, much higher than seen in screening practice) could have influenced the reader performance, likely explaining the remarkable low specificity, ranging from 45% to 52%.

In 2016, Laura Heacock and coworkers [26] retrospectively evaluated the utility of an abbreviated T1-weighted imaging protocol in detecting 107 known breast cancers (88% invasive and 12% in situ) as well as to analyze the impact of adding clinical history and prior imaging to cancer detection and determine the impact of T2-weighted imaging in cancer detection and lesion conspicuity. The abbreviated protocol, consisting of a T2-weighted fat-suppressed sequence and a pre- and post-contrast T1-weighted sequence, reached a sensitivity of 97.8–99.4%, comparable to previously mentioned studies [23–25]. In addition, in the Heacock's study [26], information about prior imaging and clinical history increased detection rates. T2-weighted imaging increased confidence and lesion conspicuity; however, it did not increase detection rates. Initial enhancement rate was significantly correlated to tumor grade, invasive disease, and lesion conspicuity, supporting the idea that rapid wash-in characteristics of malignancy may underpin the efficacy of abbreviated MRI sequences. This finding raises *the possibility that cancers detected by an abbreviated MRI examination only may be of higher grade,* i.e.*, more biologically active lesions, potentially counteracting the drawback of overdiagnosis intrinsically associated to every screening program*.

From the studies investigating abbreviated protocols, we can conclude that *there is still no clear consensus in which sequences are beneficial and needed for an abbreviated protocol*. Studies reporting on "abbreviated" protocols varied widely in acquisition times ranging from approximately 3–15 min. In particular, the role of a T2-weighted sequence for screening purposes needs to be investigated. In addition, *the number of patients scanned and the amount of cancers detected are currently still too low to draw solid conclusions. Future larger prospective trials need to prove the non-inferiority of abbreviated protocols.*

Nevertheless, shortened breast MRI protocols could play a relevant role in lowering costs and allowing more widespread availability of MRI as a screening tool.

4.8 Ultrafast Breast MRI

All the abbreviated protocols discussed in the previous paragraph discard dynamic information. Only one of those investigated by Grimm and coworkers [25] used the second dynamic post-contrast scan. This is not problematic for larger malignant lesions, which are generally well recognized based upon their morphological features. However, in particular for the classification of small mass lesions, which are typical findings in breast screening, additional dynamic information is important. This implies that *dynamic information is appreciated, while imaging time should not be extended*.

Conventional dynamic information cannot be obtained, as this requires acquisition of the washout phase of contrast which takes up to 6–7 min after contrast administration. However, even in the early days of breast MRI, it was already shown that dynamic information obtained from the inflow phase had better discriminating capacity than the washout phase. Nevertheless, in previous years, the temporal resolution, typically in the range of 60–75 s of high-spatial-resolution bilateral images, was not sufficient to document this inflow phase. Therefore, acquiring scans at a high temporal resolution re-enables the use of contrast dynamics for the classification of suspicious breast lesions [48].

Karl-Heinz Herrmann and coworkers [49] were among the first to describe a new ultrafast sequence named time-resolved imaging with stochastic trajectories (TWIST) for breast MRI (Fig. 4.4). With this technique, the outer part of k-space is heavily under-sampled, and data points are shared between successive time points to increase the obtained spatial resolution to diagnostic quality. Sophisticated sampling patterns are used to minimize the disadvantage of data

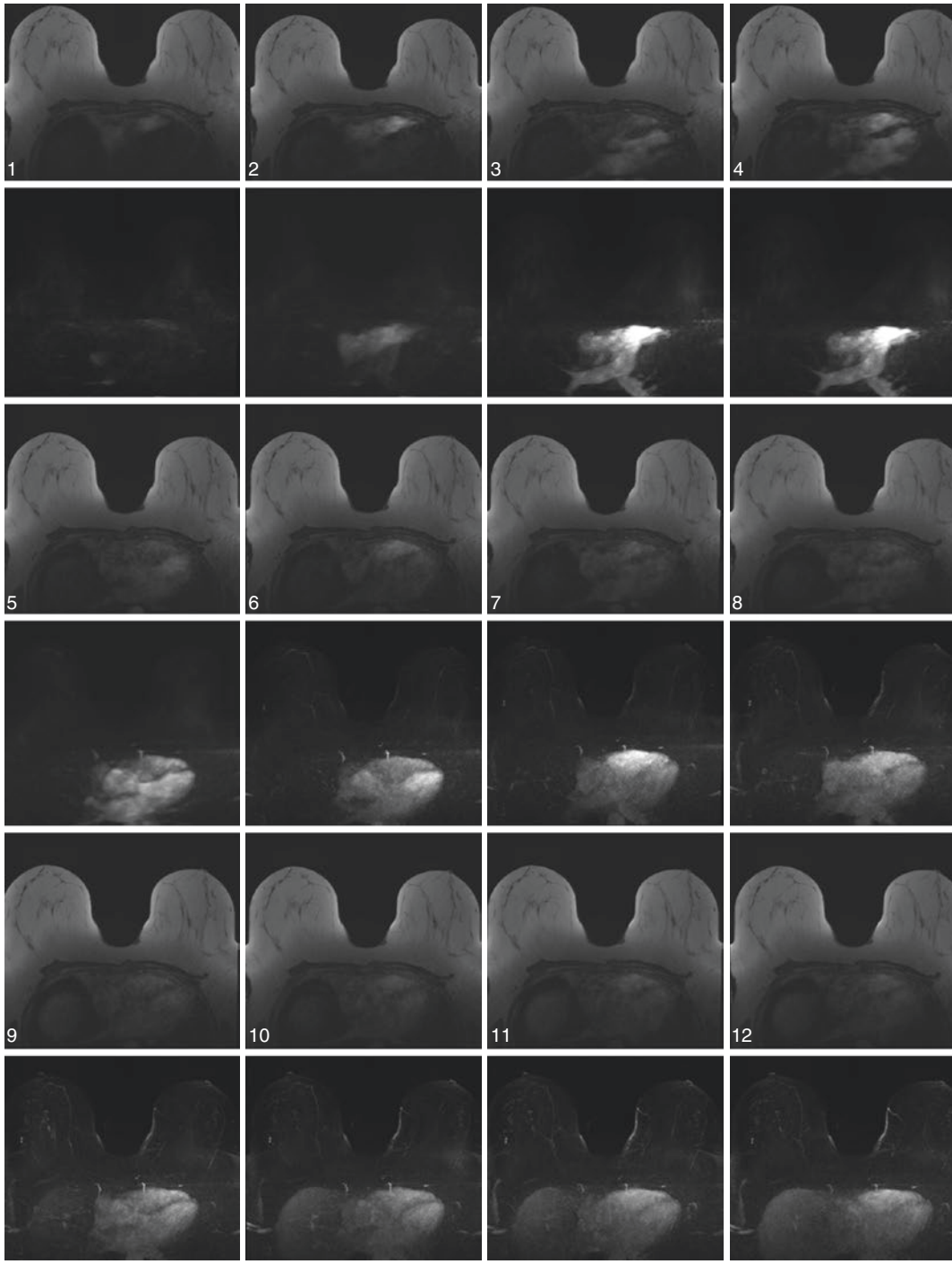

Fig. 4.4 Ultrafast axial images in a 42-year-old *BRCA2* mutation carrier, using a TWIST sequence (temporal resolution 4.57 s). The central slice of each of the first 12 acquisitions after aorta enhancement is shown, numbered from 1 to 12. The corresponding volumetric MIPs are shown at every time point, below the original central unsubtracted images. These clearly show the arrival of the contrast, first in the thoracic vessels and the heart and subsequently in the breasts and liver. No suspicious early enhancement is visible in the breasts

sharing. These authors showed, in a pilot study of 14 patients, that this TWIST sequence can be used to obtain dynamic images at a very high temporal resolution (5.7 s). Furthermore, they showed that benign lesions enhance at a later time point than malignant lesions.

Luminita A. Tudorica and coworkers [50] reduced the temporal resolution to 18 s, showing that the dynamic images were very comparable with the images provided by the conventional protocol. Yuan Le and coworkers [51] showed that a TWIST sequence can be combined with a *dual-echo (two-point) Dixon technique* to obtain fat-suppressed images with a high temporal resolution. Our group [27] investigated the use of maximum slope of the contrast enhancement versus time curve obtained from the TWIST sequence at a temporal resolution of 4.3 s as a novel dynamic parameter for the differentiation between benign and malignant lesions. The total acquisition time was 102 s. Of the 199 enhancing lesions included, 95 were proven benign and 104 malignant. We found that maximum slope achieved a much higher accuracy in differentiating benign and malignant lesions than the BI-RADS curve type does, thus solidifying the use of ultrafast breast MRI, and allowing the creation of new protocols with a short post-contrast period (~85 s). While we did not evaluate TWIST for morphological features, the technique meets every breast MRI requirement that is stated in guidelines. Results of a recently presented reader study in which four radiologists evaluated 200 screening cases showed that the use of ultrafast MRI alone was just as accurate as evaluating a full diagnostic protocol including high-spatial-resolution acquisitions, T2-weighted imaging, and DWI [52].

Federico D. Pineda and coworkers [48] investigated a bilateral, fat-suppressed ultrafast acquisitions with a time resolution of 6.9–9.9 s during the first min after contrast injection, followed by four high-spatial-resolution acquisitions with a time resolution of 60–79.5 s. They confirmed that first-minute ultrafast dynamic imaging can add valuable information, increasing the radiologists' confidence in identifying lesions in the presence of marked background parenchymal enhancement. A hybrid construction, where ultrafast acquisitions are interleaved in an abbreviated breast MRI protocol, allows the collection of dynamic data for lesion classification without a penalty in acquisition time.

Further improvements of ultrafast MRI are still increasing image quality. Radial imaging using a golden-angle approach, as is performed in the *golden-angle radial sparse parallel (GRASP)* sequence, enables dynamic imaging using continuous data acquisition and retrospective reconstruction of image series with arbitrary temporal resolution by grouping different numbers of consecutive radial lines into temporal frames. This means that, with the use of GRASP, images of every temporal resolution can be reconstructed; thus, both ultrafast and regular high-spatial-resolution acquisitions can be obtained using the same sequence, as described for liver, pediatrics, breast, and neck [53]. This approach can help to improve clinical workflow by enabling data acquisition without the need for synchronization with breath-hold commands or for selection of predefined rigid temporal resolution. A recently published study [54] showed that the performance of the GRASP sequence in terms of conspicuity of benign and malignant breast lesions is near comparable to that of conventional *volumetric imaging breath-hold examination* (VIBE) imaging. Thus, techniques that employ compressed sensing might be used to further improve image quality of ultrafast imaging. Table 4.5 lists multiparametric protocols that include ultrafast MRI sequences recently described in literature.

4.9 Future Perspectives: Contrastless Screening

As earlier discussed, one major disadvantage of breast MRI is the need for intravenous contrast agent administration. This is not solved by either abbreviated, ultrafast, or hybrid protocols. Since the recent observation of gadolinium deposition/retention in the brain in a fraction of patients who underwent multiple injections of gadolinium-based contrast agents [55–57], this has become a

Table 4.5 Multiparametric protocols containing ultrafast sequences

First author [reference #]	Protocol
Pineda [48]	1. Ultrafast sequence 2. High-resolution sequences
Herrmann [49]	1. Pre-contrast 2D gradient-echo 2. Ultrafast sequence (TWIST)
Tudorica [50]	1. Ultrafast sequence (TWIST) with fat saturation 2. Axial T2-weighted sequence with fat saturation 3. 3D T1-weighted sequence without fat saturation
Le [51]	Healthy volunteers, no contrast agent administration 1. TWIST Dixon sequence 2. VIBE SPAIR
Mann [27]	1. DWI 2. VIBE (T1-weighted) 3. TWIST (T1-weighted) 4. T2-weighted
Feng [53]	GRASP
Heacock [54]	1. Sagittal T1-weighted gradient-echo 2. Sagittal T2-weighted gradient-echo 3. Sagittal T1-weighted gradient-echo When breast biopsy images were acquired: Sagittal GRASP sequence continuously acquired before, during, and after contrast injection

See text for the sequences here indicated by acronyms

debated subject, especially for breast MRI screening, because these healthy women at increased risk for breast cancer are annually exposed to gadolinium-based contrast agents. The reader will find a more extensive discussion on this topic in Chap. 5.

Even though there are currently no clinical sequels reported to be associated with gadolinium deposition/retention and guidelines for the use of breast MRI have remained unchanged [58], this is an additional reason (next to the associated costs, need for intravenous cannulation, and risks of already known adverse events such as allergic reactions) to investigate alternative MRI screening strategies that do not rely on contrast administration. The recent technological developments in cancer imaging have led to a shift toward functional assessment of tissue characteristics, possibly making contrast administration in the future unnecessary.

Of all techniques in use, DWI appears the strongest candidate for contrastless breast MRI. Like T2-weighted imaging, DWI does not require contrast agent administration; however, its sensitivity is much higher than that of T2-weighted imaging. This makes that DWI can be used in patients with a poor renal function or patients with an allergy to gadolinium-based contrast agents. Although currently not as good as contrast-enhanced MRI, the sensitivity of DWI is already competitive with that of mammography.

Sebastian Bickelhaupt and coworkers [59] investigated the fusion of T2-weighted images and DWI for characterization of BI-RADS 4 or 5 mammographic findings. Combining morphological information from the former with biophysiological characteristics from the latter allowed radiologists to get a high diagnostic accuracy for lesion characterization (92%) comparable to that of the full DCE protocol (95%). Research is needed to investigate whether this can be used for breast MRI screening.

Further diffusion-based approaches to contrastless breast MRI include *diffusion tensor imaging* (DTI) that appears to improve the diagnostic capacity of DWI and allows imaging at a substantially higher resolution than that common for DWI [60] and *intravoxel incoherent motion* (IVIM), although the spatial resolution of the latter currently still precludes any screening [61].

An approach to obtain vascular information without contrast administration is *arterial spin labeling* (ASL). The arterial blood supplying the tissue of interest is "labeled" by altering its lon-

gitudinal magnetization; perfusion quantification can be easily performed as the signal changes are proportional to blood flow [62, 63]. The technique has already been successfully implemented to improve disease detection and characterization in the brain, pancreas, and kidney [62]. Several ASL techniques exist, all based on three different spin states (equilibrium, saturation, and inversion), and can also be categorized as on- and off-slice tagging sequences. Pilot studies showed an ASL potential for distinguishing malignant from benign breast tissues (as malignant tumors had a higher water content than normal tissue and a higher perfusion than both normal tissues and benign lesions) [63] and a correlation between MRI perfusion values of breast tissue by ASL as compared to computed tomography perfusion [64]. Unfortunately, the ASL sequences for breast imaging are still under development, and some cannot even cover the whole breast. In addition, the obtained signals are still too weak, and reconstruction artifacts too strong to use it as a screening tool. It is a matter of time to see whether ASL can evolve into a technique that can replace contrast-enhanced breast MRI.

Metabolic imaging, predominantly proton MRS, is another path for exploration. It is well established that total choline, in particular phosphocholine, is elevated in breast cancer [22, 39–42, 65]. As spectroscopic techniques improve, quantification of in vivo spectra can be done more reliably. This replaces the criterion of seeing or not seeing the choline peak with more sophisticated quantitative criteria for judging whether a breast lesion might be malignant [22]. However, for future screening application, multivoxel 2D or, better, 3D techniques are needed. Moreover, the SNR is so low that voxels are in the size order of cubic centimeters, thus still not suitable for screening. Nevertheless, novel approaches to metabolic imaging, such as phosphorous MRS and chemical exchange saturation transfer (CEST) imaging, may enable much higher resolution levels in the near future that might give them access to a new platform for screening research [66].

4.10 Conclusions

Breast MRI is solidly established as the most accurate screening technique for breast cancer available, even though currently mainly applied to women at increased risk of breast cancer. Current state-of-the-art protocols are multiparametric in nature and focus on achieving both a high sensitivity and a high specificity. As the added value of additional sequences on top of simple T1-weighted acquisitions in a screening setting appears questionable and is likely not cost-effective, current research focuses on shortening of MRI protocols. Both abbreviated and ultrafast approaches to breast MRI allow acquisition within minutes without losing in accuracy.

Future research focuses on the use of non-contrast techniques for screening. DWI currently seems most suitable. However, so far, this technique cannot deliver the quality of screening obtained with contrast-enhanced techniques.

References

1. Heywang SH, Hahn D, Schmidt H et al (1986) MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr 110:199–204
2. Heywang SH, Hilbertz T, Pruss E et al (1988) Dynamic contrast medium studies with flash sequences in nuclear magnetic resonance tomography of the breast. Digitale Bilddiagn 8:7–13
3. Kriege M, Brekelmans CT, Boetes C et al (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427–443
4. Leach MO, Boggis CR, Dixon AK et al (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
5. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
6. Rijnsburger AJ, Obdeijn IM, Kaas R et al (2010) BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol 28:5265–5273

7. Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D (2010) Multimodality breast cancer screening in women with a familial or genetic predisposition. Curr Oncol 17:28–36
8. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Invest Radiol 46:94–105
9. Passaperuma K, Warner E, Causer PA et al (2012) Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 107:24–30
10. Riedl CC, Luft N, Bernhart C et al (2015) Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 33:1128–1135
11. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
12. Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 18:1307–1318
13. Gillman J, Toth HK, Moy L (2014) The role of dynamic contrast-enhanced screening breast MRI in populations at increased risk for breast cancer. Womens Health (Lond Engl) 10:609–622
14. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
15. DeMartini WB, Rahbar H (2013) Breast magnetic resonance imaging technique at 1.5 T and 3 T: requirements for quality imaging and American College of Radiology accreditation. Magn Reson Imaging Clin N Am 21:475–482
16. Orel SG (2000) MR imaging of the breast. Radiol Clin North Am 38:899–913
17. Lourenco AP, Donegan L, Khalil H, Mainiero MB (2014) Improving outcomes of screening breast MRI with practice evolution: initial clinical experience with 3T compared to 1.5T. J Magn Reson Imaging 39:535–539
18. Dhillon GS, Bell N, Ginat DT, Levit A, Destounis S, O'Connell A (2011) Breast MR imaging: what the radiologist needs to know. J Clin Imaging Sci 1:48
19. Gaillard F, Ballinger JR et al (2017) MRI pulse sequences. https://radiopaedia.org/. Accessed 30 Jun 2020
20. Kuhl CK, Schild HH (2000) Dynamic image interpretation of MRI of the breast. J Magn Reson Imaging 12:965–974
21. American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
22. Hendrick RE (2004) Breast MRI: using physics to maximize its sensitivity and specificity to breast cancer. Med Phys 31(6):1737
23. Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB (2014) Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection—a novel approach to breast cancer screening with MRI. J Clin Oncol 32:2304–2310
24. Mango VL, Morris EA, Dershaw D et al (2015) Abbreviated protocol for breast MRI: are multiple sequences needed for cancer detection? Eur J Radiol 84:65–70
25. Grimm LJ, Soo MS, Yoon S, Kim C, Ghate SV, Johnson KS (2015) Abbreviated screening protocol for breast MRI: a feasibility study. Acad Radiol 22:1157–1162
26. Heacock L, Melsaether AN, Heller SL et al (2016) Evaluation of a known breast cancer using an abbreviated breast MRI protocol: correlation of imaging characteristics and pathology with lesion detection and conspicuity. Eur J Radiol 85:815–823
27. Mann RM, Mus RD, van Zelst J, Geppert C, Karssemeijer N, Platel B (2014) A novel approach to contrast-enhanced breast magnetic resonance imaging for screening: high-resolution ultrafast dynamic imaging. Invest Radiol 49:579–585
28. Elster A.D. Questions and answer in MRI. http://www.mriquestions.com/index.html. Accessed 30 Jun 2020
29. Kuhl CK, Klaschik S, Mielcarek P, Gieseke J, Wardelmann E, Schild HH (1999) Do T2-weighted pulse sequences help with the differential diagnosis of enhancing lesions in dynamic breast MRI? J Magn Reson Imaging 9:187–196
30. Hagmann P, Jonasson L, Maeder P, Thiran JP, Wedeen VJ, Meuli R (2006) Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. Radiographics 26(Suppl 1):S205–S223
31. Dorrius MD, Dijkstra H, Oudkerk M, Sijens PE (2014) Effect of b value and pre-admission of contrast on diagnostic accuracy of 1.5-T breast DWI: a systematic review and meta-analysis. Eur Radiol 24:2835–2847
32. Partridge SC, McDonald ES (2013) Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. Magn Reson Imaging Clin N Am 21:601–624
33. Pinker K, Bickel H, Helbich TH et al (2013) Combined contrast-enhanced magnetic resonance and diffusion-weighted imaging reading adapted to the "breast imaging reporting and data system" for multiparametric 3-T imaging of breast lesions. Eur Radiol 23:1791–1802
34. Bickel H, Pinker-Domenig K, Bogner W et al (2015) Quantitative apparent diffusion coefficient as a noninvasive imaging biomarker for the differentiation of

invasive breast cancer and ductal carcinoma in situ. Invest Radiol 50:95–100
35. Kul S, Cansu A, Alhan E, Dinc H, Gunes G, Reis A (2011) Contribution of diffusion-weighted imaging to dynamic contrast-enhanced MRI in the characterization of breast tumors. AJR Am J Roentgenol 196:210–217
36. Bansal R, Shah V, Aggarwal B (2015) Qualitative and quantitative diffusion-weighted imaging of the breast at 3T—a useful adjunct to contrast-enhanced MRI in characterization of breast lesions. Indian J Radiol Imaging 25:397–403
37. Chavhan GB, Babyn PS, Thomas B, Shroff MM, Haacke EM (2009) Principles, techniques, and applications of T2*-based MR imaging and its special applications. Radiographics 29:1433–1449
38. Kvistad KA, Rydland J, Vainio J et al (2000) Breast lesions: evaluation with dynamic contrast-enhanced T1-weighted MR imaging and with T2*-weighted first-pass perfusion MR imaging. Radiology 216:545–553
39. Sardanelli F, Fausto A, Podo F (2008) MR spectroscopy of the breast. Radiol Med 113:56–64
40. Sardanelli F, Fausto A, Di Leo G, de Nijs R, Vorbuchner M, Podo F (2009) In vivo proton MR spectroscopy of the breast using the total choline peak integral as a marker of malignancy. AJR Am J Roentgenol 192:1608–1617
41. Montemezzi S, Cavedon C, Camera L et al (2017) ^{1}H-MR spectroscopy of suspicious breast mass lesions at 3T: a clinical experience. Radiol Med 122:161–170
42. Sardanelli F, Carbonaro LA, Montemezzi S, Cavedon C, Trimboli RM (2016) Clinical breast MR using MRS or DWI: who is the winner? Front Oncol 6:217
43. Bernstein MA, Huston J, Ward HA (2006) Imaging artifacts at 3.0T. J Magn Reson Imaging 24:735–746
44. Czervionke LF, Czervionke JM, Daniels DL, Haughton VM (1988) Characteristic features of MR truncation artifacts. AJR Am J Roentgenol 151:1219–1228
45. Kuhl CK, Jost P, Morakkabati N, Zivanovic O, Schild HH, Gieseke J (2006) Contrast-enhanced MR imaging of the breast at 3.0 and 1.5 T in the same patients: initial experience. Radiology 239:666–676
46. Kuhl C, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
47. Emaus MJ, Bakker MF, Peeters PH et al (2015) MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. Radiology 277:527–537
48. Pineda FD, Medved M, Wang S et al (2016) Ultrafast bilateral DCE-MRI of the breast with conventional Fourier sampling: preliminary evaluation of semiquantitative analysis. Acad Radiol 23:1137–1144
49. Herrmann KH, Baltzer PA, Dietzel M et al (2011) Resolving arterial phase and temporal enhancement characteristics in DCE MRM at high spatial resolution with TWIST acquisition. J Magn Reson Imaging 34:973–982
50. Tudorica LA, Oh KY, Roy N et al (2012) A feasible high spatiotemporal resolution breast DCE-MRI protocol for clinical settings. Magn Reson Imaging 30:1257–1267
51. Le Y, Kroeker R, Kipfer HD, Lin C (2012) Development and evaluation of TWIST Dixon for dynamic contrast-enhanced (DCE) MRI with improved acquisition efficiency and fat suppression. J Magn Reson Imaging 36:483–491
52. van Zelst J, Vreemann S, Witt H-J et al (2018) Multireader study on the diagnostic accuracy of ultrafast breast magnetic resonance imaging for breast cancer screening. Invest Radiol 53:579–586
53. Feng L, Grimm R, Block KT et al (2014) Golden-angle radial sparse parallel MRI: combination of compressed sensing, parallel imaging, and golden-angle radial sampling for fast and flexible dynamic volumetric MRI. Magn Reson Med 72:707–717
54. Heacock L, Gao Y, Heller SL et al (2017) Comparison of conventional DCE-MRI and a novel golden-angle radial multicoil compressed sensing method for the evaluation of breast lesion conspicuity. J Magn Reson Imaging 45:1746–1752
55. Kanda T, Fukusato T, Matsuda M et al (2015) Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology 276:228–232
56. Radbruch A, Weberling LD, Kieslich PJ et al (2015) Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 275:783–791
57. McDonald RJ, McDonald JS, Kallmes DF et al (2015) Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 275:772–782
58. Mainiero MB, Lourenco A, Mahoney MC et al (2016) ACR appropriateness criteria. Breast cancer screening. J Am Coll Radiol 13(11S):R45–R49
59. Bickelhaupt S, Tesdorff J, Laun FB et al (2017) Independent value of image fusion in unenhanced breast MRI using diffusion-weighted and morphological T2-weighted images for lesion characterization in patients with recently detected BI-RADS 4/5 x-ray mammography findings. Eur Radiol 27:562–569
60. Furman-Haran E, Eyal E, Shapiro-Feinberg M et al (2012) Advantages and drawbacks of breast DTI. Eur J Radiol 81(Suppl 1):S45–S47
61. Liu C, Liang C, Liu Z, Zhang S, Huang B (2013) Intravoxel incoherent motion (IVIM) in evaluation of breast lesions: comparison with conventional DWI. Eur J Radiol 82:e782–e789
62. Buchbender S, Obenauer S, Mohrmann S et al (2013) Arterial spin labelling perfusion MRI of breast cancer using FAIR TrueFISP: initial results. Clin Radiol 68:e123–e127

63. Zhu DC, Buonocore MH (2003) Breast tissue differentiation using arterial spin tagging. Magn Reson Med 50:966–9675
64. Kawashima M, Katada Y, Shukuya T, Kojima M, Nozaki M (2012) MR perfusion imaging using the arterial spin labeling technique for breast cancer. J Magn Reson Imaging 35:436–440
65. Podo F, Paris L, Cecchetti S et al (2016) Activation of phosphatidylcholine-specific phospholipase C in breast and ovarian cancer: impact on MRS-detected choline metabolic profile and perspectives for targeted therapy. Front Oncol 6:171
66. Schmitt B, Trattnig S, Schlemmer HP (2012) CEST-imaging: a new contrast in MR-mammography by means of chemical exchange saturation transfer. Eur J Radiol 81(Suppl 1):S144–S146

5 Gadolinium-Based Contrast Agents for Breast MRI and Uncertainties About Brain Gadolinium Retention

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Abbreviations

ADC	Apparent diffusion coefficient
DWI	Diffusion-weighted imaging
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GBCAs	Gadolinium-based contrast agents
ICAs	Iodinated contrast agents
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NSF	Nephrogenic systemic fibrosis
tCho	Total choline peak

5.1 Introduction

During the 1980s, unenhanced magnetic resonance imaging (MRI) showed limited diagnostic usefulness in the evaluation of breast diseases. A dramatic improvement occurred in 1986, when the introduction of paramagnetic gadolinium-based contrast agents (GBCAs) [1] inaugurated the era of contrast-enhanced breast MRI. More than 30 years after, contrast-enhanced breast MRI is routinely performed in clinical practice for all indications, except for breast implant integrity assessment, where unenhanced MRI scans remain sufficient [2–4]. Indeed, screening of high-risk women is now one of the main indications to contrast-enhanced breast MRI.

Analysis of five registries from the Breast Cancer Surveillance Consortium in the United States [5], across a 5-year study period (2005–2009), showed that screening women at increased risk for breast cancer was the second most common indication (31.7%) after the diagnostic workup of a non-MRI finding or of an otherwise unresolved clinical finding (40.3%), ahead of cancer staging before treatment (16.2%) or other indications (11.8%). Notably, there was an increasing trend in breast cancer screening from less than 20% in 2005 to 34.5% in 2009, with the population-based rate of screening breast MRI increasing by more than five times from 0.8 to 4.3 breast MRI examinations per 1,000 women from 2005 to 2009 [5]. Almost 84% of radiologists who responded to a survey from the European Society of Breast Imaging reported high-risk screening as a practiced indication to breast MRI [6].

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Given the importance of breast MRI screening, detailed knowledge of GBCAs properties and of their administration effects is paramount to reach an appropriately tailored risk-benefit balance in breast MRI screening practice. Such an assessment should consider the fact that screened women are typically asymptomatic (i.e., over 95% healthy), are required to undergo an MRI examination yearly, and, if at high risk, should begin screening at about 25–30 years of age.

In this chapter we discuss GBCAs physicochemical properties, GBCAs effects on diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS), the incidence of acute adverse reactions compared with the incidence observed after iodinated contrast agents (ICAs) administration, specific issues related to GBCAs administration during pregnancy or breastfeeding, as well as the late effects of these agents, including nephrogenic systemic fibrosis (NSF) and tissue (primarily brain) Gd retention. As a consequence, we propose a positive risk-benefit balance in favor of continuing and extending contrast-enhanced MRI screening of high-risk women. Finally, we outline possible future directions for clinical research on breast MRI as a screening tool for high-risk women.

5.2 Physicochemical Properties of GBCAs Utilized in Breast MRI

According to breast cancer genesis theories, a subgroup of breast tumor cells showing an angiogenetic phenotype determines two phenomena: tumor growth and the formation of new vessels from neighboring vascular structures, through the production of pro-neoangiogenic factors, such as the *vascular endothelial growth factor* [7]. These new vessels show wider wall fenestrations which allow a permeability increase up to eight times that of normal breast glandular tissue. Furthermore, tumor interstitial space is three to five times larger than that of normal breast glandular tissue. After intravenous injection, MRI contrast agents permeate outside the new vessels and accumulate much more within the cancerous tissue than in the normal glandular tissue [7]. The presence of GBCAs can be indirectly observed as a reduction of water relaxation times, particularly on T1-weighted images, where an increased signal intensity in tissues with a higher GBCA concentration (or in which a GBCA with higher relaxivity is present) can be appreciated [8]. In fact, the relaxivity of a GBCA reflects how the relaxation times of a solution or a tissue change as a function of GBCA concentration.

In clinical breast MRI, two-compartment (vascular/interstitial) paramagnetic GBCAs are used, typically at a standard dose of 0.1 mmol/kg of body weight, injected at a flow rate of 2–3 ml/s, and followed by saline flushing (20–30 ml) at the same flow rate [2]. These contrast agents are defined as "*extracellular,*" since they do not accumulate in organs nor they penetrate cell membranes, presenting a linear relationship between dose and tissue concentration. GBCAs are created by chelation of a Gd atom (a *rare earth* metal) with an organic ligand which suppresses the high toxicity of the Gd^{3+} ion by preventing its release and subsequent cell absorption.

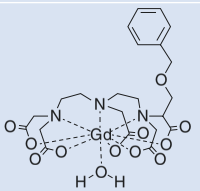
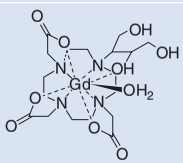
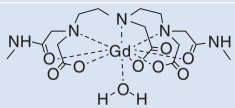
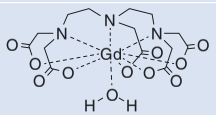
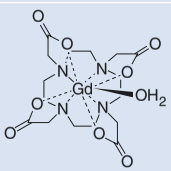
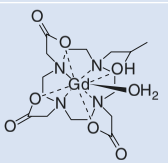
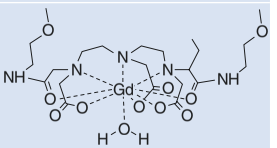
Paramagnetic GBCAs can be subdivided:

1. According to the chemical structure of the chelating moiety, into *macrocyclic* GBCAs (in which the Gd^{3+} ion is caged in the pre-organized cavity of the ligand) or so-called *linear*[1] GBCAs (in which Gd^{3+} is coordinated with an open chain ligand structure).
2. According to the electric charge of the GBCA, either *ionic* or *nonionic.*

Macrocyclic GBCAs are generally considered more stable than linear GBCAs, while ionic linear GBCAs are more stable than nonionic linear GBCAs. The characteristics of GBCAs employed in breast MRI are summarized in Table 5.1.

[1]This is a conventional term. They are not *linear* molecules, even though they are noncyclic. We should also subdivide the so-called linear molecules into *simple linear* (gadopentetate dimeglumine, gadodiamide) and *substituted linear* (gadobenate dimeglumine) which has an aromatic substituent on the molecule which gives it different properties.

Table 5.1 Gadolinium-based contrasts agents utilized for breast MRI

Generic name	Gadobenate dimeglumine	Gadobutrol	Gadodiamide	Gadopentetate dimeglumine	Gadoterate meglumine	Gadoteridol	Gadoversetamide
Brand name	MultiHance®	Gadovist®	Omniscan®	Magnevist®	Dotarem®	ProHance®	OptiMARK®
Chemical name	Gd-BOPTA	Gd-BT-DO3A	Gd-DTPA-BMA	Gd-DTPA	Gd-DOTA	Gd-HP-DO3A	Gd-DTPA-BMEA
Structural formula							
Manufacturer	Bracco, Italy	Bayer Healthcare, Germany	General Electric Healthcare, USA	Bayer Healthcare, Germany	Guerbet, France	Bracco, Italy	Mallinckrodt, USA
Molarity (mol/l)	0.5	1.0	0.5	0.5	0.5	0.5	0.5
Molecular structure	Linear	Cyclic	Linear	Linear	Cyclic	Cyclic	Linear
Charge	Ionic	Nonionic	Nonionic	Ionic	Ionic	Nonionic	Nonionic
Osmolality (mOsm/kg H_2O at 37 °C)	1,970	1,603	650	1,960	1,350	630	1,110
r1-relaxivity at 1.5 T (l/mmol s)[a]	6.3, 6.7, or 7.9	4.7, 5.2, or 5.3	4.3 or 4.6	3.9, 4.1, or 4.3	3.6 or 4.2	4.1 or 4.4	4.7 or 5.2
Thermodynamic stability constant (log K_{therm})	22.6	21.8	16.8	22.1	25.4	22.8	16.6
Conditional stability constant at pH 7.4	18.4	14.7	14.9	17.7	18.8	17.1	15.0
Elimination half-life (minutes, mean ± SD)	72 ± 5	NA	77.8 ± 16	94 ± 11	91 ± 14	94.2 ± 4.8	103.6 ± 19.5
Elimination pathway	Renal 97%, biliary 3%[a]	Renal	Renal	Renal	Renal	Renal	Renal

Sources: References [8–16]. *NA* not available. Gadoversetamide is no longer available for clinical use. It is included in this table for the sake of completeness

Take into account that r1-relaxivity values can change according to the method of measure: they depend on serum albumin concentration in plasma used for in vitro measures [13]

[a]In patients with renal impairment, the amount excreted into the bile increases to 7–8%

Considering the intrinsic Gd^{3+} ion toxicity, the ligand must be highly selective for this ion and tightly bound to it in order to prevent its release into blood circulation and its possible binding to different cations (*transmetallation*). The stability of Gd chelates represents a very complex issue [9–11] and can be defined in several ways:

1. The *thermodynamic stability constant*, which indicates the affinity of the unprotonated chelator for the metal ion; this parameter (which is determined at nonphysiological pH 14) is determined by the in vitro energy required for the metalloligand to release the ion; of note, when thermodynamic stability is weak, the chelator more readily releases Gd^{3+} ions.
2. The *thermodynamic conditional stability constant*, which is a measure of the stability of the complex at physiological pH (note that its value at pH 7.4 is always substantially lower than the thermodynamic stability constant).
3. The *selectivity constant* which describes the transmetallation from a thermodynamic point of view (i.e., at equilibrium) and corresponds to the difference between the thermodynamic stability constants of the Gd chelate and other metalloligands (e.g., endogenous cations such as Fe^{3+}, Ca^{2+}, Mg^{2+}, Zn^{2+}, and Cu^{2+} ions).
4. The *kinetic rate of the metalloligands* in vivo, estimated from their half-life dissociation.

The concept of kinetic and thermodynamic stability should be considered very carefully since it remains a somewhat controversial topic, especially in predicting the amount of Gd^{3+} ion which may result from dechelation in physiological or pathological situations [11]. Other important GBCAs characteristics are the elimination pathway (primarily renal, with the only exception of gadobenate dimeglumine which is partially eliminated [3–5% of the injected dose] by the hepatobiliary pathway) and osmolality [9]. Importantly, the limited amount of GBCA administered for clinical use is insufficient to affect the overall plasma osmolality.

There is a positive correlation between GBCA relaxivity and the increase in signal intensity in those tissues in which GBCAs preferentially accumulate. Most GBCAs used for breast MRI (gadopentetate dimeglumine, gadoterate meglumine, gadoteridol, gadodiamide, gadobutrol, gadoversetamide) show variable r1-relaxivities at 1.5 T, ranging from 3.6 to 5.3 l/mmol s^{-1}. Instead, due to its weak and transient interaction with serum albumin, gadobenate dimeglumine has higher r1-relaxivity (6.7–7.9 l/mmol s^{-1} at 1.5 T) [12–15].

Because of this higher r1-relaxivity, gadobenate dimeglumine demonstrates significantly better diagnostic performance for detection and characterization of breast lesions when compared to GBCAs with standard r1-relaxivity [16–21]. Although an intraindividual study showed noninferior diagnostic performance for gadobutrol compared to gadobenate dimeglumine for preoperative breast MRI [22], that study was criticized for its methodology and adopted assessment criteria [23, 24]. A more recent study comparing a three-quarter dose (0.075 mmol/kg) of gadobenate dimeglumine to a twofold higher dose (0.15 mmol/kg) of gadoterate meglumine at 3 T revealed significantly better breast lesion detection and characterization with the lower dose of gadobenate dimeglumine [25]. This was attributed to the fact that gadobenate dimeglumine has the highest available r1-relaxivity while gadoterate meglumine the lowest. We will come back to the issue of dose reduction below, when outlining future perspectives.

Most GBCAs are formulated at a concentration of 0.5 mol/l. The only exception among GBCAs available for breast MRI is gadobutrol, which is formulated at a twofold higher concentration (1.0 mol/l). This means that an equivalent volume of the gadobutrol formulation contains twice the number of GBCA molecules and that therefore the volume of gadobutrol necessary to achieve an approved dose is half that of the other available GBCAs. While this characteristic may be of interest for certain first-pass perfusion studies, for dynamic studies with a time resolution usually not less than 60 s, this higher concentration is diluted in the blood volume without any effect on signal increase. The enhancement is therefore mainly determined by the GBCA r1-relaxivity, assum-

ing otherwise identical imaging conditions. Recent studies [26, 27] have shown that the diagnostic performance of the higher concentration gadobutrol is similar to that of gadoterate meglumine, despite slightly higher relative enhancement with gadobutrol. The difference in relative enhancement can again be attributed to the fact that gadoterate meglumine has the lowest r1-relaxivity, while r1-relaxivity of gadobutrol is among the highest between available standard relaxivity GBCAs.

5.3 Effects of GBCAs on ^{1}H-MRS and DWI

Proton (^{1}H) MRS can provide metabolic information on the studied breast tissue, based on the presence and amount of total choline peak (tCho) at 3.14–3.34 ppm [28–30], which is the consequence of a dysregulation of tumor cell phosphocholine metabolism [31–33]. A significant reduction (about 40%) of the tCho peak after ionic GBCAs was observed on phantom and murine animal models, when compared to nonionic GBCAs [34]. These results were confirmed by an in vivo randomized study that showed a tCho peak reduction of about 30% in patients after the administration of an ionic GBCA (gadopentetate dimeglumine) compared to the tCho peak after administration of a nonionic GBCA (gadodiamide) [35]. Therefore, nonionic GBCAs should be preferred when a ^{1}H-MRS examination is planned. However, this is not an issue in a routine screening setting. In fact, despite the efforts of researchers, ^{1}H-MRS remains so far only a tool for interesting research and has not entered routine clinical practice [36].

Conversely, in the last decade, DWI has increasingly been introduced as a routine component of standard breast MRI protocols, with the aim of increasing diagnostic accuracy, especially specificity [3, 36, 37]. Importantly, DWI is not hampered by previous GBCAs administration. In this regard, one study showed that when using b values of 50, 400, and 800 s/mm^2, the ADC value of the malignant lesions changed from $0.90 \pm 0.14 \times 10^{-3}$ mm^2/s before GBCA administration to $0.80 \pm 0.14 \times 10^{-3}$ mm^2/s after GBCA injection, with just a 11% diffusivity reduction. Conversely, the ADC value of benign lesions changed from $1.99 \pm 0.37 \times 10^{-3}$ mm^2/s before to $1.97 \pm 0.30 \times 10^{-3}$ mm^2/s after GBCA administration, with just a 1% (nonsignificant) diffusivity reduction [38].

While DWI is not overly hampered by previous GBCA administration, ^{1}H-MRS, which often needs a preliminary GBCA administration to localize the volume of interest, appears to have its sensitivity for tCho peak detection limited if ionic GBCAs are used. Furthermore, apart from the frequently low signal-to-noise ratio of the tCho peak, even when obtained at 3 T [39], the advantage of DWI sequences over MRS (performed with a single-voxel technique in most published studies) is that the former is panoramic, allowing bilateral breast examination to be completed in a few minutes [36]. These advantages make DWI an important tool for future research on non-contrast breast MRI screening (see Chap. 4).

To summarize, *while nonionic GBCAs should be preferred when ^{1}H-MRS examination has to be subsequently performed (always considering that ^{1}H-MRS is not routinely used in clinical practice, particularly not in a screening setting), GBCA injection may have a positive effect on DWI. However, a DWI-induced increase in specificity or, more appropriately, in positive predictive value (without impacting sensitivity) has not yet been specifically demonstrated in a high-risk screening setting.*

5.4 Acute Adverse Reactions to GBCAs

Considering acute adverse reactions, contraindications to GBCAs administration in breast MRI screening are similar to those of other clinical applications. However, some particular issues should be taken into account.

Acute adverse reactions are categorized as *allergic-like* (also called *anaphylactoid* or *idiosyncratic*) or *physiologic* (*nonallergic-like*) and are classified by the American College of

Table 5.2 Categories of acute adverse reactions to contrast agents

Grade	Subtype	Signs/symptoms
Mild (self-limiting)	Allergic-like	Limited urticaria/pruritus, limited cutaneous edema, limited *itchy*/*scratchy* throat, nasal congestion, sneezing/conjunctivitis/rhinorrhea
	Physiologic	Limited nausea/vomiting, transient flushing/warmth/chills, headache/dizziness/anxiety/altered taste, mild hypertension, vasovagal reaction that resolves spontaneously
Moderate (requiring treatment)	Allergic-like	Diffuse urticaria/pruritus, diffuse erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, wheezing/bronchospasm, mild or no hypoxia
	Physiologic	Protracted nausea/vomiting, hypertensive urgency, isolated chest pain, vasovagal reaction requiring (and responsive to) treatment
Severe (life-threatening)	Allergic-like	Diffuse edema or facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm, significant hypoxia, anaphylactic shock (hypotension and tachycardia)
	Physiologic	Vasovagal reaction resistant to treatment, arrhythmia, convulsions, seizures, hypertensive emergency

Modified from American College of Radiology 2017 [40]

Radiology (ACR) [40] and the European Society of Urogenital Radiology (ESUR) [41] according to severity: mild (typically self-limiting, nonprogressive, and not requiring treatment), moderate (commonly requiring treatment), or severe (life threatening, requiring immediate medical attention and treatment) (Table 5.2).

Most adverse reactions are mild physiologic reactions. Allergic-like reactions are uncommon and vary in frequency from 0.004% to 0.7% [42], with a mortality rate close to zero [43]. Overall, the incidence of acute adverse events falls between 0.1% and 0.45% [44, 45].

The ACR Manual on Contrast Media [40] states that the adverse event rate for GBCAs administered at clinical doses (0.1–0.2 mmol/kg for most GBCAs) ranges from 0.07% to 2.4%, while ESUR Guidelines on Contrast Agents [41] state that there is no difference in the incidence of acute adverse reactions among available extracellular GBCAs, also specifying that the incidence of adverse reactions is much lower for GBCAs compared to ICAs used in x-ray and computed tomography procedures. Studies to compare adverse event rates after GBCAs and ICAs have corroborated this statement, showing that the relative risk for an acute adverse reaction is more than five times higher for low-osmolar ICAs than for GBCAs, while the relative risk for an acute adverse reaction requiring treatment is almost three times higher for ICAs [46] (Table 5.3).

No studies have assessed the relative risk for adverse reactions in a breast MRI screening setting yet. However, it has been shown that the incidence of adverse reactions may be higher for female than for male patients (odds ratio 1.687) and that there might be a correlation between the incidence of adverse reactions and the number of previous exposures to GBCAs [45].

Specific issues relevant to the breast cancer screening setting include:

1. How to manage a high-risk woman with a previous acute reaction to a GBCA which is starting or continuing annual screening with contrast-enhanced MRI.
2. How to manage a high-risk woman with a history of asthma or allergy to drugs or ICAs which is starting or continuing annual screening with contrast-enhanced MRI.

In these cases, it would seem appropriate to adopt one of the two elective prophylactic protocols suggested by the ACR [40]:

1. Prednisone 50 mg per os at 13, 7, and 1 h before contrast administration AND diphenhydramine 50 mg per os, intramuscularly, or intravenously, 1 h before contrast administration [47].
2. Methylprednisolone 32 mg per os 12 and 2 h before contrast administration; diphenhydramine 50 mg as in protocol 1 can be also added [48].

Table 5.3 Acute adverse reactions (AARs): comparison between gadolinium-based contrast agents (GBCAs) and low-osmolar iodinated contrast agents (LOICAs)

	GBCAs	LOICAs	*p*-value[a]
Number of doses	158,439	298,491	
Total AARs	45	458	
Incidence	0.028% (0.021–0.038%)	0.153% (0.140–0.168%)	<0.001
Relative risk[b]	1.00	5.40	
AARs requiring treatment	15	79	
Incidence	0.009% (0.005–0.016%)	0.026% (0.021–0.033%)	<0.001
Relative risk[b]	1.00	2.80	
AARs requiring transfer to emergency department	6	10	
Incidence	0.004% (0.001–0.008%)	0.003% (0.002–0.006%)	0.812
Relative risk[b]	1	0.88	
Death	0 (0.000–0.002%)	1 (0.000–0.019%)	

Calculations on data from Hunt et al. [44]; in parentheses, 95% confidence intervals calculated according to the binomial distribution

[a]χ^2 test

[b]Here we opted for calculating the relative risk instead of the odds ratio because, even though data come from a retrospective analysis, the authors did not enroll cases of acute reactions verifying how many of them were exposed; they instead analyzed two concurrent prospective series of patients exposed to GBCAs or LOICAs, evaluating how many of them had adverse reactions. However, in this case, due to the very small number of events compared to the number of exposures, the relative risk and the odds ratio gave equivalent results

In addition, for patients with a previous acute reaction to GBCAs, the specific GBCA should be changed, ideally to one of a different class [49]. Above all, as with all MRI procedures, it is necessary that imaging departments are adequately prepared to deal with adverse reactions if and whenever they occur [50].

When starting or continuing a yearly contrast-enhanced breast MRI screening program, we should carefully consider that (1) we are dealing with women who are invariably (over 95%) healthy, even if they are carriers of a deleterious *BRCA* mutation or other high-risk conditions, and (2) the effectiveness of the screening is dependent on being performed annually. This means that, *if breast MRI screening is the chosen approach, we should explain that a prophylactic protocol will be repeated every year before the examination to reduce any chance of reactions.*

In setting up an annual screening program, an individualized approach is necessary to ensure adequate women's information. Specifically, an open discussion of advantages and disadvantages of the MRI examination is needed, especially considering the alternative options to GBCA injection, such as:

1. Non-contrast imaging strategies combining mammography, digital breast tomosynthesis, ultrasonography (manual or automated), and unenhanced MRI sequences (in particular DWI).
2. Breast cancer chemoprevention (see Chap. 17).
3. Prophylactic mastectomy and/or oophorectomy (see Chap. 18).

A standardized approach is not feasible in these circumstances. In our view, in particular for *BRCA1* mutation carriers, prophylactic surgery should be carefully considered. In high-risk women, the choice among all options, including annual performance of contrast-enhanced breast MRI, may require psycho-oncologic counselling (see Chap. 19).

5.5 Administration of GBCAs During Pregnancy and Breastfeeding

Other specific female conditions needing to be considered before GBCA administration are pregnancy and breastfeeding. Whenever possible, a high-risk woman who is annually screened with contrast-enhanced MRI should plan her pregnancy in order to avoid a prolonged delay of the screening round. In case of unplanned pregnancy, breast ultrasonography can be used up to childbirth. Thereafter, breast MRI can be performed, although its diagnostic performance may be limited by benign physiological changes during breastfeeding. For example, abnormal rapid dynamic contrast enhancement may be seen in normal lactating breast tissue, which may mimic or obscure some cancer lesions. On the other hand, malignant lesions may show an even faster and stronger enhancement than the lactating tissue, as well as suspicious morphologic features, such as rim enhancement [51]. An Italian multidisciplinary guideline [52] suggested to avoid administering gadopentetate dimeglumine, gadodiamide, and gadoversetamide, considered at higher risk of nephrogenic systemic sclerosis (NSF), to breastfeeding women. Anyway, as we will see below, clinical use of these contrast agents for breast MRI is no longer allowed in Europe.

Again, in these circumstances, a personalized approach to patient management is needed to provide a tailored solution to continue breast MRI screening in high-risk women, in order to minimize the risk of a delayed diagnosis of breast cancer.

5.6 GBCAs Late Effects: Nephrogenic Systemic Fibrosis (NSF)—The *Perfect Storm*

The assumption that GBCAs have a uniquely safe profile changed in 2006, when an association between gadodiamide and NSF was firstly described [53]. The risk-benefit balance for this and other GBCAs became matter of a hot debate. NSF is not an imaging finding but a very late and sometimes fatal adverse reaction to GBCA exposure that occurs in some patients already suffering from acute renal failure or severe chronic renal failure (estimated glomerular filtration rate [eGFR] < 15 ml/min × 1.73 m^2) [41].

NSF is a scleroderma-like illness that typically presents from few weeks to years after exposure to one of the least stable GBCAs [54]. The most commonly held theory on the pathophysiology of NSF is that Gd^{3+} ions dissociate from their chelating ligands in the interstitial space forming insoluble salts (e.g., phosphates and carbonates) which are taken up by fibroblasts, ultimately causing fibrotic reactions that result in the symptoms exhibited by sufferers [55]. In patients with normal or moderate renal function, GBCAs are excreted sufficiently rapidly before overt dechelation occurs. However, in patients with severely decreased renal elimination, the ensuing prolonged GBCA retention favors greater opportunity for dechelation and subsequent fibrosis.

Initial symptoms are primarily skin lesions associated with swelling and pain, particularly in the upper and lower extremities from the ankles to below the knees, usually in a symmetrical manner. Subsequent sclerosis involving joints and major organs typically leads to reduced movement, with resultant significant disability and increased mortality. Unfortunately, there is still no specific treatment for this disease.

In 2007–2008, many international and national scientific societies, together with important health authorities, like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), established specific safety policies for GBCA use. Until recently, according to ESUR [41], GBCAs were classified into three groups in terms of risk for NSF: *high risk* (gadodiamide, gadopentetate dimeglumine, and gadoversetamide), *intermediate risk* (gadobenate dimeglumine), and *low risk* (gadobutrol, gadoterate meglumine, and gadoteridol). However, concerns about potential long-term harm from Gd retention in the brain (see below) prompted the EMA to suspend *high-risk agents*

for all clinical applications and to restrict the *intermediate risk agent* gadobenate dimeglumine to liver imaging only. Although *low-risk agents* are still available for use in breast MRI, they are recommended to be used with caution in patients with eGFR lower than 30 ml/min × 1.73 m^2. While serum creatinine testing (eGFR) is not mandatory for *low-risk agents*, it is recommended that at least questionnaire-based renal function screening is performed before their injection [41]. In the United States, the ACR [40] classified GBCAs available for breast MRI as belonging to group I (GBCAs associated with the greatest number of NSF cases: gadodiamide, gadopentetate dimeglumine, and gadoversetamide) or group II (GBCAs associated with few, if any, indisputable cases of NSF: gadobenate dimeglumine, gadobutrol, gadoteridol, gadoterate meglumine). Based on the lack of clinical evidence of harm associated with brain Gd retention, no GBCAs have been suspended from the market in the United States, and all are still available for breast MRI. While underpinned by the same evidence, EMA recommendations are very different from the FDA and the ACR approaches.

Contraindication of the *high-risk* GBCAs in patients with severe chronic kidney disease, in both United States and Europe, reflects the fact that approximately 85% of unquestionable NSF cases were associated with gadodiamide, while the remaining others were associated primarily with gadopentetate dimeglumine and gadoversetamide [41]. Although a recent report notes that three indisputable cases of NSF occurred after administration of the macrocyclic GBCA gadobutrol [56], all others occurred after administration of a simple linear GBCA. The contraindication of these three *high-risk* GBCAs, together with routine screening of kidney function and GBCA dose curtailing to no more than the approved one (0.1 mmol/kg of body weight), appears to have eliminated NSF as a current disease entity.

Notably, since 2007–2008, in many institutions worldwide, serum creatinine testing (eGFR) became a routine practice, and GBCAs use at a dosage higher than 0.1 mmol/kg was limited to few cases. A strong decrease of the number of NSF cases was observed after 2009, with rare isolated exceptions [57], and we currently consider NSF a disease of the past, as confirmed by a very recent systematic review reporting a total of 639 NSF cases, only seven of them after GBCA exposure after 2008 [58]. In this review [58], out of 525 patients with documented exposure to GBCAs, 307 had been administered with gadodiamide (58.5%), 49 with gadopentetate dimeglumine (9.3%), and 6 with gadoversetamide (1.1%), gadobutrol (0.2%), gadobenate dimeglumine (0.2%), multiple GBCAs (7.8%), or unknown GBCAs (22.9%).

The emergence of NSF was a consequence of a "perfect storm" [59], arising from multiple factors such as (1) a long-held belief that GBCAs were inherently safe even in patients with renal dysfunction, (2) off-label use of high (often triple or quadruple) doses of GBCAs particularly for MR angiography, and (3) late understanding of the link between GBCA administration and NSF, which mainly reflected the variable interval between injection(s) and disease onset. *One important lesson from NSF is that the "available evidence" up until 2006 was in favor of a high safety of GBCAs also in patients with renal failure.*

Discrepancies in NSF incidence between different countries were highlighted in 2014 by H. S. Thomsen [60]. Out of about 1,600 cases reported to the FDA, 93% came from the United States, 3% came from various countries around the world, and the remaining 4% came from Denmark, the only country in which a dedicate national investigation has been initiated. Thomsen estimates that, applying the Denmark incidence (20 per 1 million inhabitants) to Europe and North America, NSF patients, all disease degrees included, should be around 10,000. Thus, even though no further cases of NSF have been reported after 2009, what we have seen is "the tip of the iceberg." Thomsen's conclusion has to be considered when discussing safety of GBCAs: *NSF is still relevant* [60].

Manifold consequences emerged in current practice. Among various positive effects on radiologists' clinical practice, we have seen the following:

1. Rethinking of the value of unenhanced MRI and better exploitation of technical tools to allow for accurate diagnosis without GBCA injection.
2. Screening patients for renal failure when GBCA injection is indicated.
3. Halting (or limiting) GBCAs administration in high-risk patients (those with an eGFR ≤30 ml/min × 1.73 m^2).
4. Stopping (or curtailing) the use of GBCA doses higher than 0.1 mmol/kg.
5. Administration of GBCA doses calculated as mmol/kg of body weight, ending the administration of fixed GBCA volumes such as 15 or 20 ml.
6. Accurate description of GBCA type and dose for each patient in the technical section of the structured radiological report.

Although NSF risk seems to increase along with the number of doses for each examination and many reported cases occurred after multiple injections, records of the used GBCA and of the administered dose have often not been made available, making the knowledge about possible cumulative effects after multiple injections very limited [41].

To summarize, the application of screening policies for renal function and the use of a standard dose of 0.1 mmol/kg of GBCAs lowered the risk of NSF close to zero, even for those linear GBCAs related to the disease, whenever these guidelines were applied [61]. Depending on local regulations, questionnaires or mandatory serum creatinine and eGFR tests are required as screening for renal function before administering GBCAs. GBCA administration is contraindicated in patients with an eGFR below 30 ml/min/1.73 m^2 [40].

> These recommendations should be considered valid also for high-risk candidates for contrast-enhanced MRI breast cancer screening.

5.7 Late Effects of GBCAs: Brain Tissue Gd Retention

Despite the absence of new NSF cases since 2010, concern over the risk of NSF was still rife when a first article appeared reporting T1-signal increases in the dentate nucleus and globus pallidus on unenhanced T1-weighted images after cumulative administration of gadopentetate dimeglumine or gadodiamide (i.e., two simple linear GBCAs) to patients with normal renal function [62]. Numerous reports based on studies performed in human subjects and animal models subsequently appeared, confirming the appearance of T1-signal increases after cumulative administration of gadopentetate dimeglumine and gadodiamide but not after the administration of macrocyclic GBCAs. The authors of these studies compared only one linear GBCA and one macrocyclic GBCA, but titles and conclusions of the articles mentioned "class-based" differences [63]. With concern about NSF still fresh in mind, the assumption was that linear GBCAs release Gd^{3+} ions in a manner similar to that seen in NSF and that this Gd^{3+} is then retained in brain and body tissues indefinitely, likely bound to cellular proteins and macromolecules, leading to high r1-relaxivity and thus visible T1 hyperintensity. Conversely, it was assumed that Gd^{3+} is not released from the more stable macrocyclic GBCAs, hence the lack of evident T1-signal increases.

Although it had been known for many years that Gd is retained in body tissues (primarily the bone [64, 65]) after GBCA administration, the demonstration of T1-signal changes in the brain had a profound, discordant, and divisive effect, not only within the radiology community but also among patients and regulatory authorities. While no clinical manifestations or adverse clinical outcomes related to brain Gd retention have been observed following repeated administration of any GBCA, fear and concern revolve around potential long-term repercussions of Gd retention on human health.

Regulatory authorities have responded in very different ways to the Gd retention phenomenon. The EMA, concluding a GBCAs review according to data from the Pharmacovigilance Risk Assessment Committee, confirmed recommendations to suspend marketing authorizations of the simple linear GBCAs (gadopentetate dimeglumine, gadodiamide, and gadoversetamide) and to restrict the use of the substituted linear GBCA gadobenate dimeglumine just to

liver imaging [66]. Then, as now, there was no evidence that Gd retention in the brain causes any harm to patients. Nevertheless, the rationale for this decision was "*to prevent any risks that could potentially be associated with gadolinium brain deposition*" [66].

Elsewhere, a very different approach has been adopted. Both the ACR [67] and FDA [68] have independently issued statements affirming their positions, and no GBCA has been suspended from clinical use in the United States.

ACR [67]:

> At this time, there is no compelling evidence that any GBCAs, including linear ones, poses any safety risk with respect to brain deposition of gadolinium. Further, linear agents have significant and well-documented diagnostic utility, and in some instances, may have more desirable pharmacologic properties or a lower acute reaction risk than macrocyclic agents.

FDA [68]:

> An FDA review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because FDA identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time.

The underlying message of both ACR [67] and FDA [68] statements is the radiologist is responsible for the decision to inject a GBCA, and this decision should be based on a careful individualized assessment of the risk-benefit ratio, which takes into account not only the risk of acute reactions and potential late effects but also the possibility of a missed diagnosis if the appropriate contrast-enhanced examination is not performed.

The clinical relevance of gadolinium brain deposition remains unknown. What is now clear, however, is that T1-signal changes can and do occur after administration of all GBCAs, both linear and macrocyclic. Although T1-signal increases are most frequently seen after administration of simple linear GBCAs, changes after administration of macrocyclic GBCAs are increasingly being reported [69–74]. Moreover, it is well established that measurable amounts of Gd are retained in brain and body tissues even after the administration of very small doses of both linear and macrocyclic GBCAs [75].

As stated by the Safety Committee of the International Society for Magnetic Resonance in Medicine [76]:

> Some commercially available macrocyclic agents might deposit less gadolinium than some linear agents; however, evidence shows that gadolinium deposition in the brain can also occur after the administration of macrocyclic agents. Evidence suggests differences in gadolinium deposition rates among macrocyclic agents and among linear agents, although some data are discordant.

The ACR [67] gives an explanation for the mistaken—albeit widespread—belief which holds that Gd retention is exclusively associated with linear GBCAs, pointing out that MRI is insufficiently sensitive to detect the changes in T1 signal elicited by macrocyclic GBCAs:

> While less sensitive studies that rely upon visually observable changes in T1-weighted MRI signal do not suggest macrocyclic agents deposit gadolinium within brain tissues, more quantitative mass spectrometry data from multiple sources have confirmed that they do, albeit at lower levels. Further, other studies using mass spectrometry have revealed that gadolinium deposition rates for linear and macrocyclic agents vary within a given class, and that different chemical forms of gadolinium (i.e. different gadolinium complexes) appear to be depositing within tissues, some of which would be undetectable using MRI. Therefore, although MRI signal changes led to the observation that gadolinium was being deposited in the brain, they are less reliable for determining the quantity of gadolinium deposition in general. This is particularly true for gadolinium species that are not detectable with MRI and for lower concentrations of retained gadolinium.

It is therefore clear that T1-signal changes suggestive of Gd retention are common to all GBCAs, even though visible effects on T1 signal are predominantly seen after cumulative administration of linear GBCAs. The key questions, which remain to be answered, relate to the form in which Gd is retained and to whether Gd retention entails any clinical risk. Regarding the form in which Gd is retained, it is possible that macro-

cyclic GBCAs are retained intact in tissues, reflecting their greater stability. However, even here, there are differences between macrocyclic GBCAs in terms of retained amounts and their elimination speeds [77, 78]. In the case of linear GBCAs, there appear to be large differences between simple linear GBCAs and the substituted linear GBCA gadobenate dimeglumine [77]. Whether the T1-signal increases seen with linear GBCAs reflect Gd release, and its subsequent binding to macromolecules and cellular proteins, remains to be seen. This may be the case for simple linear GBCAs mirroring a mechanism analogous to that seen in NSF. However, no NSF cases have been associated yet with the substituted GBCA gadobenate dimeglumine; again, there may be differences between individual GBCAs within each class, with some retained as intact GBCA and others (principally the simple linear GBCAs) as a mix of intact GBCA and dechelated Gd bound to macromolecules.

As to whether retained Gd poses a long-term risk to human health, no clinical consequences and no neurological symptoms have hitherto been associated with this phenomenon. Although only a few years passed since the first report of T1 hyperintensities in the brain following GBCA administration [62], more than 30 years have passed since the first GBCA, gadopentetate dimeglumine, was approved for use in humans, and still no long-term effects have been reported, apart from NSF which was effectively dealt with by the contraindication of the simple linear GBCAs (see Sect. 5.6).

Studies that assessed potential long-term harm following GBCA administration have frequently focused on patients with multiple sclerosis since these patients typically undergo regular follow-up with contrast-enhanced MRI examinations and thus receive relatively large volumes of GBCA over a period of many years. Although one retrospective study attempted, somewhat tenuously, to correlate increased signal intensity in the dentate nucleus and globus pallidus with loss of verbal fluency in long-term multiple sclerosis patients [79], other studies revealed no evidence of harm associated with Gd exposure [80, 81]. Indeed, since multiple sclerosis is associated with wide-ranging and worsening neurological symptomatology, it is extremely difficult to differentiate potential effects of cumulative GBCA administration from normal disease progression.

Another important study in patients older than 66 years who underwent an initial non-brain/spinal MRI found no effect of GBCA on the incidence of parkinsonism [82]. Specifically, the incidence of parkinsonism was 1.16% among patients never exposed to GBCAs and 1.17% among patients exposed to GBCAs. Adjusted analyses showed no significantly increased risk of parkinsonism among patients with cumulative gadolinium exposure to GBCAs compared with those who underwent unenhanced MRI (hazard ratio 1.04, 95% confidence interval, 0.98–1.09]. This is a particularly important finding given the physiological roles of the dentate nucleus in the extrapyramidal system, including planning, initiation, and control of voluntary movements [76].

Finally, in patients affected by Crohn disease, who also regularly undergo contrast-enhanced MRI and show Gd-related dentate nucleus hyperintensity on T1-weighted images, no resting-state functional connectivity changes were found [83].

Although research into potential long-term effects is necessary and ongoing, initial findings have not revealed any detrimental effects. This has paramount importance if routine GBCA-enhanced MRI is to be accepted as a screening procedure for women at high risk of breast cancer.

5.8 Self-Reported Gadolinium Toxicity

We should also mention a newly reported entity named “gadolinium storage condition” [42] or “gadolinium deposition disease” [84], probably more correctly defined as “self-reported gadolinium toxicity” [85, 86]. It has been proposed as a possible immediate or late effect of GBCA injection, especially by gadolinium toxicity patients support groups. A series of chronic symptoms were attributed to GBCA administration: *“clouded mentation”*; headache; central, peripheral, and bone pain; leg and arm skin thickening;

and vision and/or hearing change [42, 84–87]. Lawsuits were filed against GBCA producers. However, so far, no evidence that any GBCA actually causes these symptoms was found.

5.9 Risk-Benefit Balance of GBCAs for Screening High-Risk Women

Aforementioned considerations outline the background against which an accurate risk-benefit evaluation should be made for breast MRI screening in high-risk women. We have already discussed in Sect. 5.4 how to manage high-risk women who had previous acute reactions to GBCAs. The risk of NSF is not an issue if renal function is appropriately screened and a GBCA dose of 0.1 mmol/kg of body weight is used (see Sect. 5.6).

Three questions in relation to tissue Gd retention must now be answered.

The first question is, *Are we sure that GBCA injection is indispensable for MRI diagnosis of breast cancer? The answer is, Yes, it is.* Overall, about one in three MR examinations includes contrast enhancement [57]. *Rethinking GBCAs indications* could reduce this number, thanks both to the refinement of non-contrast MR sequences and to our ability to always make better use of them. Typical examples of these approaches are arterial spin labelling for brain perfusion, non-brain applications of DWI, and unenhanced magnetic resonance angiography. What about breast MRI screening? *So far, no evidence from prospective studies exists in favor of using non-contrast MRI for early diagnosis of breast cancer in a screening setting. If we want to screen for breast cancer using MRI in high-risk women, we need to inject GBCAs.*

The second question is, *Is the probable cumulative late effect of repeated doses of GBCAs a relevant issue for breast MRI screening? The answer is, We don't know.* If we begin MRI screening at 25 or 30 years of age and continue it well past 50 years of age due to superior sensitivity of contrast-enhanced MRI [88], we are speaking of women who could receive over 30–40 GBCA doses, i.e., 3–4 mmol/kg of body weight during lifetime. However, as discussed in the previous section, we do not know whether there is any long-term effect of repeated GBCA exposure yet.

The routine use of GBCAs for breast MRI screening of high-risk women must take into consideration what we know as well as what we do not know about tissue Gd retention. A yearly repetition of contrast injection for over 30 or 40 years is something we should not discard as irrelevant because these women are at high risk. We cannot forget that the penetrance of *BRCA1/2* deleterious mutations is not 100% (see Chap. 4). At least one in five of these women will not develop breast cancer at all.

In the absence of any demonstration of clinical effects of Gd retention, we think that *the risk-benefit ratio is in favor of contrast-enhanced screening MRI in high-risk women.*

If imaging surveillance is chosen for women at high risk of breast cancer, to the best of current knowledge, annual contrast-enhanced breast MRI remains the test of choice. Due to the fact that these women are likely to undergo a large number of repeated examinations, a principal precaution would be to avoid simple linear GBCAs in those countries where they are still available. For other breast applications such as preoperative assessment or neoadjuvant therapy, which involve only one or a few examinations, diagnostic performance is likely more important than concerns about Gd retention. In these settings, GBCAs with higher relaxivity, better able to visualize lesions, may be the agents of choice. In any case, in the MRI screening setting, the choice of the GBCA to use is in the radiologist's hands. As is well established, *the regular use of the same GBCA at a dose of 0.1 mmol/kg of body weight with a standardized injection protocol (see Sect. 5.3), as well as of standardized pulse sequences and post-processing, will facilitate the comparison of each new examination against prior examinations.* In all cases, the report of MRI screening should record the type and the dose of the GBCA used.

The risk-benefit ratio could be more problematic for a woman without relevant familial history or only dense breasts. Gd retention adds some

concern to the doubts about the use of contrast-enhanced breast MRI in women at intermediate risk for breast cancer (see Chap. 22). We discourage MRI screening in women at average risk.

5.10 Future Perspectives

Continuous reevaluation of available evidence on GBCAs late effects is needed, in particular of brain Gd retention. This field requires high-quality multicenter studies on T1 shortening of human tissues as a late effect after GBCA injection, as highlighted by the United States National Institute of Health [89]. However, it is paramount to plan studies with higher methodological quality than those we have had so far, possibly prospective in design and with minimized confounding factors, aiming to reduce the uncertainties we still have in this topic.

The research road map outlined by the 2018 NIH/ACR/RSNA Workshop [90] defined the following major priorities: to determine (a) if gadolinium retention adversely affects the function of human tissues, (b) if retention is causally associated with short- or long-term clinical manifestations of disease, and (c) if vulnerable populations, such as children, are at greater risk for experiencing clinical disease.

We agree on these priorities and also on the fact that *women undergoing breast cancer screening or men undergoing prostate cancer screening without known central nervous system abnormality* are ideal normal populations to be compared with a healthy unexposed population using standardized neurologic assessments. Conversely, we have some ethical concerns on planning studies aimed at evaluating signal intensity and/or T1 relaxation times in the brain of high-risk women who attended MRI screening programs. We would risk creating anxiety in these women without obtaining any relevant knowledge advancement.

An interesting possible research line might be GBCA dose reduction. Here, the natural candidates are high-relaxivity GBCAs such as gadobenate dimeglumine (Fig. 5.1), but this research line could also involve gadobutrol, gadoterate meglumine, or gadoteridol.

In body parts other than the breast, MRI studies have already shown good diagnostic performance of gadobenate dimeglumine administered at 75% of the standard dose (0.075 mmol/kg) for brain examinations [91], half the standard dose (0.05 mmol/kg) for the evaluation of kidney lesions [92] or for non-cirrhotic liver assessment [93], or a quarter of the standard dose (0.025 mmol/kg) for the evaluation of abdominal MRI at both 3 and 1.5 T [94, 95]. GBCA dose reduction in breast MRI has been explored by Paola Clauser and coworkers [25]. They reported on 104 women with 142 histologically verified breast lesions (109 malignant, 33 benign) using 0.75 mmol/kg of gadobenate dimeglumine at 3 T. The three readers showed a sensitivity/specificity performance of 95%/76%, 92%/73%, and 93%/88%.

Even the old simple adjustment of the contrast dose for the patient's body weight may be changed into adjustments for body composition, considering that different proportions of fat and muscle imply different biodistribution volumes for extracellular contrast agents [96], a perspective that could reduce GBCA doses in postmenopausal women.

We should not forget that more than 40 doses are expected to be injected if MRI screening starts at age 25–30 and continues at least up to the upper limit of typical mammography screening programs in Europe (70–74 years of age). Therefore, especially for women who are not mutation carriers and have a comparatively lower lifetime risk, intervals between MRIs longer than 1 year might also be explored.

MRI screening in high-risk women still remains a research field of primary interest with profound implications beyond the world of breast cancer prevention, diagnosis, and care.

While abbreviated contrast-enhanced protocols, unless performed with reduced contrast doses, do not reduce the concerns about Gd retention, the most intriguing future scenario for breast MRI screening is to bypass contrast agent administration. Unenhanced MRI protocols (mainly based on DWI and T2-weighted short-tau-inversion-recovery or turbo-spin-echo sequences) [97–100] were investigated with interesting results, especially for mass-type lesions.

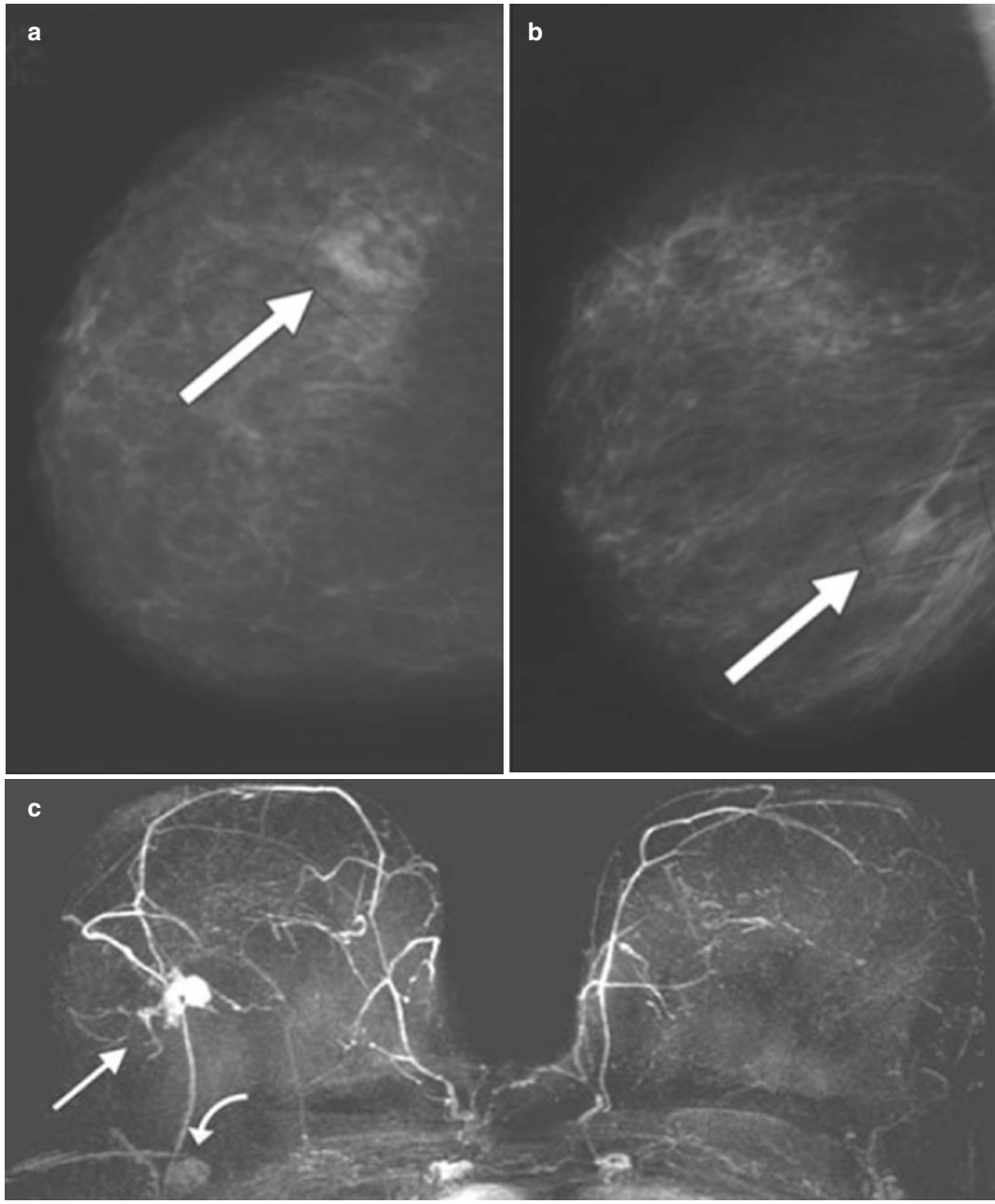


Fig. 5.1 A 54-year-old woman with pathologically diagnosed invasive lobular carcinoma. Mammography: Craniocaudal (**a**) and mediolateral oblique (**b**) views show irregular mass in the lower outer quadrant (arrow in **a** and **b**). The patient had an estimated glomerular filtration rate of 55 ml/min × 1.73 m^2. Due to concerns regarding the risk of nephrogenic systemic fibrosis, half dose of gadobenate dimeglumine (0.05 mmol/kg) was used. (**c**) Axial maximum intensity projection shows unifocal mass enhancement (straight arrow) with a 21 mm diameter. Asymmetric vascular maps are well defined, also showing feeding vessels. Suspicious axillary lymph node (curved arrow) was also detected. At pathologic examination, 4 of 15 dissected lymph nodes were positive for tumor metastasis. (**d**) Graph shows washout dynamic curve (on *x*-axis, time reported as min:s; on *y*-axis, percentage of signal intensity increase) (*Reproduced with permission from: Carbonaro* et al., *AJR Am J Roentgenol 2011* [16]. Request of permission submitted to the publisher (ARRS) on Jan 14, 2019)

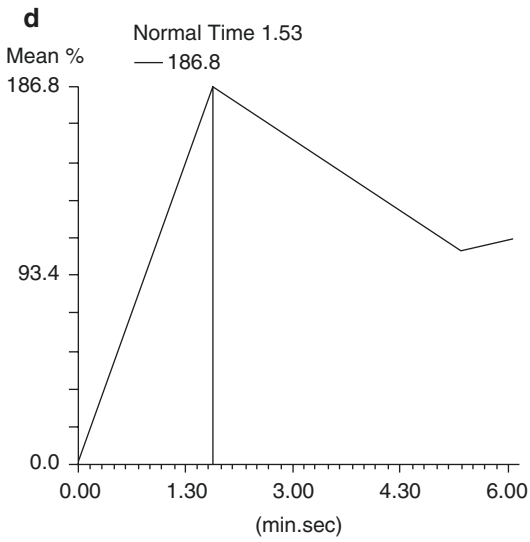


Fig. 5.1 (continued)

However, lesion conspicuity and visibility was reduced in unenhanced sequences, and no prospective study using unenhanced MRI screening protocols has been published so far.

Thus, we confirm the indication for yearly GBCA-enhanced breast MRI screening for high-risk women. While waiting for clinical application of new approaches, a word of caution should be said on the introduction of breast MRI screening for non-high-risk women. Possible late effects of dozens of GBCA injections pose the following dilemma: *the absence of evidence is not the evidence of absence but also that the evidence of presence is not an evidence of harm.* When offering breast MRI screening, we must always inform women about the risk-benefit balance; for non-high-risk women, we must also strive to communicate a higher grade of uncertainty, as a transparent approach fostering patient empowerment [101].

References

1. Heywang SH, Hahn D, Schmidt H et al (1986) MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr 10:199–204
2. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
3. Morris EA, Comstock CE, Lee CH et al (2013) ACR BI-RADS Magnetic Resonance Imaging. In: American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
4. Mann RM, Balleyguier C, Baltzer PA et al; European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678
5. Wernli KJ, DeMartini WB, Ichikawa L et al; Breast Cancer Surveillance Consortium (2014) Patterns of breast magnetic resonance imaging use in community practice. JAMA Intern Med 174:125–132
6. Clauser P, Mann R, Athanasiou A et al (2018) A survey by the European Society of Breast Imaging on the utilisation of breast MRI in clinical practice. Eur Radiol 28:1909–1918
7. Heywang-Kobrunner SH, Beck R (1995) Contrast enhanced MRI of the breast, 2nd edn. Springer, Berlin
8. Lin SP, Brown JJ (2007) MR contrast agents: physical and pharmacologic basics. J Magn Reson Imaging 25:884–899
9. Ersoy H, Rybicki FJ (2007) Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. J Magn Reson Imaging 26:1190–1197
10. Aime S, Caravan P (2009) Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging 30:1259–1267
11. Port M, Idée JM, Medina C, Robic C, Sabatou M, Corot C (2008) Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. Biometals 21:469–490
12. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ (2005) Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 40:715–724
13. Pintaske J, Martirosian P, Graf H et al (2006) Relaxivity of gadopentetate dimeglumine (Magnevist), gadobutrol (Gadovist), and gadobenate Dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. Invest Radiol 41:213–221. Erratum in. Invest Radiol 41:859
14. Giesel FL, von Tengg-Kobligk H, Wilkinson ID et al (2006) Influence of human serum albumin on longitudinal and transverse relaxation rates (r1 and r2) of magnetic resonance contrast agents. Invest Radiol 41:222–228
15. Bellin MF, Van Der Molen AJ (2008) Extracellular gadolinium-based contrast media: an overview. Eur J Radiol 66:160–167
16. Carbonaro LA, Pediconi F, Verardi N, Trimboli RM, Calabrese M, Sardanelli F (2011) Breast MRI using a high-relaxivity contrast agent: an overview. AJR Am J Roentgenol 196:942–955

17. Pediconi F, Catalano C, Occhiato R et al (2005) Breast lesion detection and characterization at contrast-enhanced MR mammography: gadobenate dimeglumine versus gadopentetate dimeglumine. Radiology 237:45–56
18. Pediconi F, Catalano C, Padula S et al (2008) Contrast-enhanced MR mammography: improved lesion detection and differentiation with gadobenate dimeglumine. AJR Am J Roentgenol 191: 1339–1346
19. Knopp MV, Bourne MW, Sardanelli F et al (2003) Gadobenate dimeglumine-enhanced MRI of the breast: analysis of dose response and comparison with gadopentetate dimeglumine. AJR Am J Roentgenol 181:663–676
20. Martincich L, Faivre-Pierret M, Zechmann CM et al (2011) Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for breast MR imaging (DETECT Trial). Radiology 258:396–408
21. Gilbert FJ, van den Bosch HC, Petrillo A et al (2014) Comparison of gadobenate dimeglumine-enhanced breast MRI and gadopentetate dimeglumine-enhanced breast MRI with mammography and ultrasound for the detection of breast cancer. J Magn Reson Imaging 39:1272–1286
22. Pediconi F, Kubik-Huch R, Chilla B, Schwenke C, Kinkel K (2013) Intra-individual randomised comparison of gadobutrol 1.0 M versus gadobenate dimeglumine 0.5 M in patients scheduled for preoperative breast MRI. Eur Radiol 23:84–92
23. Schneider G, Fries P (2013) Intra-individual randomised comparison of gadobutrol 1.0 M versus gadobenate dimeglumine 0.5 M in patients scheduled for preoperative breast MRI. Eur Radiol 23:2095–2096
24. Kinkel K, Schwenke C, Kubik-Huch R, Pediconi F (2013) Intra-individual randomised comparison of gadobutrol 1.0 M versus gadobenate dimeglumine 0.5 M in patients scheduled for preoperative breast MRI. Eur Radiol 23:2097–2099
25. Clauser P, Helbich TH, Kapetas P et al (2019) Breast lesion detection and characterization with contrast-enhanced magnetic resonance imaging: Prospective randomized intraindividual comparison of gadoterate meglumine (0.15 mmol/kg) and gadobenate dimeglumine (0.075 mmol/kg) at 3T. J Magn Reson Imaging 49:1157–1165
26. Renz DM, Durmus T, Böttcher J et al (2014) Comparison of gadoteric acid and gadobutrol for detection as well as morphologic and dynamic characterization of lesions on breast dynamic contrast-enhanced magnetic resonance imaging. Invest Radiol 49:474–484
27. Fallenberg EM, Renz DM, Karle B et al (2015) Intraindividual, randomized comparison of the macrocyclic contrast agents gadobutrol and gadoterate meglumine in breast magnetic resonance imaging. Eur Radiol 25:837–849
28. Sardanelli F, Fausto A, Podo F (2008) MR spectroscopy of the breast. Radiol Med 113:56–64
29. Sardanelli F, Fausto A, Di Leo G, de Nijs R, Vorbuchner M, Podo F (2009) In vivo proton MR spectroscopy of the breast using the total choline peak integral as a marker of malignancy. AJR Am J Roentgenol 192:1608–1617
30. Baltzer PA, Dietzel M (2013) Breast lesions: diagnosis by using proton MR spectroscopy at 1.5 and 3.0 T—systematic review and meta-analysis. Radiology 267:735–746
31. Podo F, Sardanelli F, Iorio E et al (2007) Abnormal choline phospholipid metabolism in breast and ovary cancer: molecular bases for noninvasive imaging approaches. Curr Med Imaging Rev 3:123–137
32. Cheng M, Bhujwalla ZM, Glunde K (2016) Targeting phospholipid metabolism in cancer. Front Oncol 6:266
33. Podo F, Paris L, Cecchetti S et al (2016) Activation of phosphatidylcholine-specific phospholipase C in breast and ovarian cancer: impact on MRS-detected choline metabolic profile and perspectives for targeted therapy. Front Oncol 6:171
34. Lenkinski RE, Wang X, Elian M, Goldberg SN (2009) Interaction of gadolinium-based MR contrast agents with choline: implications for MR spectroscopy (MRS) of the breast. Magn Reson Med 61:1286–1292
35. Baltzer PA, Gussew A, Dietzel M et al (2012) Effect of contrast agent on the results of in vivo ^{1}H MRS of breast tumors—is it clinically significant? NMR Biomed 25:67–74
36. Sardanelli F, Carbonaro LA, Montemezzi S, Cavedon C, Trimboli RM (2016) Clinical breast MR using MRS or DWI: who is the winner? Front Oncol 6:217
37. Tomassin-Naggara I, De Bazelaire C, Chopier J, Bazot M, Marsault C, Trop I (2013) Diffusion-weighted MR imaging of the breast: advantages and pitfalls. Eur J Radiol 82:435–443
38. Janka R, Hammon M, Geppert C, Nothhelfer A, Uder M, Wenkel E (2014) Diffusion-weighted MR imaging of benign and malignant breast lesions before and after contrast enhancement. Rofo 186: 130–135
39. Montemezzi S, Cavedon C, Camera L et al (2017) 1H-MR spectroscopy of suspicious breast mass lesions at 3T: a clinical experience. Radiol Med 122:161–170
40. American College of Radiology (2018) Manual on contrast media v10.3. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed 30 Jun 2020
41. 10.0 Contrast Media Safety Guidelines, ESUR Guidelines. http://www.esur-cm.org/index.php/en/e-appendix-2. Accessed 30 Jun 2020
42. Semelka RC, Ramalho M, AlObaidy M, Ramalho J (2016) Gadolinium in humans: A family of disorders. AJR Am J Roentgenol 207:229–233

43. Jordan RM, Mintz RD (1995) Fatal reaction to gadopentetate dimeglumine. AJR Am J Roentgenol 164:743–744
44. Okigawa T, Utsunomiya D, Tajiri S et al (2014) Incidence and severity of acute adverse reactions to four different gadolinium–based MR contrast agents. Magn Reson Med Sci 13:1–6
45. Jung JW, Kang HR, Kim MH et al (2012) Immediate hypersensitivity reaction to gadolinium–based MR contrast media. Radiology 264:414–422
46. Hunt CH, Hartman RP, Hesley GK (2009) Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. AJR Am J Roentgenol 193:1124–1127
47. Lasser EC, Berry CC, Talner LB et al (1987) Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. N Engl J Med 317:845–849
48. Greenberger PA, Patterson R (1991) The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. J Allergy Clin Immunol 87:867–872
49. Ryoo CH, Choi YH, Cheon JE et al (2019) Preventive effect of changing contrast media in patients with a prior mild immediate hypersensitivity reaction to gadolinium-based contrast agent. Invest Radiol 54:633–637
50. Morzycki A, Bhatia A, Murphy KJ (2017) Adverse reactions to contrast material: a canadian update. Can Assoc Radiol J 68:187–193
51. Espinosa LA, Daniel BL, Vidarsson L, Zakhour M, Ikeda DM, Herfkens RJ (2005) The lactating breast: contrast-enhanced MR imaging of normal tissue and cancer. Radiology 237:429–436
52. Cova MA, Stacul F, Quaranta R et al (2014) Radiological contrast media in the breastfeeding woman: a position paper of the Italian Society of Radiology (SIRM), the Italian Society of Paediatrics (SIP), the Italian Society of Neonatology (SIN) and the Task Force on Breastfeeding, Ministry of Health, Italy. Eur Radiol 24:2012–2022
53. Grobner T (2006) Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 21:1104–1108
54. Heverhagen JT, Krombach GA, Gizewski E (2014) Application of extracellular gadolinium-based MRI contrast agents and the risk of nephrogenic systemic fibrosis. Rofo 186:661–669
55. Abraham JL, Thakral C, Skov L, Rossen K, Marckmann P (2008) Dermal inorganic gadolinium concentrations: evidence for in vivo transmetallation and long-term persistence in nephrogenic systemic fibrosis. Br J Dermatol 158:273–280
56. Endrikat J, Vogtlaender K, Dohanish S, Balzer T, Breuer J (2016) Safety of gadobutrol: results from 42 clinical Phase II to IV studies and postmarketing surveillance after 29 million applications. Invest Radiol 51:537–543
57. Larson KN, Gagnon AL, Darling MD, Patterson JW, Cropley TG (2015) Nephrogenic systemic fibrosis manifesting a decade after exposure to Gadolinium. JAMA Dermatol 151:1117–1120
58. Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR (2019) A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. Radiology 292:376–386
59. Colletti PM (2008) Nephrogenic systemic fibrosis and gadolinium: a perfect storm. AJR Am J Roentgenol 191:1150–1153
60. Thomsen HS (2014) NSF: still relevant. J Magn Reson Imaging 40:11–12
61. Prince MR, Zhang H, Morris M et al (2008) Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology 248:807–816
62. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D (2014) High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 270:834–841
63. Radbruch A, Weberling LD, Kieslich PJ et al (2015) Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 275:783–791
64. Gibby WA, Gibby KA, Gibby WA (2004) Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. Invest Radiol 39:138–142
65. White GW, Gibby WA, Tweedle MF (2006) Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. Invest Radiol 41:272–278
66. European Medicines Agency (2017). https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents. Accessed 30 Jun 2020
67. American College of Radiology (2017) ACR response to the European PRAC recommendations. https://www.acr.org/About-Us/Media-Center/Press-Releases/2017-Press-Releases/20170404-ACR-Response-to-the-European-PRAC-Recommendations. Accessed 30 Jun 2020
68. Unites States Food and Drug Administration (2017) Gadolinium-based contrast agents for magnetic resonance imaging (MRI): drug safety communication—no harmful effects identified with brain retention. https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm559709.htm. Accessed 30 Jun 2020
69. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S (2016) Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with

cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. Eur Radiol 26:807–815
70. Bjørnerud A, Vatnehol SAS, Larsson C, Due-Tønnessen P, Hol PK, Groote IR (2017) Signal enhancement of the dentate nucleus at unenhanced MR imaging after very high cumulative doses of the macrocyclic gadolinium-based contrast agent gadobutrol: an observational study. Radiology 285:434–444
71. Rossi Espagnet MC, Bernardi B, Pasquini L, Figà-Talamanca L, Tomà P, Napolitano A (2017) Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol 47:1345–1352
72. Splendiani A, Perri M, Marsecano C et al (2018) Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. Radiol Med 123:125–134
73. Kelemen P, Alaoui J, Sieron D et al (2018) T1-weighted grey matter signal intensity alterations after multiple administrations of gadobutrol in patients with multiple sclerosis, referenced to white matter. Sci Rep 8:16844
74. Moreno J, Vaz NB, Soler JC et al (2018) High signal intensity in the dentate nucleus on unenhanced T1-weighted MR images in melanoma patients receiving macrocyclic gadolinium-based contrast. J Radiol Diagn Methods 1:101–107
75. Murata N, Gonzalez-Cuyar LF, Murata K et al (2016) Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: preliminary results from 9 patients with normal renal function. Invest Radiol 51:447–453
76. Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB; International Society for Magnetic Resonance in Medicine (2017) Gadolinium deposition in the brain: summary of evidence and recommendations. Lancet Neurol 16:564–570
77. McDonald RJ, McDonald JS, Dai D et al (2017) Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. Radiology 285:536–545
78. Bussi S, Coppo A, Botteron C et al (2018) Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats. J Magn Reson Imaging 47:746–752
79. Forslin Y, Shams S, Hashim F et al (2017) Retention of gadolinium-based contrast agents in multiple sclerosis: retrospective analysis of an 18-year longitudinal study. AJNR Am J Neuroradiol 38:1311–1316
80. Cocozza S, Pontillo G, Lanzillo R et al (2019) MRI features suggestive of gadolinium retention do not correlate with Expanded Disability Status Scale worsening in Multiple Sclerosis. Neuroradiology 61:155–162
81. Ackermans N, Taylor C, Tam R et al (2019) Effect of different doses of gadolinium contrast agent on clinical outcomes in MS. Mult Scler J Exp Transl Clin 5(1):2055217318823796
82. Welk B, McArthur E, Morrow SA et al (2016) Association between gadolinium contrast exposure and the risk of parkinsonism. JAMA 316:96–98
83. Mallio CA, Piervincenzi C, Gianolio E et al (2019) Absence of dentate nucleus resting–state functional connectivity changes in nonneurological patients with gadolinium–related hyperintensity on T1–weighted images. J Magn Reson Imaging 50:445–455
84. Semelka RC, Ramalho J, Vakharia A et al (2016) Gadolinium deposition disease: Initial description of a disease that has been around for a while. Magn Reson Imaging 34:1383–1390
85. Burke LM, Ramalho M, AlObaidy M, Chang E, Jay M, Semelka RC (2016) Self-reported gadolinium toxicity: a survey of patients with chronic symptoms. Magn Reson Imaging 34:1078–1080
86. Lord ML, FE MN, Gräfe JL, Noseworthy MD, Chettle DR (2018) Self-identified gadolinium toxicity: comparison of gadolinium in bone and urine to healthy gadolinium-based contrast agent exposed volunteers. Physiol Meas 39:115008
87. Ramalho J, Ramalho M (2017) Gadolinium deposition and chronic toxicity. Magn Reson Imaging Clin N Am 25:765–778
88. Phi XA, Houssami N, Obdeijn IM et al (2015) Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age $\geq$ 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol 33:349–356
89. Malayeri AA, Brooks KM, Bryant LH et al (2016) National Institutes of Health perspective on reports of gadolinium deposition in the brain. J Am Coll Radiol 13:237–241
90. McDonald RJ, Levine D, Weinreb J et al (2018) Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. Radiology 289(2):517–534
91. Khouri Chalouhi K, Papini GD, Bandirali M et al (2014) Less is better? Intraindividual and interindividual comparison between 0.075 mmol/kg of gadobenate dimeglumine and 0.1 mmol/kg of gadoterate meglumine for cranial MRI. Eur J Radiol 83:1245–1249
92. Schneider G, Probst T, Kirchin MA, Stroeder J, Fries P, Buecker A (2015) Low-dose gadobenate dimeglumine-enhanced MRI of the kidney for the differential diagnosis of localized renal lesions. Radiol Med 120:1100–1111
93. Homayoon B, Diwakar H, Strovski E et al (2014) Half-dose gadobenate dimeglumine versus standard-dose gadodiamide in dynamic magnetic resonance imaging of non-cirrhotic livers: a retrospective intra-individual crossover comparison. Abdom Imaging 39:955–962

94. de Campos RO, Heredia V, Ramalho M et al (2011) Quarter-dose (0.025 mmol/kg) gadobenate dimeglumine for abdominal MRI in patients at risk for nephrogenic systemic fibrosis: preliminary observations. AJR Am J Roentgenol 196:545–552
95. Ramalho M, AlObaidy M, Busireddy KK, Altun E, Liu B, Semelka RC (2015) Quantitative and qualitative comparison of 0.025 mmol/kg gadobenate dimeglumine for abdominal MRI at 1.5T and 3T MRI in patients with low estimated glomerular filtration rate. Eur J Radiol 84:26–32
96. Zanardo M, Doniselli FM, Esseridou A et al (2018) Abdominal CT: a radiologist-driven adjustment of the dose of iodinated contrast agent approaches a calculation per lean body weight. Eur Radiol Exp 2:41
97. Baltzer PA, Benndorf M, Dietzel M, Gajda M, Camara O, Kaiser WA (2010) Sensitivity and specificity of unenhanced MR mammography (DWI combined with T2-weighted TSE imaging, ueMRM) for the differentiation of mass lesions. Eur Radiol 20:1101–1110
98. Trimboli RM, Verardi N, Cartia F, Carbonaro LA, Sardanelli F (2014) Breast cancer detection using double reading of unenhanced MRI including T1-weighted, T2-weighted STIR, and diffusion-weighted imaging: a proof of concept study. AJR Am J Roentgenol 203:674–681
99. Telegrafo M, Rella L, Stabile Ianora AA, Angelelli G, Moschetta M (2015) Unenhanced breast MRI (STIR, T2-weighted TSE, DWIBS): An accurate and alternative strategy for detecting and differentiating breast lesions. Magn Reson Imaging 33: 951–955
100. Shin HJ, Chae EY, Choi WJ et al (2016) Diagnostic performance of fused diffusion-weighted imaging using unenhanced or postcontrast T1-weighted MR imaging in patients with breast cancer. Medicine (Baltimore) 95:e3502
101. Sardanelli F, Cozzi A, Trimboli RM, Schiaffino S (2020) Gadolinium deposition/retention and breast MRI screening: more harm than good? AJR Am J Roentgenol 214:324–327

6 Applying the MRI BI-RADS in a High-Risk Population

Paola Clauser and Chiara Zuiani

Abbreviations

ACR	American College of Radiology
ADC	Apparent diffusion coefficient
BI-RADS	Breast Imaging Reporting and Data System
BPE	Background parenchymal enhancement
DWI	Diffusion-weighted imaging
MRI	Magnetic resonance imaging
PPV	Positive predictive value
US	Ultrasonography/Ultrasound

6.1 Introduction

Contrast-enhanced magnetic resonance imaging (MRI) is the imaging method with the highest sensitivity for breast cancer detection, reported to be between 71% and 100% by high-risk screening studies [1]. Breast MRI is not limited by breast density [2–4] and does not make use of radiation. MRI is not only able to identify the majority of invasive and in situ carcinomas, but it also shows several benign lesions that might not be evident on mammography and ultrasound. In a screening setting, it is of outmost importance to be able to differentiate benign from suspicious findings, in order to avoid unnecessary follow-up controls or biopsies. Although good, specificity values for breast MRI, ranging from 75% to 98%, were reported to be lower as compared to mammography, a limitation counterbalanced by the higher sensitivity of MRI [1]. Currently, MRI is indicated as the screening modality of choice in high-risk women, usually along with mammography [5–8].

The American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS), now available as fifth edition [9], was firstly introduced in the early 1990s in order to standardize terminology, report organization, assess the structure, and give a classification system for breast imaging; in 2003, a section dedicated to breast MRI was also added to the fourth edition [10]. The BI-RADS lexicon has also been used to report on MRI performed in high-risk women, with the aim of facilitating management and allowing comparisons of MRI versus mammography and ultrasonography (US), as well as comparisons across different studies.

Despite the high sensitivity and specificity of breast MRI, in particular for the characterization of mass lesions, there are still open issues for the

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application of BI-RADS, in particular in the screening setting: the difficulty in interpreting moderate and marked *background parenchymal enhancement* (BPE) and the management of probably benign findings, i.e., the use of the BI-RADS 3 diagnostic category.

6.2 MRI BI-RADS and Its Use in the General Population

After the introduction of a dedicated lexicon for breast MRI [10], most of the diagnostic performance studies used the BI-RADS for lesion classification and evaluation of diagnostic performance. In fact, the BI-RADS lexicon is easy to introduce into clinical practice and allows a high accuracy for lesion detection and characterization [11]. The breast radiologist can chose one of seven diagnostic categories, from 0 to 6 (Table 6.1), which define different levels of risk and suggest different management for the findings [9]. Of note, these categories can be applied to an individual lesion, to one breast, or to one patient overall.

The general application of BI-RADS is not trivial and is related to the operational nature of these categories. For instance, when you are staging an already known cancer, if you do not detect any other finding suspicious for an ipsilateral or contralateral additional lesion, the examination should be categorized as BI-RADS 6; however, if you find an additional lesion deserving biopsy, the examination will become BI-RADS 4 or 5.

Table 6.1 Description of the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) classification system for breast MRI [12]

Category	Clinical meaning	Level of risk	Suggested management
0	Inconclusive findings	Unknown	Further imaging
1	Normal breast, no lesions	Essentially 0%	Control in screening interval
2	Benign lesion	Essentially 0%	Control in screening interval
3	Probably benign lesion	>0% but ≤2%	Control within 6 months or biopsy
4	Suspicious	>2% but <95%	Biopsy; if benign, control
5	Highly suspicious	≥95%	Biopsy; if benign, repeat
6	Known breast cancer	–	To therapy

Since the first editions, one of the main BI-RADS limitations has been the relatively low reproducibility and its moderate inter-reader agreement for different aspects of the lexicon [10, 13–15]. In particular regarding the evaluation of breast density and BPE, inter-reader agreement has been reported to be only from fair to moderate [13, 14]. The largest source of disagreement is in the application of lesion descriptors [13, 14]. Despite this variability, the studies also showed a good agreement in terms of management of suspicious findings, irrespectively of their description and also initial classification (notably, irrespectively of whether a suspicious finding is classified as BI-RADS 4 or 5, its management remains the same, i.e., to send the patients to needle biopsy) [13, 14].

The highest variability, both in lesion description and in management, has been found for the assessment of probably benign lesions, classified as BI-RADS 3 [13, 14]. As reported by Lars J. Grimm and coworkers [14], when readers were asked to decide on the benign or malignant nature of a BI-RADS 3 finding, a wide discrepancy was seen. This is probably related to the fact that, as stated in the BI-RADS, "the use of category 3 assessment at MRI remains intuitive" [12]. This variability implies also a widely variable management for women with probably benign lesions, ranging from controls in screening intervals to biopsy.

Of note, the BI-RADS is not only currently used worldwide. It has been an example followed by similar reporting systems adapted for other organs, such as prostate and liver [16, 17].

As already underlined, BI-RADS categories define different levels of risk (Table 6.1) [9]. There is a wide variability in the level of risk within the BI-RADS 4 category. Beginning with the fourth edition [10], a subcategorization that divided BI-RADS 4 in three further groups has been introduced: BI-RADS 4A (>2% but ≤10%,

low suspicion for malignancy), BI-RADS 4B (>10% but ≤50%, intermediate suspicion for malignancy), and BI-RADS 4C (>50% but <95%, moderate concern but not classic for malignancy). This risk stratification is important in the definition of clinical management after biopsy. In clinical practice, a benign histopathological result will be concordant with a BI-RADS 4A lesion but not for a BI-RADS 4C finding. In the latter, re-biopsy or surgical excision may be indicated. The introduction of this stratification was possible, thanks to the extensive amount of literature available analyzing mammographic and sonographic features of breast lesions [18–21].

The same stratification proved to be more difficult for breast MRI. First of all, MRI is a relatively new technique, compared to mammography and ultrasound, and its widespread introduction in breast imaging relatively recent [22, 23]. Furthermore, it is only in the last two decades that strong efforts have been made in order to ensure the use of standardized protocols [7, 8, 24]. Thus, the variability in image acquisition and terminology in the first years of research in breast MRI made a systematical evaluation of imaging features difficult. At the same time, MRI is an evolving technique, with new imaging features and sequences in constant analysis and development [25]. Roberta M. Strigel and coworkers [26] were recently able to stratify the risk of malignancy for BI-RADS 4 findings in more of 90% of the initially MRI BI-RADS 4 lesions found during screening in high-risk women. Using this risk stratification, they obtained a PPV with MRI that met the ranges set in BI-RADS for mammography and ultrasound, proving the feasibility of risk stratification also in breast MRI. In 8.5% of the cases, the readers were not able to further categorize the finding, indicating there is still place for improvement in image interpretation. Of note, in their work, they did not specify which imaging features indicated higher or lower probability of malignancy but rather stated that categorization was done at discretion of the interpreting radiologist on the basis of personal experience and on the known PPV of established MRI descriptors [26]. It is likely that the increasing amount of evidence available and the identification of further lesion features will allow this risk stratification to be introduced also in the MRI BI-RADS [26–29]. The additional use of DWI and the measurement of ADC values could be also a valuable additional tool in the categorization of suspicious breast findings [11, 30, 31].

6.3 Performance of MRI BI-RADS in High-Risk Screening

The vast majority of studies that analyzed the usefulness of breast MRI as a screening modality in high-risk women used the BI-RADS lexicon for lesion classification [3, 4, 32–39]. Careful and repeatable evaluations along with clear indications regarding the management are of particular importance in a screening setting. The positive predictive value (PPV) of a series of breast MRI screening studies applying BI-RADS is shown in Table 6.2, along with the recall rate, if reported. However, we should consider here that criteria for calculating these indices were not always the same in these studies.

One first methodological point is how dichotomize the BI-RADS classes into negative or positive results, i.e., how to classify BI-RADS 0 and BI-RADS 3 (BI-RADS 1 and 2 are certainly negative; BI-RADS 4 and 5 are certainly positive). The reader can note in Table 6.2 that some studies considered the BI-RADS 3 category as negative, and others considered the same category as positive. This difference partly explains the different reported PPVs. This is not a trivial point.

It is generally accepted that in a *diagnostic* setting (i.e., in symptomatic patients), a BI-RADS 3 can be included among negative results. The principle here is that if, in the presence of symptoms, we could postpone further assessment up to 6 months (as per BI-RADS 3 category definition), we consider the overall case as not suspicious to deserve immediate workup. Thus, the case is more negative than positive. Conversely, in a *screening* setting, planning further assessment up to 6 months after is a relevant deviation from sending the woman to the next screening

Table 6.2 Recall rate and positive predictive value according to major published studies investigating MRI as a screening tool in women at increased risk for breast cancer

Study	Screened women	Recall rate	Positive predictive value
Kuhl et al. (2005) [34]	529	NR	50.0% for BI-RADS 4 and 5
Leach et al. (2005) [32]	649	10.7%	7.3% for BI-RADS 0, 3, 4, and 5
Lehman et al. (2007) [35]	171	24.0%	42.8%[a] for BI-RADS 3, 4. and 5
Kuhl et al. (2010) [3]	687	NR	48.0% for BI-RADS 4 and 5
Sardanelli et al. (2011) [4]	501	NR	56.0% for BI-RADS 4 and 5
Chiarelli et al. (2014) [36]	2,150	15.1%	7.1% for immediate further testing
Riedl et al. (2015) [37]	559	NR	19.7% for BI-RADS 4 and 5
Narayan et al. (2016) [38]	235	27.9%	4.2% (PPV1), 6.7% (PPV2), 10.8% (PPV3)
Healy et al. (2016) [39]	715	10.9%	NR

NR not reported
PPV1 positive predictive value 1 = cancers/(cancers + further assessments or recalls)
PPV2 positive predictive value 2 = cancers/(cancers + biopsies recommended)
PPV3 positive predictive value 3 = cancers/(cancers + biopsies performed)
[a]PPV of biopsies performed based on MRI

round. It is a recall (even not immediate but postponed). The case is more positive than negative. The difference is given by different disease prevalence between the two settings: higher in the diagnostic setting and lower in the screening setting.

However, this way of reasoning firmly holds when we compare a diagnostic setting with screening mammography in the general population, with a disease prevalence extremely different, suppose 5%, 10%, or 20% and 0.3%, respectively. High-risk screening always implies a low prevalence, but also ten times higher than that of screening mammography in the general population, suppose over 3% (as reported in the HIBCRIT study [4]). In the presence of a strongly increased underlying risk with associated high speed of cancer growth (such as in *BRCA*, especially *BRCA1*, mutation carriers), the decision to postpone the assessment up to 6 months is more a negative judgment than a positive one. Thus, the attribution of BI-RADS 3 in the context of screening studies on women with an increased risk of breast cancer can be a matter for debate. The risk stratification is here a key aspect: higher the risk, more negative should be the impression of a BI-RADS 3 findings. Sensitivities, specificities, and predictive values require dichotomization, i.e., in these conditions, a forced simplification. Receiver operating characteristics analysis can offer here a more appropriate approach.

Important to note in this context (and reinforcing the concept of BI-RADS 3 as negative in the high-risk women) is the possibility that malignant lesions in this population present at mammography and US with features that suggest benignity and would not, per se, prompt biopsy [40, 41]. Cancer types that are more frequently encountered in women with a *BRCA1* mutation might present at mammography and US as round or oval masses, with relatively smooth margins and only slightly inhomogeneity on US [41–43]. This is a rather common appearance for aggressive, fast-growing tumors in the absence of substantial desmoplastic reaction around the lesion [41, 44]. While these lesions might pose a diagnostic dilemma in mammography and ultrasound, the same does not seem to be true for breast MRI. A careful evaluation not only of shape and margin of the lesions but also of the enhancement characteristics, of kinetic curve of enhancement, and of associated non-enhancing findings, as according to BI-RADS [12], allows for a good lesion characterization and a correct classification [43, 45, 46]. This implies that some apparently benign findings should be diagnosed as BI-RADS 4 and biopsied.

These theoretical and practical problems are important for the comparability of screening studies of women at increased risk of breast cancer. As also explained in Chap. 15, specificity tends to reach very high levels in all screening programs due to the very high probability of true negatives. Thus, a different way to evaluate the

weight of false positives is to calculate the *recall rate*. It includes the false positives and the true positives related to the number of women screened. Being usually the false positives much more than the true positive, the recall rate gives a practical measure of the impact of false positive on the screening program.

A more efficient way to consider false positives is to differentiate PPVs into PPV1, PPV2, and PPV3. While the numerator is always the number of cancers finally found, the PPV1 considers at the numerator all the cases recalled for further workup, the PPV2 the cases for which biopsy has been recommended, and the PPV3 only the cases for which biopsy has been performed. This approach gives us a more detailed description of the impact of false positives on the women screened. Bethany L. Niell and coworkers [47] reported on "auditing a breast MRI practice" presenting data on 2,444 examinations, 1,313 for screening, and 1,131 for diagnostic indications. Their interesting results are summarized in Table 6.3. The reader can appreciate the basic difference in using MRI in a diagnostic or a screening setting.

Table 6.3 Performance of breast MRI in the screening and diagnostic setting (data from Bethany L. Niell and coworkers [47])

	Screening (n = 1,313)	Diagnostic (n = 1,131)	Overall (n = 2,444)
Cancer detection rate	1.4%	4.7%	2.9%
BI-RADS 3	21%	28%	24%
Positive results (BI-RADS 0, 4, and 5)	12%	17%	14%
PPV 1	12%	28%	21%
PPV 2	24%	36%	32%
PPV 3	27%	38%	35%

PPV1 positive predictive value 1 = cancers/(cancers + further assessments or recalls)
PPV2 positive predictive value 2 = cancers/(cancers + biopsies recommended)
PPV3 positive predictive value 3 = cancers/(cancers + biopsies performed)
For cancer detection rate, BI-RADS 3, positive results, and PPV1, comparisons between screening and diagnostic setting with $p < 0.001$. For PPV2 and PPV3, only a trend for significance can be observed ($p = 0.079$ and $p = 0.103$, respectively, χ^2 test)

BI-RADS 0, the category of "inconclusive findings" for which further not postponed imaging is required, is usually considered a kind of positive result in both the diagnostic and the screening setting [47].

Finally, we should consider that, as also in non-high-risk women, while MRI BI-RADS descriptors are very helpful for the characterization of mass enhancements (in particular when the lesion diameter is equal to or greater than 5 mm), the same is not true for foci (less than 5 mm in diameter) and non-mass enhancement. Of note, the term *focus* has to be used when the small lesion (less than 5 mm in diameter) cannot be morphologically characterized due to insufficient spatial resolution; when it has suspicious features, the term *mass* should be preferred.

6.4 Background Parenchymal Enhancement in High-Risk Screening

The BPE is defined as the enhancement of the normal fibroglandular tissue of the breast [12]. Its presence is usually related to hormonal stimulation, and it shows fluctuations related with the hormonal phase [48–50]. According to the BI-RADS lexicon, BPE is classified in four categories, as is for breast density. These four categories are minimal, mild, moderate, and marked [12].

The intensity of BPE is not related to the density of breast parenchyma, which means that a woman with very dense breasts might not have a strong BPE on MRI. Being strongly related to hormonal stimulation, BPE tends to be more frequently seen in younger women [48, 50, 51]. Because high-risk women have to start screening at a young age, BPE is a rather common finding in this women subgroup.

BPE is usually symmetric, and it can be easily distinguished from a pathologic non-mass enhancement, as it generally lacks the distribution and the internal patterns typical of suspicious lesions [52]. However, when BPE appears with atypical distribution or features, it is difficult to safely discard it as non-suspicious. In

these selected cases, a short-term follow-up within 2–3 months, carefully considering the hormonal phase, can be considered as adequate [42, 53, 54]. The availability of previous examinations for comparison can be useful in order to avoid unnecessary controls. Also, the evaluation of mammographic and US images, when available, could be of help in defining a diagnosis.

Several studies already showed that the presence of BPE does not reduce the sensitivity of breast MRI. Even in a breast MRI with marked BPE, a malignant lesion is usually recognizable and distinguishable [53–55]. Rather than hide a suspicious lesions, moderate and marked BPE might complicate lesion evaluation and increase the number of additional unclear or probably benign MRI findings [54, 55].

6.5 Probably Benign Lesions: How to Manage Them?

Probably benign lesions (BI-RADS 3 diagnostic category) are described by the BI-RADS as findings with a "≤2% likelihood of malignancy but greater than the essentially 0% likelihood of malignancy of a characteristically benign finding" [9]. The lexicon continues by stating that "a probably benign finding is not expected to change over the suggested period of imaging surveillance, but the interpreting physician prefers to establish stability of the finding before recommending management limited to routine breast screening" [9]. This means, there are no specific lesions and no defined characteristics that allow to univocally identifying a finding as probably benign. Rather, a lesion is classified as BI-RADS 3 when it lacks of clearly benign characteristics and, at the same time, does not present features that hint at a malignant finding (Fig. 6.1). The attribution of BI-RADS 3 category, in particular in breast MRI, is *intuitive*, practically resulting from the inappropriateness of the other categories, in particular the two closest in the ordinal ranking, BI-RADS 2 and BI-RADS 4.

In one of the first studies on this topic, published before the introduction of the MRI BI-RADS, Laura Liberman and coworkers [56] indicated a variety of MRI findings as probably benign, ranging from small masses to regional non-mass enhancement. In this work, 24% of the lesions found in a group of 367 high-risk women were categorized as probably benign and 10% finally proved to be malignant. Subsequent works found that the BI-RADS 3 category is used to classify from 6.6% to 24% of the lesions [42, 56–59] and that malignancy is found from 0.6% to 10% of the cases [42, 56–59]. What are the factors explaining this variability? Which are the findings most often classified as BI-RADS 3? Which criteria can help guide the management?

Probably benign MRI findings are commonly areas of non-mass enhancement, small mass enhancement difficult to characterize due to small dimensions, and foci. Non-mass enhancement remains one of the biggest issues when applying BI-RADS [60]. In the absence of a distribution and an internal pattern typically suspicious, there is a lack of additional features that can help in the differential diagnosis. For example, while a persistent enhancement (type 1 dynamic curve) is strongly suggestive for benignity in mass lesions, the same is not true for non-mass enhancement [46, 56]. Also, a correlation with lesion appearance on T2-weighted images rarely helps in the characterization.

In order to avoid unnecessary biopsies or short-term follow-up, the comparison with previous examinations and with other imaging modalities (mammography and US) is important, especially in high-risk patients. In the presence of a probably benign finding, an MRI-based targeted (so-called *second-look*) US might help clarify the nature of the lesion as well as guide biopsy in the presence of suspicious findings [61, 62].

Foci are described by the BI-RADS as "small dots of enhancement that are unique and stand out from the BPE. They are too small to be accurately assessed with respect to margin or internal enhancement" [12] (Fig. 6.2). Several studies addressed the issue of the malignancy rate of foci in the general population and in high-risk patients. In many studies, also lesions with a correlate on T1- and T2-weighted imaging were assessed. The reported malignancy rate is highly

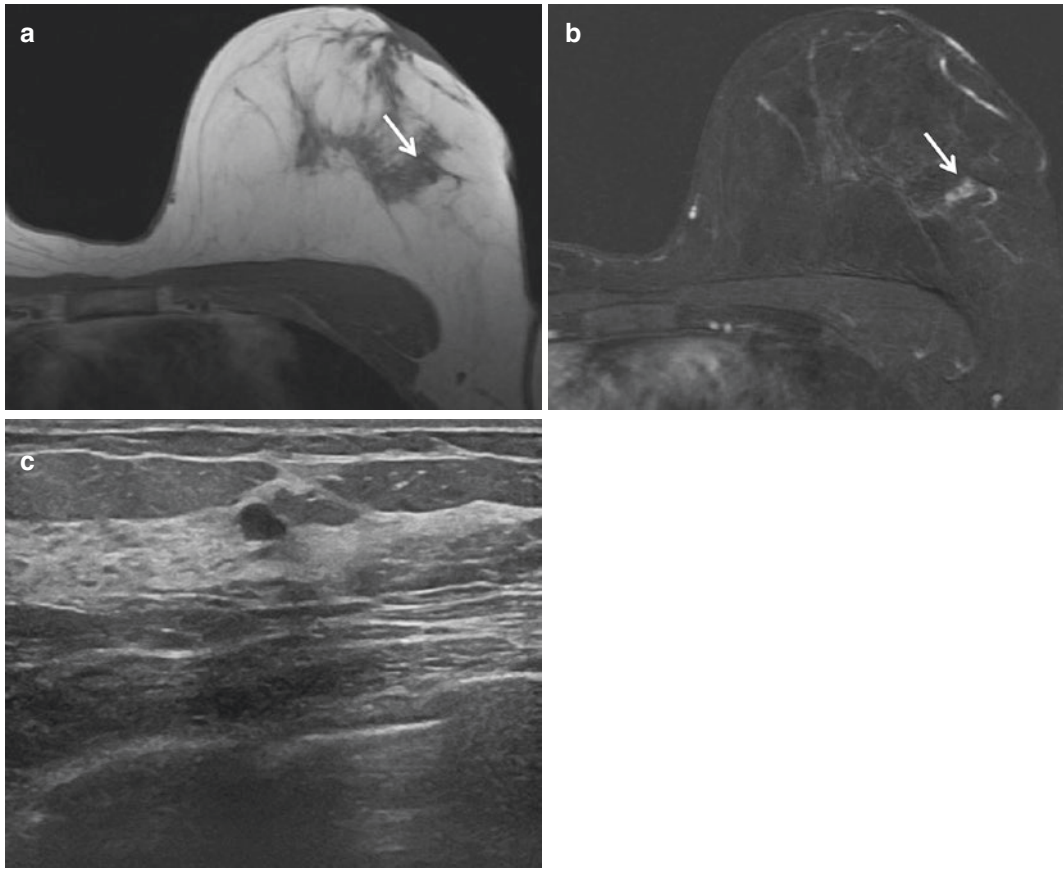

Fig. 6.1 A 48-year-old woman with *BRCA1* mutation and personal history of invasive ductal carcinoma in the right breast. MRI showed a small, oval mass enhancement with partially circumscribed margins and heterogeneous internal enhancement (arrow in **a** and **b**). The lesion was classified as BI-RADS 3, and the patient underwent second-look ultrasound. On ultrasound (**c**), a hypoechoic, oval lesion was found, corresponding to the MRI finding. US-guided biopsy was performed, and histology showed an invasive carcinoma of no special type

variable, from 0.6% to 23% [59, 63–68]. When the BI-RADS definition of focus is strictly followed, malignancy rate falls closer to 2% [63, 67, 68]. Of note, no significant difference between malignancy rates in the general population and in high-risk women were observed [63, 68].

The most helpful feature to be considered when evaluating a focus remains the comparison with previous examinations. Foci that do not show changes from 1 year to the other do not need to be followed up outside regular screening examination. On the other hand, a focus that newly appears (i.e., it was not visible the year before) or grows in size should be considered for biopsy. However, it must be remembered that, while growth is highly indicative of malignancy, in the absence of previous examinations and for new appearing foci, in more than 90–95% of the cases, a biopsy will show benign findings.

A final consideration must be done on the use of BI-RADS 3 category in high-risk women. As compared to the general population, these women present often with more aggressive cancers and at a younger age. Early diagnosis is of outmost importance [69]. Thus, *caution should be always used when deciding to choose follow-up over biopsy in this category of women.*

Sona A. Chikarmane and coworkers [70] found that the cancer rate for lesions initially classified as BI-RADS 3 in high-risk women was higher as compared to the cancer rate of the general population. Further, in this study, the only

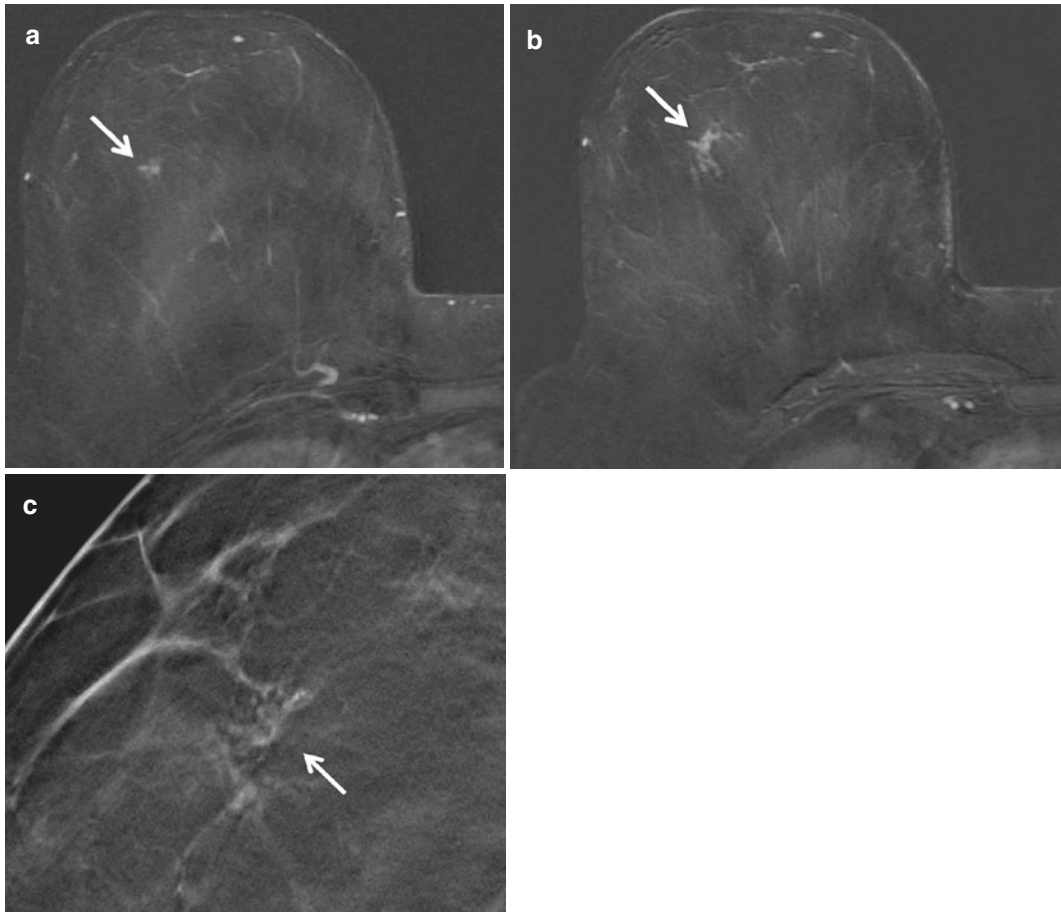

Fig. 6.2 A 49-year-old woman with a positive family history for breast cancer. Breast MRI showed a focus in the right breast (arrow in **a**), classified as BI-RADS 3. The patient returned after 1 year. The focus increased in size and appeared as a focal, heterogeneous non-mass enhancement, classified as BI-RADS 4 (arrow in **b**). No lesions were found at US. At second-look digital breast tomosynthesis (arrow in **c**), an area of architectural distortion with pleomorphic calcifications was detected. Tomosynthesis-guided vacuum-assisted biopsy was performed, and histology showed a ductal carcinoma in situ

malignant lesions initially classified as BI-RADS 3 were found in high-risk women or in women with a personal history of breast cancer. Thus, risk factors should be considered when deciding the clinical management of a woman with a probably benign finding on breast MRI [42, 56, 70].

In other studies, the percentage of lesions classified as BI-RADS 3 was lower, generally below 10%, with cancer rates below 2% [59, 71, 72]. Several explanations can be given: the improvement in hardware and software and the subsequent increase in image quality, the increased experience with breast MRI, and the wider knowledge available on MRI lesion features. An increased experience with breast MRI allows to more safely indicate a lesion as benign or suspicious and thus allows for a reduction in the number of findings classified as BI-RADS 3.

As well as for women at average risk, also in high-risk women, each MRI finding not clearly benign should be correlated with the other imaging available, usually mammography and US

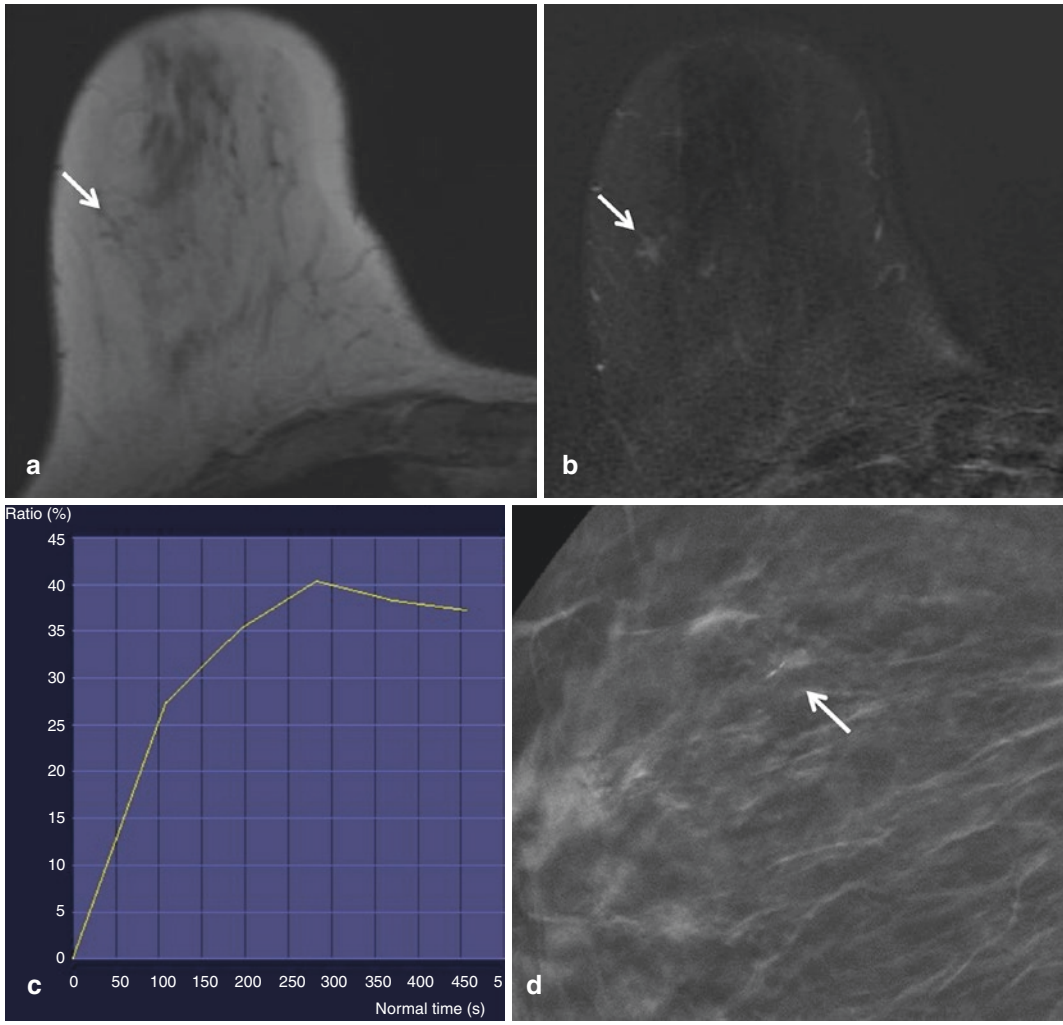

Fig. 6.3 A 61-year-old woman with *BRCA2* mutation. MRI showed a focal, non-mass enhancement with a type 2 curve (arrow in **b**, curve shown in **c**) corresponding to an architectural distortion on unenhanced images (arrow, **a**), BI-RADS 4. No lesions were found at US. On the second look of digital breast tomosynthesis (**d**), an oval mass with linear microcalcifications was found. Tomosynthesis-guided vacuum-assisted biopsy showed an invasive carcinoma of no special type with ductal carcinoma in situ

(Figs. 6.3 and 6.4). This can help in defining the nature of the lesions and guiding the management [73–77]. When correlating imaging modalities, it must be remembered that MRI is more sensitive than mammography and ultrasound. This means that the absence of findings on mammography as well as a negative targeted US do not exclude malignancy [61, 76].

6.6 Conclusions

The BI-RADS has been and is currently a great asset for the radiological world, besides the borders of breast imaging. In fact, although dedicated to this special field, it opened a general trend toward a more standardized and structured way of reporting [78], which produced, as already

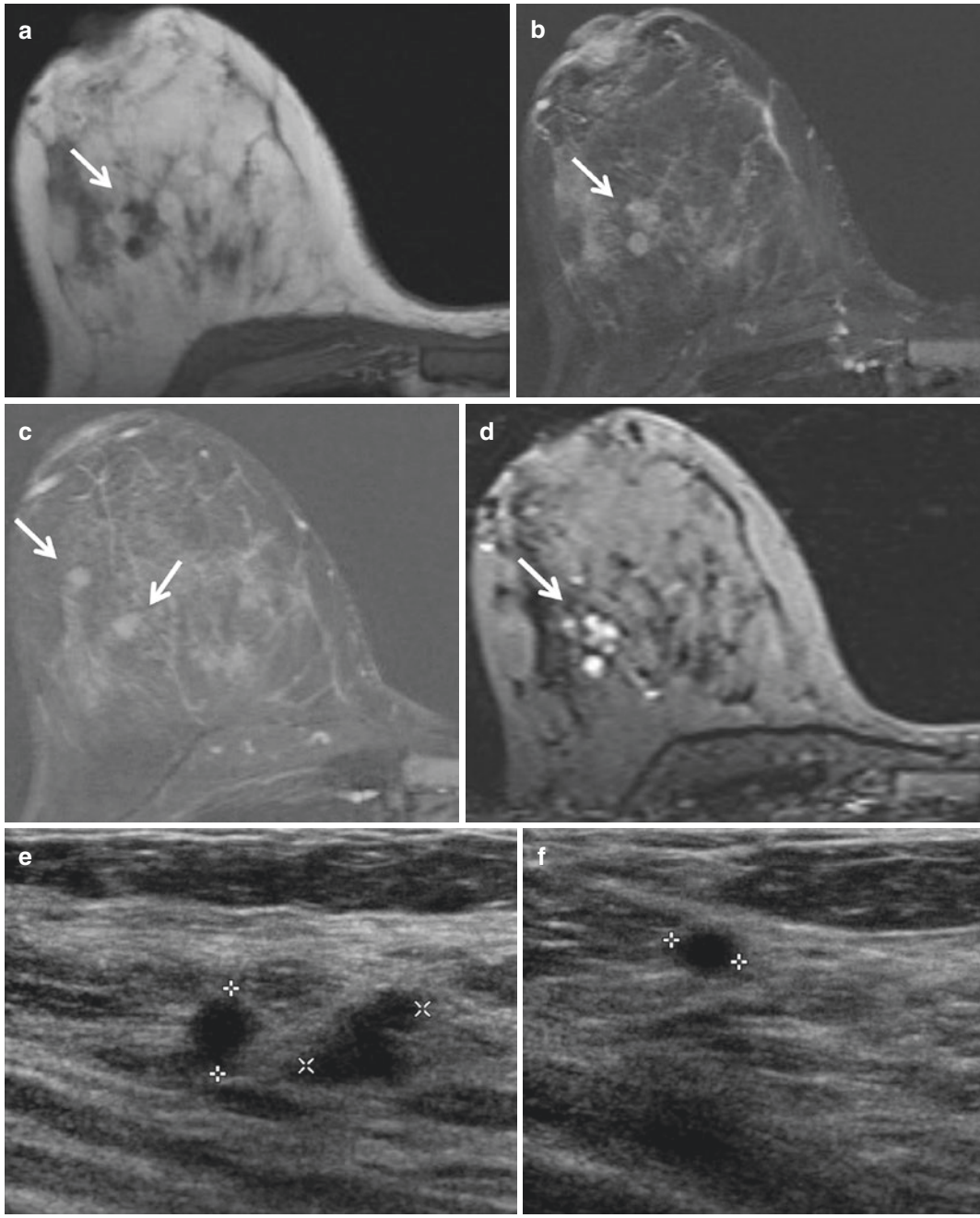

Fig. 6.4 A 46-year-old woman with a positive family history for breast cancer. MRI showed two heterogeneous round mass enhancements, with irregular margins (arrow in **a** and **b**), hyperintense on T2-weighted sequences (arrow in **d**). Further lesions with similar characteristics were found in the external quadrant of the same breast (arrow in **c**). All lesions were classified as BI-RADS 4. At targeted (second-look) US (**e** and **f**), all lesions corresponded to round or irregular hypoechoic lesions with non-circumscribed margins. US-guided biopsy showed a multicentric triple negative invasive carcinoma

mentioned, similar systems for other fields of radiology. It was probably not by chance that this pioneering role has been played by breast radiology, including MRI in the system about 15 years ago. The double role of screening and diagnostic examination that imaging modalities played since the 1960s in breast imaging is an important reason for this. We firstly faced epidemiological issues for screening, the difficult dilemma between increasing sensitivity and lowering the recall rate, as well as overdiagnosis.

The concept of risk stratification is obviously behind the practice of high-risk screening with MRI. This concept also holds when applying BI-RADS to high-risk women. We should always remember that the PPV of whatever test depends, in terms of Bayesian statistics, not only on its (our?) sensitivity and specificity but also on the disease prevalence and on the pretest probability and that this dependence becomes stronger and stronger when this probability is very high or very low [79]. *In practice, the higher the risk the woman has, the more cautious should we be in deciding for follow-up instead of biopsy.*

References

1. Warner E, Messersmith H, Causer P et al (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 148:671–679
2. Berg WA, Gutierrez L, NessAiver MS et al (2004) Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology 233:830–849
3. Kuhl C, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
4. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol 46:94–105
5. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
6. Mann RM, Balleyguier C, Baltzer PA et al (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678
7. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
8. American College of Radiology practice parameters for the performance of contrast-enhanced magnetic resonance imaging (MRI) of the breast. http://www.acr.org/~/media/2a0eb28eb59041e2825179afb72ef624.pdf. Accessed 30 Jun 2020
9. American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
10. Burnside ES, Sickles EA, Bassett LW et al (2009) The ACR BI-RADS® experience: learning from history. J Am Coll Radiol JACR 6:851–860
11. Pinker K, Bickel H, Helbich TH et al (2013) Combined contrast-enhanced magnetic resonance and diffusion-weighted imaging reading adapted to the "breast imaging reporting and data system" for multiparametric 3-T imaging of breast lesions. Eur Radiol 23:1791–1802
12. Morris EA, Comstock C, Lee C et al (2013) ACR BI-RADS® Magnetic Resonance Imaging. In: American College of Radiology. Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
13. Berg WA, Campassi C, Langenberg P, Sexton MJ (2000) Breast imaging reporting and data system: inter- and intraobserver variability in feature analysis and final assessment. AJR Am J Roentgenol 174:1769–1777
14. Grimm LJ, Anderson AL, Baker JA et al (2015) Interobserver variability between breast imagers using the fifth edition of the BI-RADS MRI Lexicon. AJR Am J Roentgenol 204:1120–1124
15. El Khoury M, Lalonde L, David J et al (2015) Breast imaging reporting and data system (BI-RADS) lexicon for breast MRI: interobserver variability in the description and assignment of BI-RADS category. Eur J Radiol 84:71–76
16. American College of Radiology Liver Imaging Reporting and Data System (LI-RADS). https://www.acr.org/Quality-Safety/Resources/LIRADS. Accessed 30 Jun 2020
17. American College of Radiology Prostate Imaging reporting and Data System (PI-RADS). https://www.acr.org/Quality-Safety/Resources/PIRADS. Accessed 30 Jun 2020
18. Stavros AT, Thickman D, Rapp CL et al (1995) Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology 196:123–134
19. Liberman L, Abramson AF, Squires FB et al (1998) The breast imaging reporting and data system: positive predictive value of mammographic features and final assessment categories. AJR Am J Roentgenol 171:35–40
20. Berg WA, Arnoldus CL, Teferra E, Bhargavan M (2001) Biopsy of amorphous breast calcifications:

pathologic outcome and yield at stereotactic biopsy. Radiology 221:495–503
21. Rominger M, Wisgickl C, Timmesfeld N (2012) Breast microcalcifications as type descriptors to stratify risk of malignancy: a systematic review and meta-analysis of 10665 cases with special focus on round/punctate microcalcifications. Rofo 184:1144–1152
22. Kaiser WA, Zeitler E (1989) MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 170:681–686
23. Heywang-Köbrunner SH (1994) Contrast-enhanced magnetic resonance imaging of the breast. Invest Radiol 29:94–104
24. Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 18:1307–1318
25. Sardanelli F, Carbonaro LA, Montemezzi S et al (2016) Clinical Breast MR Using MRS or DWI: Who Is the Winner? Front Oncol 6:217
26. Strigel RM, Burnside ES, Elezaby M et al (2017) Utility of BI-RADS assessment category 4 subdivisions for screening breast MRI. AJR Am J Roentgenol 208:1392–1399
27. Baltzer PAT, Dietzel M, Kaiser WA (2013) A simple and robust classification tree for differentiation between benign and malignant lesions in MR-mammography. Eur Radiol 23:2051–2060
28. Marino MA, Clauser P, Woitek R et al (2016) A simple scoring system for breast MRI interpretation: does it compensate for reader experience? Eur Radiol 26:2529–2537
29. Woitek R, Spick C, Schernthaner M et al (2017) A simple classification system (the Tree flowchart) for breast MRI can reduce the number of unnecessary biopsies in MRI-only lesions. Eur Radiol 27:3799–3809
30. Baltzer A, Dietzel M, Kaiser CG, Baltzer PA (2016) Combined reading of contrast enhanced and diffusion weighted magnetic resonance imaging by using a simple sum score. Eur Radiol 26:884–891
31. Maltez de Almeida JR, Gomes AB, Barros TP et al (2015) Subcategorization of suspicious breast lesions (BI-RADS category 4) according to MRI criteria: role of dynamic contrast-enhanced and diffusion-weighted imaging. AJR Am J Roentgenol 205:222–231
32. Leach MO, Boggis CRM, Dixon AK et al (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
33. Berg WA, Zhang Z, Lehrer D et al (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
34. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
35. Lehman CD, Isaacs C, Schnall MD et al (2007) Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 244:381–388
36. Chiarelli AM, Prummel MV, Muradali D et al (2014) Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program. J Clin Oncol 32:2224–2230
37. Riedl CC, Luft N, Bernhart C et al (2015) Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 33:1128–1135
38. Narayan AK, Visvanathan K, Harvey SC (2016) Comparative effectiveness of breast MRI and mammography in screening young women with elevated risk of developing breast cancer: a retrospective cohort study. Breast Cancer Res Treat 158:583–589
39. Healy NA, O'Keeffe SA (2016) Determination of recall rates for assessment in high-risk women undergoing annual surveillance breast MRI. Clin Radiol 71:1143–1147
40. Eisinger F, Noguès C, Birnbaum D et al (1998) BRCA1 and medullary breast cancer. JAMA 280:1227–1228
41. Tilanus-Linthorst M, Verhoog L, Obdeijn I-M et al (2002) A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography. Int J Cancer 102:91–95
42. Kuhl CK, Schmutzler RK, Leutner CC et al (2000) Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 215:267–279
43. Schrading S, Kuhl CK (2008) Mammographic, US, and MR imaging phenotypes of familial breast cancer. Radiology 246:58–70
44. Lamb PM, Perry NM, Vinnicombe SJ, Wells CA (2000) Correlation between ultrasound characteristics, mammographic findings and histological grade in patients with invasive ductal carcinoma of the breast. Clin Radiol 55:40–44
45. Veltman J, Mann R, Kok T et al (2008) Breast tumor characteristics of BRCA1 and BRCA2 gene mutation carriers on MRI. Eur Radiol 18:931–938
46. Gilbert FJ, Warren RML, Kwan-Lim G et al (2009) Cancers in BRCA1 and BRCA2 carriers and in women at high risk for breast cancer: MR imaging and mammographic features. Radiology 252:358–368
47. Niell BL, Gavenonis SC, Motazedi T et al (2014) Auditing a breast MRI practice: performance measures for screening and diagnostic breast MRI. J Am Coll Radiol 11:883–889
48. Pfleiderer SOR, Sachse S, Sauner D et al (2004) Changes in magnetic resonance mammography due to hormone replacement therapy. Breast Cancer Res 6:R232–R238
49. King V, Gu Y, Kaplan JB et al (2012) Impact of menopausal status on background parenchymal enhance-

ment and fibroglandular tissue on breast MRI. Eur Radiol 22:2641–2647
50. Kang SS, Ko EY, Han B-K et al (2014) Background parenchymal enhancement on breast MRI: influence of menstrual cycle and breast composition. J Magn Reson Imaging 39:526–534
51. Hansen NL, Kuhl CK, Barabasch A et al (2014) Does MRI breast "density" (degree of background enhancement) correlate with mammographic breast density? J Magn Reson Imaging 40:483–489
52. Giess CS, Raza S, Birdwell RL (2013) Patterns of nonmasslike enhancement at screening breast MR imaging of high-risk premenopausal women. Radiographics 33:1343–1360
53. DeMartini WB, Liu F, Peacock S et al (2012) Background parenchymal enhancement on breast MRI: impact on diagnostic performance. AJR Am J Roentgenol 198:W373–W380
54. Hambly NM, Liberman L, Dershaw DD et al (2011) Background parenchymal enhancement on baseline screening breast MRI: impact on biopsy rate and short-interval follow-up. AJR Am J Roentgenol 196:218–224
55. Baltzer PA, Dietzel M, Vag T et al (2011) Clinical MR mammography: impact of hormonal status on background enhancement and diagnostic accuracy. RöFo 183:441–447
56. Liberman L, Morris EA, Benton CL et al (2003) Probably benign lesions at breast magnetic resonance imaging: preliminary experience in high-risk women. Cancer 98:377–388
57. Kriege M, Brekelmans CTM, Boetes C et al (2004) Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427–437
58. Sadowski EA, Kelcz F (2005) Frequency of malignancy in lesions classified as probably benign after dynamic contrast-enhanced breast MRI examination. J Magn Reson Imaging 21:556–564
59. Eby PR, DeMartini WB, Gutierrez RL et al (2009) Characteristics of probably benign breast MRI lesions. AJR Am J Roentgenol 193:861–867
60. Baltzer PAT, Kaiser WA, Dietzel M (2015) Lesion type and reader experience affect the diagnostic accuracy of breast MRI: a multiple reader ROC study. Eur J Radiol 84:86–91
61. Spick C, Baltzer PAT (2014) Diagnostic utility of second-look US for breast lesions identified at MR imaging: systematic review and meta-analysis. Radiology 273:401–409
62. Lee SH, Kim SM, Jang M et al (2015) Role of second-look ultrasound examinations for MR-detected lesions in patients with breast cancer. Ultraschall Med 36:140–148
63. Liberman L, Mason G, Morris EA, Dershaw DD (2006) Does size matter? Positive predictive value of MRI-detected breast lesions as a function of lesion size. AJR Am J Roentgenol 186:426–430
64. Weinstein SP, Hanna LG, Gatsonis C et al (2010) Frequency of malignancy seen in probably benign lesions at contrast-enhanced breast MR imaging: findings from ACRIN 6667. Radiology 255:731–737
65. Raza S, Sekar M, Ong EMW, Birdwell RL (2012) Small masses on breast MR: is biopsy necessary? Acad Radiol 19:412–419
66. Jansen SA, Shimauchi A, Zak L et al (2011) The diverse pathology and kinetics of mass, nonmass, and focus enhancement on MR imaging of the breast. J Magn Reson Imaging 33:1382–1389
67. Ha R, Sung J, Lee C et al (2014) Characteristics and outcome of enhancing foci followed on breast MRI with management implications. Clin Radiol 69:715–720
68. Clauser P, Cassano E, De Nicolò A et al (2016) Foci on breast magnetic resonance imaging in high-risk women: cancer or not? Radiol Med 121: 611–617
69. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 358:1389–1399
70. Chikarmane SA, Birdwell RL, Poole PS et al (2016) Characteristics, malignancy rate, and follow-up of BI-RADS category 3 lesions identified at breast MR imaging: implications for MR image interpretation and management. Radiology 280:707–715
71. Edwards SD, Lipson JA, Ikeda DM, Lee JM (2013) Updates and revisions to the BI-RADS magnetic resonance imaging lexicon. Magn Reson Imaging Clin N Am 21:483–493
72. Lourenco AP, Chung MTM, Mainiero MB (2014) Probably benign breast MRI lesions: frequency, lesion type, and rate of malignancy. J Magn Reson Imaging JMRI 39:789–794
73. Abe H, Schmidt RA, Shah RN et al (2010) MR-directed ("second-look") ultrasound examination for breast lesions detected initially on MRI: MR and sonographic findings. AJR Am J Roentgenol 194:370–377
74. Thomassin-Naggara I, Trop I, Chopier J et al (2011) Nonmasslike enhancement at breast MR imaging: the added value of mammography and US for lesion categorization. Radiology 261:69–79
75. Bahrs SD, Baur A, Hattermann V et al (1987) (2014) BI-RADS® 3 lesions at contrast-enhanced breast MRI: is an initial short-interval follow-up necessary? Acta Radiol 55:260–265
76. Clauser P, Carbonaro LA, Pancot M et al (2015) Additional findings at preoperative breast MRI: the value of second-look digital breast tomosynthesis. Eur Radiol 25:2830–2839
77. Peter P, Dhillon R, Bose S, Bourke A (2016) MRI screening-detected breast lesions in high-risk young women: the value of targeted second-look ultrasound and imaging-guided biopsy. Clin Radiol 71:1037–1043
78. Sardanelli F (2017) Trends in radiology and experimental research. Eur Radiol Exp 1:1
79. Sardanelli F, Di Leo G (2009) Biostatistics for radiologists. Springer, Milan, pp 21–32

CAD and Machine Learning for Breast MRI

7

Anne L. Martel

Abbreviations

3D	Three-dimensional
3TP	Three-time-point
ANN	Artificial neural network
ASM	Angular second moment
AUC	Area under the curve
BI-RADS	Breast Imaging Reporting and Data System
CAD	Computer-aided detection/diagnosis
CADD	Computer-aided detection and diagnosis
CADe	Computer-aided detection
CADx	Computer-aided diagnosis
CAE	Computer-aided evaluation
CNN	Convolutional neural networks
DCE	Dynamic contrast-enhanced
LDA	Linear discriminant analysis
LOO	Leave-one-out
MRI	Magnetic resonance imaging
PK	Pharmacokinetic
ROC	Receiver operating characteristic
ROI	Region of interest
SER	Signal enhancement ratio
SVM	Support vector machines

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7.1 Introduction

Computerized support systems for mammography have been commercially available for many years and are used widely for diagnostic support and as a second reader. For mammographic systems, the term *computer-aided detection* (CADe) is typically used to denote a system that detects suspicious lesions while the term *computer-aided diagnosis* (CADx) is used to describe systems that provide an estimate of the probability that a detected lesion is cancer. The acronym "CAD" can indicate computed-aided detection, computed-aided diagnosis, or both. For breast MRI, the challenges are somewhat different. A typical MRI breast exam can result in thousands of image slices being acquired; images are volumetric and can be acquired in different planes; and there are multiple sequences, each of them resulting in a different tissue contrast, while dynamic contrast-enhanced (DCE) sequences provide additional temporal information. Computerized support systems are needed to help the radiologist to navigate through these images effectively. The high signal intensity in cancerous lesions that results from contrast enhancement provides excellent sensitivity, but the presence of many enhancing benign lesions and, in some cases, enhancing parenchymal tissue means that the differentiation between malignant and benign lesions is a difficult task. This chapter divides computerized decision sup-

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port systems for breast MRI into three main categories: *computer-aided evaluation* (CAE) systems, which provide improved visualization of the image data and support the radiologists workflow; *computer-aided diagnosis* (CADx) systems, which provide an estimate of the probability of a specific lesion being a cancer; and *computer-aided detection and diagnosis* (CADD) systems, which first identify possible lesions and then classify them in terms of probability of being malignant or benign.

7.2 Computer-Aided Evaluation (CAE) Systems

There are several commercially available software packages that are designed to provide support to the breast radiologist evaluating a magnetic resonance imaging (MRI) examination of the breast.

The main function of these packages is to provide a color-coded parametric map of the breast based on the Breast Imaging Reporting and Data System (BI-RADS) scheme [1] where enhancement kinetics are classified as persistent, plateau, or washout of contrast material. For each pixel in the image, a signal intensity curve is generated and the classification is performed as follows. First, an enhancement threshold is set based on the percentage increase in the signal in the first post-contrast image and only pixels that exceed this threshold are retained. Next, the software calculates the change in intensity in a delayed post-contrast image relative to the first post-contrast image. Finally, it determines whether each pixel intensity curve increases, decreases, or remains constant and assigns the corresponding color coding to an overlay map. The precise details of which time points are used, what the initial enhancement threshold should be, and which metric is used to distinguish between pixels that show washout, plateau, or continuous enhancement vary from platform to platform; but the essential principles are the same. In Fig. 7.1, signal enhancement ratio (SER) pixel-by-pixel maps are shown for a malignant and a benign lesion, together with the corresponding relative signal curves in Fig. 7.2. Here the signal enhancement ratio is defined as $SER = (S_{first} - S_0)/(S_{last} - S_0)$ where S_0, S_{first}, and S_{last} are the pre-contrast, first post-contrast, and last post-contrast signal intensities, respectively.

Changes in magnet field strength, equipment vendor and model, software version, image acquisition protocols, contrast type, dose, and rate of administration, flushing with saline solution, and threshold values used to generate the color maps mean that overlay maps produced in one breast imaging center cannot be directly compared with those generated elsewhere. Pharmacokinetic (PK) models attempt to overcome this variability by estimating physiologically meaningful parameters such as the rate of exchange between capillaries and the extracellular space by fitting mathematical models to signal intensity curves [2]; however, these models require that images are acquired at a much higher temporal resolution than is common in clinical practice. The three-time-point (3TP) method [3] proposes a solution where just three images are acquired at specified time points and then a calibration scheme is used to estimate the pharmacokinetic parameters.

In addition to an overlay that color codes each pixel according to enhancement kinetics, some CAE systems provide tools for radiologists to identify and outline lesions of interest. The average signal intensity curve over the whole lesion can then be assessed, which reduces the effect of noise. Summary statistics that describe the area and extent of the lesion can also be produced from the segmented region of interest (ROI). Although CAE systems do provide some quantitative information, they are not designed to assign probabilities of malignancy to lesions in the image.

Several studies have evaluated commercially available CAE systems, including CADstream (Confirma, Bellevue, WA, USA) [4], Aegis (Sentinelle Medical, Toronto, Canada) [5], dynaCAD (Invivo, Pewaukee, WI, USA) [6], and 3TP [7]. Monique D. Dorrius and coworkers [8] carried out a systematic review and meta-analysis considering ten publications referencing commercially available systems. They reported that

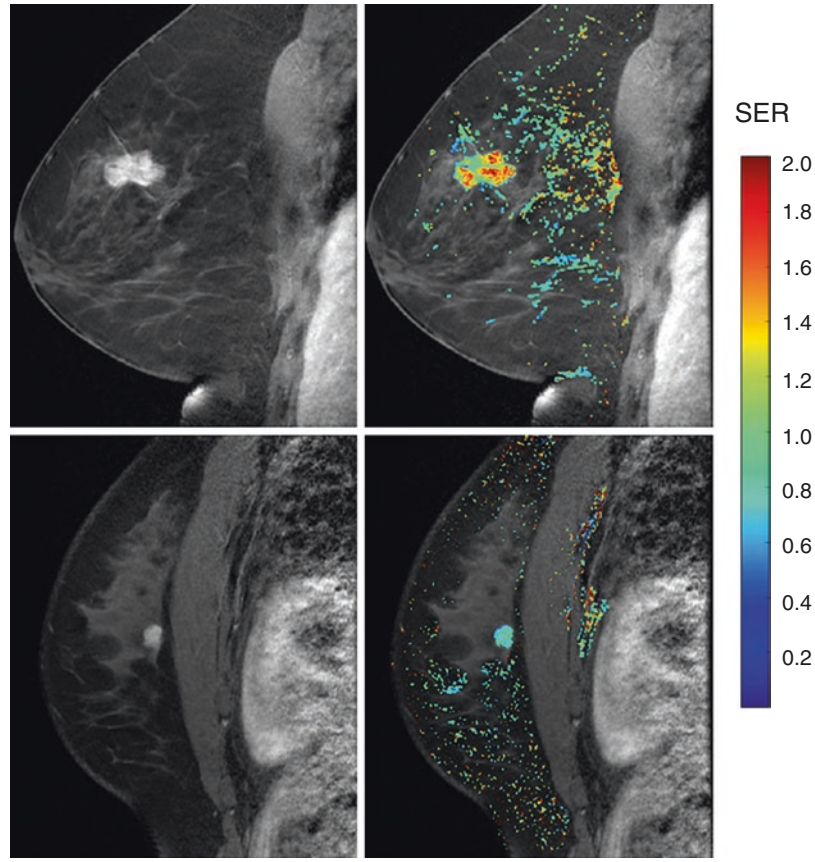

Fig. 7.1 On the top row are images showing an invasive lobular carcinoma and on the bottom row images show a fibroadenoma. The left column shows the sagittal sections through the center of the lesions obtained as the first post-contrast frame using a fat-saturated gradient-echo sequence. On the right column, the signal enhancement ratio (SER) values are displayed as a color overlay on a pixel-by-pixel basis. Note the inhomogeneous color distribution with multiple yellow-red pixels in the malignant lesion and the homogeneous light blue color of the benign lesion

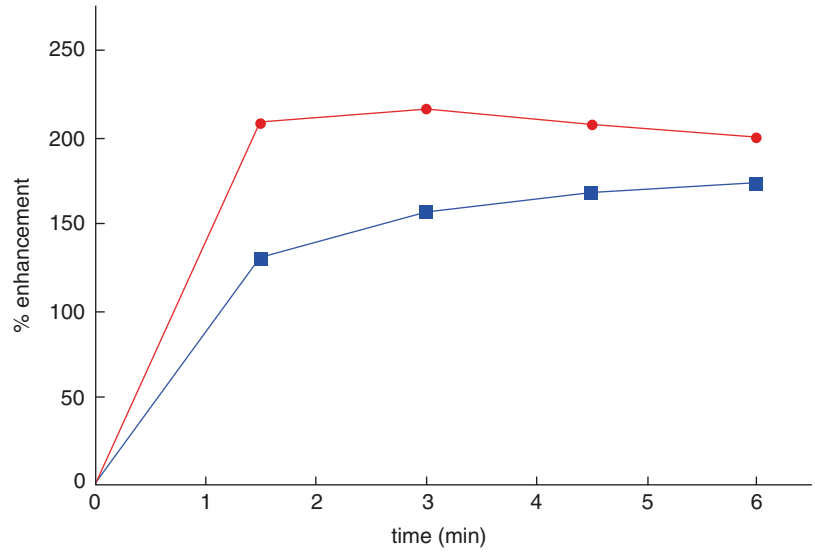

Fig. 7.2 The signal enhancement curves corresponding to the lesions shown in Fig. 7.1. The malignant carcinoma (red) shows a more rapid initial enhancement followed by a slight late washout phase. The benign lesion has a slower initial enhancement without washout; i.e., it shows a continuous increase curve. These curves were obtained by considering the pixels showing the highest initial enhancement

for experienced radiologists the sensitivity was unchanged by the use of a CAE system and there was a small but non-significant decrease in specificity. For residents with less than 6 months' breast MRI experience, there was a significant improvement in sensitivity with CAE and no

significant change in specificity. *The authors concluded that CAE systems had little impact on accuracy overall and that inexperienced radiologists and residents benefitted the most from their use* [8].

7.3 Computer-Aided Diagnosis (CADx) Systems

CAE systems can be very helpful in highlighting enhancing regions of the breast so that the radiologist can quickly direct their attention to these suspicious areas; however, they do not make use of other information such as the texture and the morphology of the lesion. CADx systems provide further support to the radiologist by combining kinetic, morphological, and textural information to predict whether a particular lesion is malignant or not. This is achieved by first delineating the suspicious lesion, then extracting multiple image features from the DCE sequence, and finally using a trained classifier to assign a probability of malignancy to the lesion. This is achieved using a *machine learning* algorithm, which is trained on previously labeled examples of malignant and benign lesions. Each of these components will be described in more detail below.

7.3.1 Lesion Segmentation

The accurate delineation of enhancing lesions is essential as it allows us to quantify the variation in contrast enhancement kinetics within the lesion and to extract morphological features that can represent its shape. Manual segmentation is a time-consuming and subjective process. Semi-automated methods have been shown to be faster and to reduce inter-observer variability [9]. Typically, such methods require the radiologist to mark a point at the center of the enhancing lesion or to draw a crude boundary or bounding box around the lesion. Upper and lower intensity thresholds are then set by the user, and pixels within the defined range, which are either connected to the seed point or lie within the bounding box, are defined as belonging to the lesion ROI. Usually the subtraction images or the enhancement maps are used to define the ROI as they have higher contrast between the lesion and the background.

More sophisticated approaches remove the need to manually define intensity threshold values and make use of all the DCE information available to improve the contrast between lesion and background. Weijie Chen and coworkers [10] developed an improved lesion segmentation algorithm based on fuzzy clustering that used the difference in contrast enhancement dynamics to identify pixels belonging to the foreground lesion. Yunfeng Cui and coworkers [11] used a Gaussian mixture model to automatically estimate threshold values that are used to identify pixels lying inside and outside of the lesion. A marker-controlled watershed method is then used to further refine the boundary. Other authors [12] described a system where the operator places two ellipses on the image, one identifying pixels inside the lesion the other containing background; and this information is used to classify all the remaining pixels. Alternative methods are those using a graph-cut-based algorithm that incorporates a spatial smoothness constraint [13].

Fully automated systems that carry out both detection and segmentation of lesions are discussed separately in Sect. 7.4.

7.3.2 Feature Extraction

Radiologists use well-defined descriptors [1] to characterize lesions, and these help to discriminate between malignant and benign lesions. Although there have been some attempts to build CADx systems based on categorical descriptors provided by radiologists [14], it is more common to extract continuous quantitative values that capture the same information. There are many papers describing different feature sets for use in CADx systems, and they can be grouped into three groups: kinetic (also called dynamic), morphological, and texture features.

7.3.2.1 Kinetic Features

There are many different ways of quantifying contrast enhancement in a lesion, but model-free methods, which attempt to characterize the shape of the signal enhancement curve, are the most commonly used. Features include the *maximum enhancement*, the *time-to-peak enhancement*, the *rate of contrast uptake*, and the *rate of washout* [15]. The normalized signal intensity values have been used directly [16]; however, when Jacob Levman and coworkers [17] compared several feature vectors, including one that used relative signal intensity alone and another that combined relative signal enhancement with the derivatives of the enhancement curve, they found that the more conventional feature vector based on the traditional parameters of maximum signal intensity enhancement, time of maximum enhancement, and maximum washout gave the most accurate results. *Pharmacokinetic models* require high temporal resolution and therefore are not suitable for most breast MRI exams, which typically only have 3–5 post-contrast images acquired at a lower temporal resolution, typically not lower than 60 s. Sanaz A. Jansen and coworkers [18] describe an empirical model that has just three parameters to fit and does not require an arterial input function. This approach may help to standardize kinetic parameters extracted from studies acquired at differing temporal resolutions, and features obtained using this model have been found to be relevant in lesion classification [19].

The contrast enhancement curve generated over an entire lesion will result in the averaging of pixel signal intensity curves. Several groups have attempted to cluster together pixels that show similar enhancement patterns in order to capture regions that show the greatest wash in and wash out of contrast. These include the mean-shift algorithm [20], vector quantization [21], and fuzzy c-means clustering [22]. Another approach is to differentiate between the signal enhancement in the center of the lesion and at the edge of the lesion [19].

7.3.2.2 Morphological Features

Radiologists use several morphological features such as the shape of the lesion, and the uniformity (i.e., pattern of internal distribution) of contrast enhancement to describe a lesion. Certain characteristics are associated with benign lesions while others tend to suggest a malignant lesion. For example, a stereotypical benign lesion may have a smooth margin, with an oval shape and internal septations, whereas a malignant lesion might have a speculated appearance with an irregular shape and rim enhancement. In order to use this information in a CADx system, it is necessary to quantify these findings. Various formula have been derived to capture information about circularity, convexity, irregularity, solidity, perimeter, compactness, etc. [9, 15, 23]. The sharpness of the lesion boundary, and the change in edge sharpness over the duration of the dynamic study are also useful morphological features [24, 25].

7.3.2.3 Texture Features

Texture features provide information about the heterogeneity of the contrast enhancement in the lesion. Since the mean signal intensity curve generated over the whole lesion region of interest does not reflect inhomogeneities within the lesion, many CADx algorithms also include the variance, skew, and kurtosis of each of the kinetic parameters measured from individual pixels within the ROI [15, 19]. However, features based purely on the statistical distribution of intensity values cannot capture spatial patterns. In 1973 Robert M. Haralick [26] introduced a method of mathematically describing textures in images that uses spatially dependent intensity information. Haralick features are based on a co-occurrence matrix *Pij*, which records the number of times that two pixels with values i and j occur in the region of interest separated by a distance d and an angle θ. Fourteen feature values can be derived from this matrix, including the angular second moment (ASM), energy, entropy, and contrast. Even more features can be obtained by varying values for d, θ, and the number of gray levels used to generate the matrix. Peter Gibbs and coworkers [27] showed that a combination of texture features could produce very accurate results, and Weijie Chen and coworkers [28] extended the method to three-dimensional (3D)

volumetric regions of interest. Other texture features have also been used to discriminate between malignant and benign lesions, such as Gabor filters [13] or entropy of enhancement assessed by moving a 3 × 3 window over the lesion ROI [29].

7.3.3 Lesion Classification

Individual features rarely achieve high accuracy in isolation. However, when several features are combined, it is possible to achieve a better separation between malignant and benign lesions. Classification algorithms work by finding a boundary in multi-dimensional feature space that best separates two sets of labeled data points; once this boundary has been identified using training data, a new test case is projected into the feature space and, depending on which side of the decision boundary it falls, it is classified as malignant or benign. There are many different classifiers available that can take a set of features and return either a binary decision or a probability of malignancy.

7.3.3.1 Classifiers

Simple linear classifiers, such as *linear discriminant analysis* (LDA), have the advantage that they are easily understood and the contribution that each individual feature makes to the final decision can be calculated [27]. The disadvantage is that they cannot cope with data where the decision boundary is non-linear.

Support vector machines (SVMs) are more robust than LDA with small training datasets as they identify the decision boundary that maximizes the distance to the data points on either side. They can be extended to produce non-linear boundaries using different kernel functions and provide a mechanism for coping with misclassified points. The disadvantage of SVMs is that understanding the contribution of individual features to the classifier becomes much more difficult [17].

Decision trees are simple to understand, and Pascal Baltzer and coworkers achieved excellent results on a dataset of over 1,000 patients [14] using categorical features. The resulting tree could be represented by a series of simple decision rules; however, this approach is known to be prone to overfitting. *Random forests*, which are ensembles of many individual decision trees, are more robust [30] and have been used successfully to train breast CAD systems [19, 31]. It is possible to extract useful information about the importance of individual features using random forests, and methods of interpreting random forest models have also been explored [32].

Artificial neural networks (ANNs) attempt to mimic the way in which a human brain processes information. The features are connected to a layer of hidden nodes, and then these hidden nodes are connected to output nodes that represent the classes. A back-propagation method is used to learn the weights that connect the nodes together. Several groups have used neural networks for lesion characterization on breast MRI in the past [16, 33, 34], but the small size of the labeled training datasets that were available meant that these ANNs were restricted to a single hidden layer with just a few nodes. More recently there has been an explosion of interest in the use of deeper neural networks and more advanced networks that are specifically designed for images—these will be mentioned in later sections.

7.3.3.2 Feature Selection

Hundreds of quantitative features can be extracted from a DCE-MRI study, but using too many features increases computational complexity and may lead to overfitting. In practice, therefore, it is usually better to train a classification algorithm using a subset of the most discriminative features. Many methods of feature selection exist in the literature, and the simplest approach is to identify the top-ranking features individually. The discriminative power of a single feature can be quantified by using the *receiver operating characteristic* (ROC) analysis and calculating the area under the curve (AUC). Looking at one feature at a time, however, does not take into account the correlations between features, so methods that attempt to find the best combination of features have been proposed. Sequential forward search methods find the most discriminating feature first, and then search for a second feature that

results in the greatest improvement in accuracy, and so on until the required number of features has been identified [34, 35]. Silvano Agliozzo and coworkers [23] used a genetic algorithm to identify the best subset of features. Some classification algorithms are able to automatically determine the relevance of features, for example, random forests [19] and Bayesian neural networks with automatic relevance determination [33].

7.3.3.3 Training and Evaluation of Classifiers

When a classifier is trained on labeled data, it is important to use a separate testing dataset to evaluate performance; otherwise the calculated accuracy will be overly optimistic. *Overfitting* of a classifier is said to occur when predictions made on the training set are very accurate but the performance on new unseen data is poor; i.e., the classification model fails to generalize. This can be avoided by careful attention to the way the labeled training data is used to create and test predictive models. Figure 7.3 illustrates a general framework for selecting the model parameters (for example, the number of trees in a random forest, hidden nodes in a neural network, or feature selection) using a labeled data set.

The best test of generalizability is obtained by using a completely independent *testing dataset*. This should be separated from the training data before any experiments are started to ensure that the choice of parameters or features is not biased. The remaining data is then split into a *training set* and a *tuning set* (often referred to as the *validation set* in the computer science literature). The training set is used to create the predictive model, and the tuning set is used to estimate performance. This process can then be repeated by switching cases in the training and tuning sets using a process known as *cross-fold validation*. The number of cases in the training, tuning, and testing datasets and the number of folds used will depend on the size of the available labeled dataset and the number of classes. For very small datasets, it is common to carry out a *leave-one-out* (LOO) experiment where all of the cases except one are used to train a classifier that is then used to predict the label on the remaining case. This process is repeated until each case has been held out and the reported accuracy is calculated. This procedure usually yields overly optimistic results. If the research then uses repeated LOO experiments to select model parameters and then reports on the most accurate configuration, then the results are also biased.

The independent testing set cannot be too small, or it will fail to capture the variability of the data and there will be a high variance in the error accuracy. In many cases, researchers will attempt to increase the number of labeled cases by using several lesions from a single patient. If this is done, then *it is important to ensure that all of the lesions from a single patient are in the same dataset*; i.e. it is incorrect to include lesions from the same patient in both the training set and the tuning or testing set.

Most classifiers return a numerical score between zero (definitely negative) and 1 (definitely positive). For a simple binary classifier, it is common to set a threshold of 0.5: everything with a higher score is considered to be positive and everything with a lower score is considered to be negative. Lowering this threshold results in a higher sensitivity (true positive fraction) and a lower specificity (true negative fraction) while raising the threshold produces a lower sensitivity and a higher specificity. The optimum setting for this threshold, which is also referred to as the decision point, will depend on the clinical context. The effect of changing the threshold can be visualized using the ROC curve, which plots sensitivity against (1-specificity) for different decision points. The AUC is often used to evaluate the performance of different CADx systems because it is independent of the single threshold.

7.4 Fully Automated Lesion Detection

In Sect. 7.3, it is assumed that a lesion has already been detected. A system that is capable of detecting suspicious lesions automatically, i.e., a CADe system, has the potential to speed up radiologists' workflow and also to improve sensitivity by

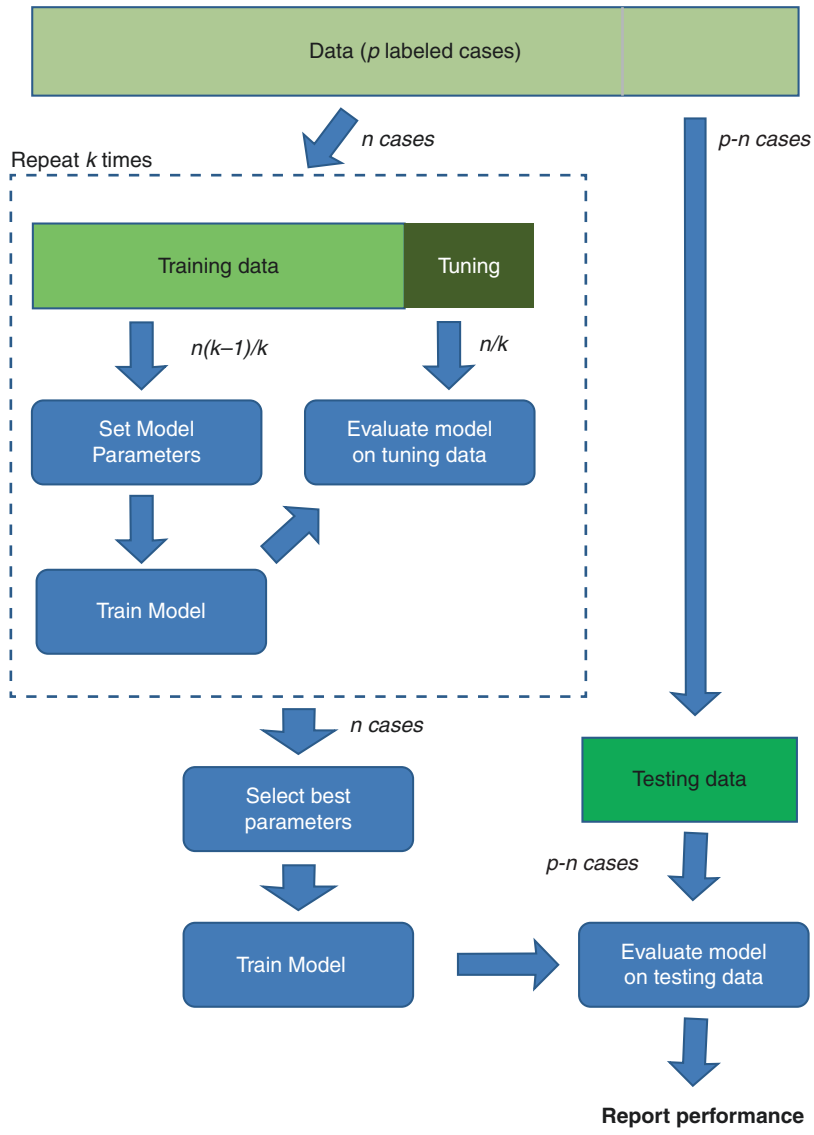

Fig. 7.3 Flow diagram for the training, tuning, and testing of a classification algorithm

detecting otherwise overlooked cancers. In breast MRI, however, there are many regions of non-specific enhancement that may also be identified as lesions, and if a CADe system is to be useful, it is essential that the number of false positive detections is minimized. This makes the combined task of detection and diagnosis very challenging.

Several attempts to automatically detect lesions have been described in the literature. Mayer et al. [36] automatically segmented images into clusters of similar pixels using a hierarchical Gaussian pyramid and identified clusters with the highest local intensity values. This process led to the creation of about 2,500 objects for each breast exam from which morphological and dynamic features were extracted. After removing most of these objects using size and volume criteria, the remaining objects were classified as lesions or artifacts by a first ANN and then the lesions were classified as malignant or benign by a second ANN. Malignant lesions were detected with a sensitivity of 95% and a specificity of 92%. Diane M. Renz and coworkers [37] used the same approach on an independent dataset and reported a sensitivity of 97% and a specificity of 76%.

Anna Vignati and cowokers [38] proposed a lesion detection pipeline that included breast segmentation, image registration, and the normalization of contrast using the signal intensity in the blood vessels. In order to reduce the number of false-positive detections, they used a number of heuristically derived rules, which included a minimum size criteria of 20 mm^3 and the rejection of any lesions where variation in signal intensity exceed a certain threshold. They were able to detect 89% of all lesions with a false detection rate of 4 false detections per breast. Most of the false-positive detections were due to blood vessels. The lesions detected were then classified as malignant or benign using a *support vector machine* [23].

Yan-Hao Huang and coworkers [39] used a thresholding method to isolate the enhancing tissue from background and then subdivided the enhancing regions into four groups using fuzzy clustering. This process still tended to identify background enhancement and vessels as suspicious, so a multi-scale Hessian filter was used to identify mass lesions. Morphological, texture, and enhancement features were extracted from the detected lesions; and logistic regression was used to classify malignant lesions. They reported a sensitivity of 92% with 4.6 false positives per case.

Albert Gubern-Merida and coworkers [31] used both Laplacian and Hessian filters to identify bright blob-like structures as potential lesions. Their patient population included women with both mass and non-mass malignant lesions and women with negative screening examinations and no breast cancer. Women with biopsy-proven benign lesions were not included in this study. They then compared several different classification methods and found that a random forest classifier gave the best performance with 7 false-positive lesions per patient at a sensitivity of 95%.

Hongbo Wu and coworkers [40] used an ANN with two hidden layers to classify small patches of the dynamic image as either lesion or non-lesion. In order to overcome the problem of insufficient labeled data to train a deep neural network, they used a denoising autoencoder [41], which allows features to be learned directly from unlabeled data. Once the network was pre-trained using unlabeled data, a smaller number of labeled patches were used to train the classifier to differentiate between lesions and non-lesions and a sensitivity of 92% with 17 false candidate lesion regions per volume was obtained. Once the lesions have been identified, it is possible to extract more conventional morphological and textural features and Hongbo Wu [42] found that adding a cascade of random forest classifiers, one to remove false-positive detections and one to differentiate between malignant and benign lesions, gave a final sensitivity of 94% at 0.12 false-positive detections per normal study. Figure 7.4 illustrates the work flow for the final classification algorithm.

It is difficult to directly compare the results from these studies as the patient population differs in each case. In most studies, patients with biopsy-proven malignant or benign lesions are selected, but this does not assess the false-positive rate in examinations that do not contain any lesions at all. In the study by Albert Gubern-Mérida and coworkers [31], the false-positive rate is assessed on negative screening exams where 2 years' follow-up confirmed that there was no breast cancer but no biopsied benign lesions were included in the study. In the master's thesis by Hongbo Wu [42], the false-positive rate was also assessed on negative screening exams but benign lesions were present in the data used to train the classifiers.

7.5 Preprocessing: Motion Correction (Image Co-registration) and Breast Segmentation

In all CAD systems, features that quantify the change in intensity over time are used to differentiate between normal, benign, and malignant regions. Any motion between the pre- and post-contrast images will have an impact on these quantitative measures; therefore, *motion correction*, also referred to as *image co-registration*, is frequently carried out as a pre-processing step. The registration of contrast-enhanced breast MRI is challenging for two main reasons: the breast tis-

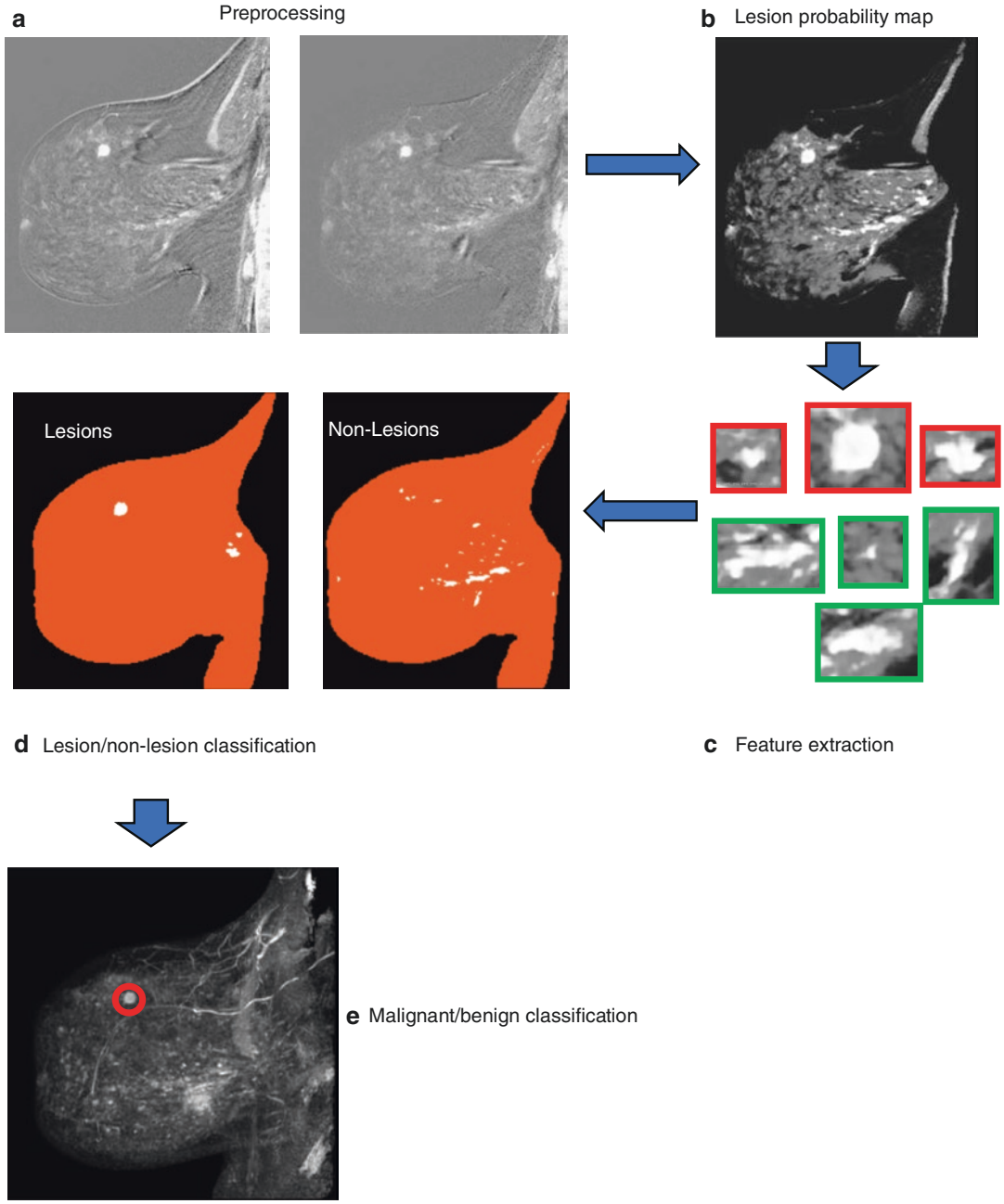

Fig. 7.4 Example of a processing pipeline for a breast MRI CADD system. (**a**) Preprocessing of the data typically involves motion correction. (**b**) An ANN is used to assign a lesion probability to each pixel in the image. (**c**) Once the lesion is identified, features can be extracted relating to enhancement, morphology, and texture. (**d**) A random forest classifier then uses these features to reduce false-positive detections. (**e**) A final classifier then differentiates between malignant and benign lesions

sue is highly deformable and the changing intensity in enhancing regions can affect the accuracy of registration. Several methods have been evaluated motion correction for breast imaging [43–46]. Additional constraints on the deformable registration in order to prevent non-physiological changes in tumor volume have been described [46]. A framework for decoupling the effects of intensity changes due to motion and due to contrast enhancement has also been proposed [47]. Validation of motion correction is very difficult as the breast lacks anatomical landmarks that can be accurately localized in 3D images, and many landmarks are needed to assess a deformable registration algorithm. Some groups have used simulation studies based on finite element models of breast deformation [44, 48, 49] whilst others have attempted to carry out a subjective evaluation [43]. Albert Gubern-Mérida and coworkers [31] assessed the effect of motion correction on the final CAD outcome: the impact on overall accuracy was small but significant and that there was a greater improvement in accuracy for non-mass lesions. Figure 7.5 illustrates how motion correction can improve the quality of subtracted MRI images.

Another useful preprocessing step for systems that perform both detection and diagnosis is *breast segmentation*. The areas of image artifact and high contrast enhancement in the chest can be misclassified as suspicious lesions, and, although radiologists are not affected by these errors, they do cause problems when evaluating automated systems. Processing time may also be affected as image features have to be calculated for every lesion identified by the system. Several breast segmentation algorithms have been developed for the purpose of assessing breast density with MRI [50–55], but Albert Gubern-Mérida and coworkers [31] noted that two lesions were missed due to segmentation errors, so there is still a need for improvements in this area.

7.6 Challenges

The use of CAD systems for mammography is widespread, but this is not true for MRI CAD despite over 15 years of research in this area. The computer-aided evaluation tools described in Sect. 7.2 are available on many commercial workstations, but these do not attempt to detect or diagnose lesions and cannot be used as a second reader.

One of the main differences between breast MRI and digital mammography is that there is much more variation in imaging protocols with

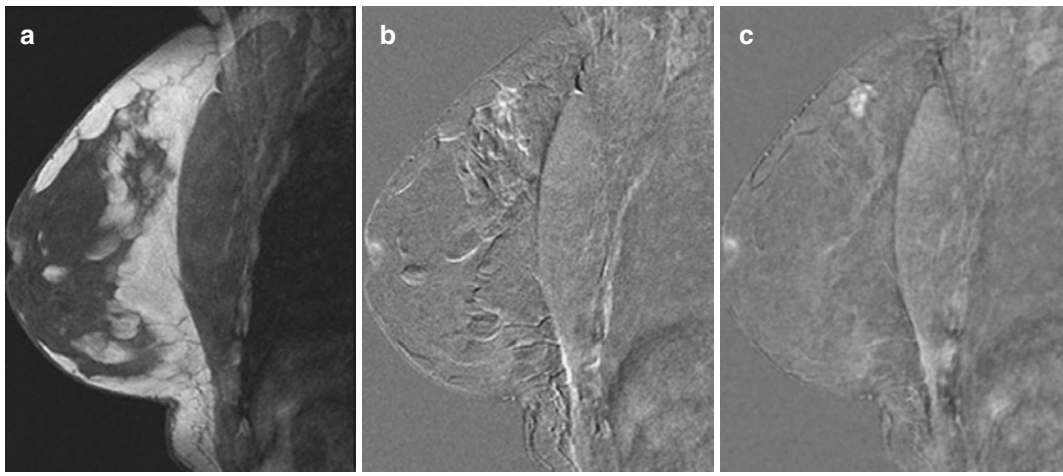

Fig. 7.5 Motion correction. (**a**) Post-contrast image. (**b**) Result of subtracting the pre-contrast image from the post-contrast image. The effect of motion between the acquisition of these two images is well visible. (**c**) Subtracted image after motion correction [43]

MRI. Some differences—such as the use of 1.5 T or 3 T field strengths, the use of fat suppression, the type and dose contrast material and its injection protocol, or the timing of post-contrast images—will affect the relative signal intensity in the lesion compared with the background. Other differences—such as the choice of acquisition plane and the pixel size used—will affect the morphological features. A few studies have evaluated the accuracy of CAD systems that have been trained using data acquired using one protocol and then tested using data acquired using a different protocol, scanner or from a different institution. Weijie Chen and coworkers [33] compared datasets acquired on scanners from two different manufacturers and found that there was no significant difference in accuracy between a classifier trained on dataset 1 and tested on dataset 2 or vice versa. However, the protocols for the two datasets were very similar; both carried out acquisition in the coronal plane, no fat suppression was used, and the temporal resolution only differed by one second. Anna Vignati and coworkers [38] designed their lesion detection algorithm to work with both fat-saturated and non-fat saturated images, and their algorithm was trained and tested using images acquired using both protocols. Their two datasets also had very different temporal resolutions, and the effect of this was minimized by taking the mean signal intensity over the sequence of images and then normalizing intensity values using the intensity in the mammary blood vessels. These studies suggest that it is possible to design a CAD algorithm to work across different datasets from different institutions, but *so far no authors have evaluated a fully automatic detection and classification algorithm in a clinically realistic scenario, where the software is tested on totally unseen images acquired using different protocols to those represented in the data used to train the algorithm*.

The lack of standardization of imaging protocols is not the only reason that comparing the results of different breast MRI CAD studies is difficult. The patient populations also vary greatly from study to study, and this has an impact on the size and types of lesions used to train and test the algorithms. In most of the earlier studies, patients were undergoing MRI as a follow-up examination after mammography to either provide additional diagnostic information or to exclude the presence of additional lesions before surgery. *In later studies, an increasing number of high-risk patients undergoing MRI screening have been included and, as a result, such studies may contain a greater proportion of very small lesions*.

It is important to determine how best to incorporate CAD into breast radiologists' workflow. For example, should the automated method be run before the radiologist reviews the images in order to speed up the work flow, or should it only be applied as a second look after the initial assessment has been made? The true impact of a breast MRI CAD system on sensitivity, specificity, and reporting times can only be evaluated in the context of the clinical workflow, which includes the breast radiologist; and only a few small studies [6, 56] have attempted this so far.

7.7 Opportunities

The use of additional MRI sequences to the DCE acquisition could improve discrimination between malignant and benign breast lesions. Although T2-weighted imaging is widely used in clinical breast MR, only a few studies have looked at the effect of adding T2 image features to classification [57, 58]. Diffusion-weighted imaging [59] and DCE-MRI with higher temporal resolution [60, 61] could also provide more discriminative features, but these sequences, especially the latter, are less commonly performed.

Incorporating information from previous MRI studies could also improve the accuracy of CAD systems. Women enrolled on MRI breast screening programs typically have annual examinations, and incorporating information from previous visits could improve specificity. Similarly, it could be advantageous to incorporate information derived from mammography.

Recent advances in machine learning have the potential to further improve the accuracy of breast MRI CAD. There has recently been a great

deal of excitement over the use of *convolutional neural networks (CNNs)*, which are capable of learning features directly from imaging data [62], and this approach has already been used to segment fibroglandular tissue in breast MRI images [53] and to classify lesions in mammography [63]. The performance of a CNN usually improves as the number of labeled training cases increases. Large databases of labeled images have been made available for several other CAD applications including mammography and nodule detection in chest computed tomography, and these have facilitated research and development in these areas. The creation of a large, publicly available, well-annotated, multi-institutional database for breast MRI would likely accelerate progress toward clinical CAD systems for breast MRI.

Significant progress has been made in the accuracy of breast MRI CAD, but in order to move this work into the clinical domain, it is essential that CAD platforms are tested in the context of the radiologist's work flow and it is also essential that large-scale, multi-institutional studies are carried out to determine how robust these methods are when data is acquired on multiple scanners and with different protocols.

References

1. Morris EA, Comstock CE, Lee CH (2013) ACR BI-RADS® Magnetic Resonance Imaging. In: American College of Radiology. Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
2. Tofts PS, Brix G, Buckley DL et al (1999) Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging 10:223–232
3. Furman-Haran E, Degani H (2002) Parametric analysis of breast MRI. J Comput Assist Tomogr 26:376–386
4. Lehman CD, Peacock S, DeMartini WB, Chen X (2006) A new automated software system to evaluate breast MR examinations: improved specificity without decreased sensitivity. AJR Am J Roentgenol 187:51–56
5. Arazi-Kleinman T, Causer PA, Jong RA, Hill K, Warner E (2009) Can breast MRI computer-aided detection (CAD) improve radiologist accuracy for lesions detected at MRI screening and recommended for biopsy in a high-risk population? Clin Radiol 64:1166–1174
6. Baltzer PA, Freiberg C, Beger S et al (2009) Clinical MR-mammography: are computer-assisted methods superior to visual or manual measurements for curve type analysis? A systematic approach. Acad Radiol 16:1070–1076
7. Kelcz F, Furman-Haran E, Grobgeld D, Degani H (2002) Clinical testing of high-spatial-resolution parametric contrast-enhanced MR imaging of the breast. AJR Am J Roentgenol 179:1485–1492
8. Dorrius MD, Jansen-van der Weide MC, van Ooijen PM, Pijnappel RM, Oudkerk M (2011) Computer-aided detection in breast MRI: a systematic review and meta-analysis. Eur Radiol 21:1600–1608
9. Liney GP, Sreenivas M, Gibbs P, Garcia-Alvarez R, Turnbull LW (2006) Breast lesion analysis of shape technique: semiautomated vs. manual morphological description. J Magn Reson Imaging 23:493–498
10. Chen W, Giger ML, Bick U (2006) A fuzzy c-means (FCM)-based approach for computerized segmentation of breast lesions in dynamic contrast-enhanced MR images. Acad Radiol 13:63–72
11. Cui Y, Tan Y, Zhao B et al (2009) Malignant lesion segmentation in contrast-enhanced breast MR images based on the marker-controlled watershed. Med Phys 36:4359–4369
12. Levman J, Warner E, Causer P, Martel A (2014) Semi-automatic region-of-interest segmentation based computer-aided diagnosis of mass lesions from dynamic contrast-enhanced magnetic resonance imaging based breast cancer screening. J Digit Imaging 27:670–678
13. Zheng Y, Englander S, Baloch S et al (2009) STEP: spatiotemporal enhancement pattern for MR-based breast tumor diagnosis. Med Phys 36:3192–3204
14. Baltzer PAT, Dietzel M, Kaiser WA (2013) A simple and robust classification tree for differentiation between benign and malignant lesions in MR-mammography. Eur Radiol 23:2051–2060
15. Chen W, Giger ML, Lan L, Bick U (2004) Computerized interpretation of breast MRI: Investigation of enhancement-variance dynamics. Med Phys 31:1076–1082
16. Lucht RE, Knopp MV, Brix G (2001) Classification of signal-time curves from dynamic MR mammography by neural networks. Magn Reson Imaging 19:51–57
17. Levman J, Leung T, Causer P, Plewes D, Martel AL (2008) Classification of dynamic contrast-enhanced magnetic resonance breast lesions by support vector machines. IEEE Trans Med Imaging 27:688–696
18. Jansen SA, Fan X, Karczmar GS, Abe H, Schmidt RA, Newstead GM (2008) Differentiation between benign and malignant breast lesions detected by bilateral dynamic contrast-enhanced MRI: a sensitivity and specificity study. Magn Reson Med 59:747–754
19. Gallego-Ortiz C, Martel AL (2016) Improving the accuracy of computer-aided diagnosis for breast MR

imaging by differentiating between mass and non-mass lesions. Radiology 278:679–688
20. Stoutjesdijk MJ, Veltman J, Huisman H et al (2007) Automated analysis of contrast enhancement in breast MRI lesions using mean shift clustering for ROI selection. J Magn Reson Imaging 26:606–614
21. Schlossbauer T, Leinsinger G, Wismuller A et al (2008) Classification of small contrast enhancing breast lesions in dynamic magnetic resonance imaging using a combination of morphological criteria and dynamic analysis based on unsupervised vector-quantization. Invest Radiol 43:56–64
22. Chen W, Giger ML, Bick U, Newstead GM (2006) Automatic identification and classification of characteristic kinetic curves of breast lesions on DCE-MRI. Med Phys 33:2878–2887
23. Agliozzo S, De Luca M, Bracco C et al (2012) Computer-aided diagnosis for dynamic contrast-enhanced breast MRI of mass-like lesions using a multiparametric model combining a selection of morphological, kinetic, and spatiotemporal features. Med Phys 39:1704–1715
24. Gilhuijs KG, Giger ML, Bick U (1998) Computerized analysis of breast lesions in three dimensions using dynamic magnetic-resonance imaging. Med Phys 25:1647–1654
25. Levman JE, Martel AL (2011) A margin sharpness measurement for the diagnosis of breast cancer from magnetic resonance imaging examinations. Acad Radiol 18:1577–1581
26. Haralick RM, Shanmugam K, Dinstein I (1973) Textural features for image classification. IEEE Trans Syst Man Cybern 6:610–621
27. Gibbs P, Turnbull LW (2003) Textural analysis of contrast-enhanced MR images of the breast. Magn Reson Med 50:92–98
28. Chen W, Giger ML, Li H, Bick U, Newstead GM (2007) Volumetric texture analysis of breast lesions on contrast-enhanced magnetic resonance images. Magn Reson Med 58:562–571
29. Ertaş G, Gülçür HO, Tunaci M (2007) Improved lesion detection in MR mammography: three-dimensional segmentation, moving voxel sampling, and normalized maximum intensity-time ratio entropy. Acad Radiol 14:151–161
30. Breiman L (2001) Random forests. Mach Learn 45:5–32
31. Gubern-Mérida A, Martí R, Melendez J et al (2015) Automated localization of breast cancer in DCE-MRI. Med Image Anal 20:265–274
32. Gallego-Ortiz C, Martel AL (2016) Interpreting extracted rules from ensemble of trees: application to computer-aided diagnosis of breast MRI. ICML workshop on human interpretability in machine learning (WHI 2016) arXiv:1606.08288. https://arxiv.org/abs/1606.08288. Accessed 30 Jun 2020
33. Chen W, Giger ML, Newstead GM, Bick U, Jansen SA, Li H, Lan L (2010) Computerized assessment of breast lesion malignancy using DCE-MRI robustness study on two independent clinical datasets from two manufacturers. Acad Radiol 17:822–829
34. Nie K, Chen J-H, Yu HJ, Chu Y, Nalcioglu O, Su M-Y (2008) Quantitative analysis of lesion morphology and texture features for diagnostic prediction in breast MRI. Acad Radiol 15:1513–1525
35. Rakoczy M, McGaughey D, Korenberg MJ, Levman J, Martel AL (2013) Feature selection in computer-aided breast cancer diagnosis via dynamic contrast-enhanced magnetic resonance images. J Digit Imaging 26:198–208
36. Mayer D, Vomweg TW, Faber H et al (2006) Fully automatic breast cancer diagnosis in contrast enhanced MRI. Int J CARS 1(Suppl 1):325–343
37. Renz DM, Böttcher J, Diekmann F et al (2012) Detection and classification of contrast-enhancing masses by a fully automatic computer-assisted diagnosis system for breast MRI. J Magn Reson Imaging 35:1077–1088
38. Vignati A, Giannini V, De Luca M et al (2011) Performance of a fully automatic lesion detection system for breast DCE-MRI. J Magn Reson Imaging 34:1341–1351
39. Huang YH, Chang YC, Huang CS, Chen JH, Chang RF (2014) Computerized breast mass detection using multi-scale Hessian-based analysis for dynamic contrastenhanced MRI. J Digit Imaging 27:649–660
40. Wu H, Gallego-Ortiz C, Martel A (2015) Deep artificial neural network approach to automated lesion segmentation in breast DCE-MRI. MICCAI-BIA 2015, Proceedings of the 3rd MICCAI workshop on breast image analysis, pp 73–80
41. Le QV (2013) Building high-level features using large scale unsupervised learning. 2013 IEEE international conference on acoustics, speech and signal processing: 8595–8598
42. Wu H (2016) Automatic computer aided diagnosis of breast cancer in dynamic contrast enhanced magnetic resonance images. Master's thesis, University of Toronto. https://tspace.library.utoronto.ca/handle/1807/76158. Accessed 30 Jun 2020
43. Herrmann KH, Wurdinger S, Fischer DR et al (2007) Application and assessment of a robust elastic motion correction algorithm to dynamic MRI. Eur Radiol 17:259–264
44. Martel AL, Froh MS, Brock KK, Plewes DB, Barber DC (2007) Evaluating an optical-flow-based registration algorithm for contrast-enhanced magnetic resonance imaging of the breast. Phys Med Biol 52:3803–3816
45. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ (1999) Nonrigid registration using free-form deformations: application to breast MR images. IEEE Trans Med Imaging 18:712–721
46. Rohlfing T, Maurer CR Jr, Bluemke DA, Jacobs MA (2003) Volume-preserving nonrigid registration of MR breast images using free-form deformation with an incompressibility constraint. IEEE Trans Med Imaging 22:730–741
47. Ebrahimi M, Martel AL (2009) A general PDE-framework for registration of contrast enhanced images. Med Image Comput Assist Interv 12:811–819

48. Schnabel JA, Tanner C, Castellano-Smith AD et al (2003) Validation of nonrigid image registration using finite-element methods: application to breast MR images. IEEE Trans Med Imaging 22:238–247
49. Mehrabian H, Richmond L, Lu Y, Martel AL (2018) Deformable registration for longitudinal breast MRI screening. J Digit Imaging 31(5):718–726
50. Nie K, Chen JH, Chan S et al (2008) Development of a quantitative method for analysis of breast density based on three-dimensional breast MRI. Med Phys 35:5253–5262
51. Martel AL, Gallego-Ortiz C, Lu Y (2016) Breast segmentation in MRI using Poisson surface reconstruction initialized with random forest edge detection. Proc. SPIE 9784, Medical Imaging 2016: Image Processing, 97841B. Accessed 27 August 2017
52. Ribes S, Didierlaurent D, Decoster N et al (2014) Automatic segmentation of breast MR images through a Markov random field statistical model. IEEE Trans Med Imaging 33:1986–1996
53. Dalmış MU, Litjens G, Holland K et al (2017) Using deep learning to segment breast and fibroglandular tissue in MRI volumes. Med Phys 44:533–546
54. Gubern-Mérida A, Kallenberg M, Mann RM, Marti R, Karssemeijer N (2015) Breast segmentation and density estimation in breast MRI: a fully automatic framework. IEEE J Biomed Heal Informatics 19:349–357
55. Fashandi H, Kuling G, Lu Y, Wu H, Martel AL (2019) An investigation of the effect of fat suppression and dimensionality on the accuracy of breast MRI segmentation using U-nets. Med Phys 46(3):1230–1244
56. Meinel LA, Stolpen AH, Berbaum KS, Fajardo LL, Reinhardt JM (2007) Breast MRI lesion classification: improved performance of human readers with a backpropagation neural network computer-aided diagnosis (CAD) system. J Magn Reson Imaging 25:89–95
57. Bhooshan N, Giger M, Lan L et al (2011) Combined use of T2-weighted MRI and T1-weighted dynamic contrast-enhanced MRI in the automated analysis of breast lesions. Magn Reson Med 66:555–564
58. Ballesio L, Savelli S, Angeletti M et al (2009) Breast MRI: Are T2 IR sequences useful in the evaluation of breast lesions? Eur J Radiol 71:96–101
59. Cai H, Liu L, Peng Y, Wu Y, Li L (2014) Diagnostic assessment by dynamic contrast-enhanced and diffusion-weighted magnetic resonance in differentiation of breast lesions under different imaging protocols. BMC Cancer 14:366
60. Platel B, Mus R, Welte T, Karssemeijer N, Mann R (2014) Automated characterization of breast lesions imaged with an ultrafast DCE-MR protocol. IEEE Trans Med Imaging 33:225–232
61. Abe H, Mori N, Tsuchiya K et al (2016) Kinetic analysis of benign and malignant breast lesions with ultrafast dynamic contrast-enhanced MRI: comparison with standard kinetic assessment. AJR Am J Roentgenol 207:1159–1166
62. Greenspan H, van Ginneken B, Summers RM (2016) Guest Editorial Deep Learning in Medical Imaging: Overview and future promise of an exciting new technique. IEEE Trans Med Imaging 35:1153–1159
63. Kooi T, Litjens G, van Ginneken B et al (2017) Large scale deep learning for computer aided detection of mammographic lesions. Med Image Anal 35:303–312

8 Radiogenomics and Phenotype Presentation of Breast Cancer with a Special Focus on High-Risk Women

Katja Pinker, Anke Meyer-Baese, and Elizabeth Morris

Abbreviations

ADC	Apparent diffusion coefficient
BPE	Background parenchymal enhancement
CEIP	Computer-extracted image phenotype
CEST	Chemical exchange saturation transfer
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DWI	Diffusion-weighted imaging
ER	Estrogen receptor
ERF	Enhancing rim fraction
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
IHC	Immunohistochemistry
lncRNA	Long noncoding RNA
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
PR	Progesterone receptor
SER	Signal enhancement ratio
TCGA	The Cancer Genome Atlas
TN	Triple negative
US	Ultrasonography

8.1 Introduction

Breast cancer is a diverse collection of diseases with varying clinical presentations, histologic subtypes, and treatment responses [1, 2]. With the discovery that cancer is a genetic disease, medical research has entered the genomic era, with the goal of devising precise cancer therapies that target specific genetic alterations of a tumor. Although traditional prognostic and predictive factors in breast cancer, such as tumor size, histologic type, tumor grade, receptor status [estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2)], as assessed by immunohistochemistry (IHC), have been well-established, it has become evident that these traditional classifications cannot fully capture the heterogeneity of breast can-

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cer and the classical approach of stratifying patients into treatment groups based on phenotypic biomarkers is insufficient.

8.2 Molecular Subtypes of Breast Cancer and Correlation with Imaging Phenotypes

In the past decade, gene expression profiling has revolutionized breast cancer classifications, and the traditional classifications based on IHC have been replaced by molecular subtypes. Four intrinsic molecular subtypes of breast cancer have been defined by extensive profiling at the DNA, microRNA, and protein levels by The Cancer Genome Atlas (TCGA) Network [3]: luminal A; luminal B; HER2-enriched; and basal-like, the last subtype being mostly, but not entirely overlapping with the triple negative (TN) subgroup (4–6). These subtypes are unevenly distributed among women with breast cancer (Fig. 8.1), with variations according to race, menopausal status, and age (7); and each has a different prognosis, response to treatment, preferential metastatic organs, and recurrence or disease-free survival outcomes [4, 5].

Since 2011, the St. Gallen International Expert Consensus panel has used the molecular subtype–based recommendations for systemic therapies for breast cancer [6, 7]. Currently, *no low-cost genetic testing is readily available, and therefore, IHC surrogates are often used to define the molecular breast cancer subtypes to guide therapy decisions* (Table 8.1). However, it should be mentioned that, although these IHC surrogates can provide clinical guidance, there is a *variable agreement about formal genetic testing (41–100%) and IHC surrogate markers have been shown to be less robust in predicting patient outcomes* [3]. Therefore, there is a strong argument for a more accurate means of differentiating molecular breast cancer subtypes, which poses a unique opportunity for imaging.

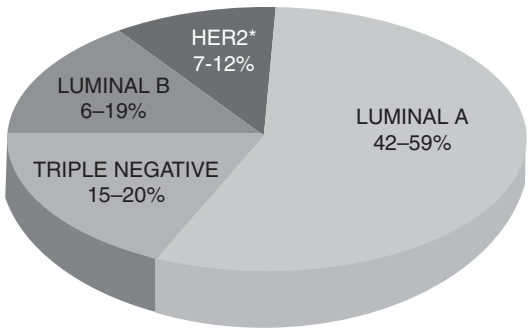


Fig. 8.1 Distribution of molecular breast cancer subtypes. (Modified from J PharmBioallied Sci. 2012 Jan–Mar; 4(1): 21–26)

8.2.1 Luminal Subtype

Hormone receptor (HR)–positive tumors constitute approximately 70% of breast tumors, and HR-positive tumors show a more favorable prognosis than HR-negative breast cancers. Within HR-positive/HER2-negative breast cancer, 90–95% of tumors are of the luminal A and B subtypes [8]. Compared to luminal A cancers, the luminal B subtypes usually have a higher expression of proliferation genes and a worse baseline, distant recurrence-free survival at 5 and 10 years [4]. The occurrence rates of the non-luminal subtypes (HER2-enriched and basal-like tumors) by gene expression profiling are approximately 5.5–11.0% for the HER2-enriched type and 1–5% for the basal-like type. It has been shown that non-luminal tumors have worse outcomes, compared to the luminal A subtype, when treated with endocrine therapy only, and might not benefit from endocrine treatment at all [9].

With respect to imaging phenotypes, it has been shown that low-grade, HR-positive tumors tend to present as masses with poorly circumscribed margins and with posterior acoustic shadowing on ultrasonography (US) (example in Fig. 8.2). Recently, a higher *signal enhancement ratio*[1] of tumor as compared to breast parenchyma

[1]The signal enhancement ratio (SER) is calculated as follows: $(S_1 - S_0)/(S_2 - S_0)$, where S_0 is the precontrast signal, S_1 is the early postcontrast signal, and S_2 is the late postcontrast signal.

Table 8.1 Treatment-oriented classification of subgroups of breast cancer from the St. Gallen Consensus 2015

	Clinico-pathologic surrogate definition						
Intrinsic subtype		ER	PR	HER2	Ki-67	Recurrence risk[a]	Therapy
Luminal A	Luminal A-like	+[b]	+	–	Low (<15%)	Low (if available)	Endocrine therapy, cytotoxic therapy may be added
Luminal B	Luminal B-like[c] (HER2-negative)	+	– or low	–	High (≥15%)	High (if available)	Endocrine therapy for all patients, cytotoxic therapy in most patients
	Luminal B-like (HER2-positive)	+	Any	Over-expressed or amplified	Any	NA	Cytotoxic + anti-HER2 + endocrine therapy
HER2 overexpression	HER2-positive (non-luminal)	Absent	Absent	Over-expressed or amplified	NA	NA	Cytotoxic + anti-HER2 therapy
Basal-like	Triple negative (ductal)	–	–	–	NA	NA	Cytotoxic therapy

Modified from Goldhirsch A et al., Ann Oncol 2013;24:2206–2223 [7]
ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *NA* not applicable
[a]Based on multi-gene-expression assay
[b]Between luminal A-like and luminal B-like subtype, PR cut-off point of ≥20% best corresponded to the luminal A subtype
[c]ER-positive and HER2-negative and at least one of: Ki-67 high, PR-negative or low, or recurrence risk high

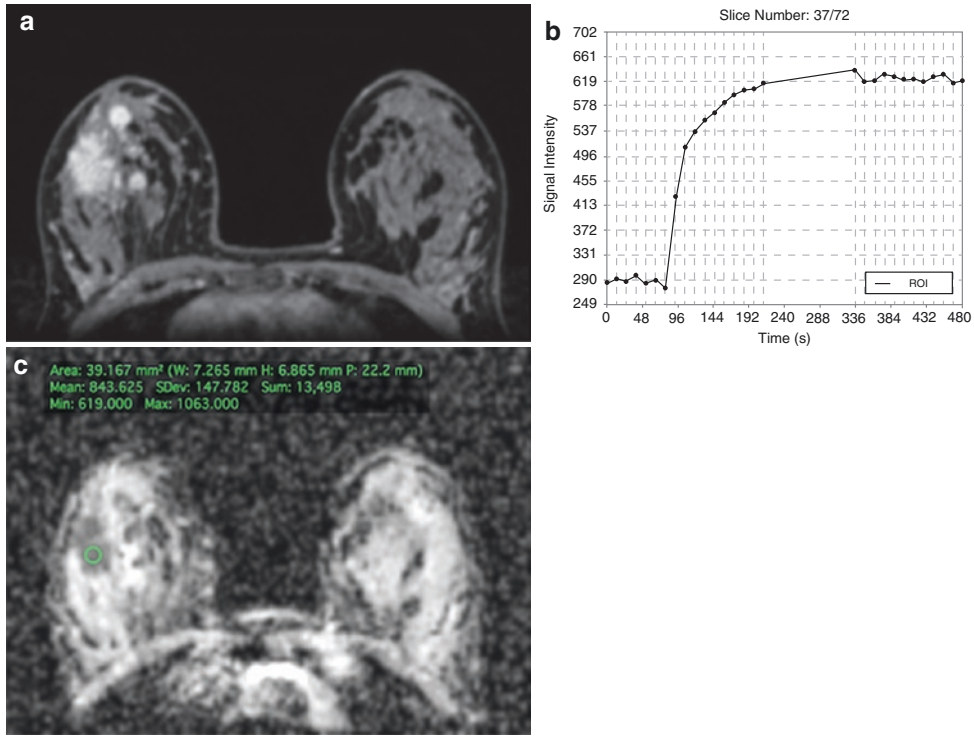


Fig. 8.2 Multifocal HR-positive, HER2-negative invasive ductal cancer grade 1 with a Ki-67 of 20% in a 48-year-old woman, lateral in the right breast. (**a**) The irregular-shaped and spiculated index mass demonstrated (**b**) a heterogeneous initial fast/plateau contrast enhancement. On DWI, the lesion also showed a restricted diffusivity (**c**) with mean ADC values below the cut-off for malignancy (0.843×10^{-3} mm²/s)

in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was found to be associated with the luminal B subtype [10, 11].

8.2.2 HER2-Enriched Subtype

Tumors with HER2 overexpression are found in 15–25% of invasive breast cancers and have a worse prognosis, but respond well to HER2-targeted therapies [12]. Within the HER2 subtype of breast cancer, HR-positive tumors are associated with increased disease-free survival and overall survival, compared to HR-negative tumors. Heterogeneous intrinsic subtypes exist within HER2-positive tumors, hinting at the potential to predict the degree of a patient response to trastuzumab [13]. A recent meta-analysis of imaging features of HER2-enriched tumors identified several features that were associated with HER2 overexpression, including fine linear or branching microcalcifications, extremely dense breasts, high suspicion for malignancy on mammography or US, irregularly shaped masses on US, and fast initial enhancement or washout kinetics on DCE-MRI (example in Fig. 8.3) [14]. Whereas a tumor presentation with a circumscribed margin shows a decreased probability of HER2 overexpression, multicentric and/or multifocal disease is more frequently found in the HER2 subtype or luminal B subtype than in the luminal A or basal-like subtype [15].

8.2.3 Basal-Like Subtype

The basal-like subtype is a unique subtype among breast cancers. Whereas luminal A cancers have the best prognosis, basal-like tumors have the worst. Most TN breast cancers, i.e., those that are ER-negative, PR-negative, and HER2-negative, correspond to the basal-like subtype [8], and therefore, the terms "TN" and "basal-like" are

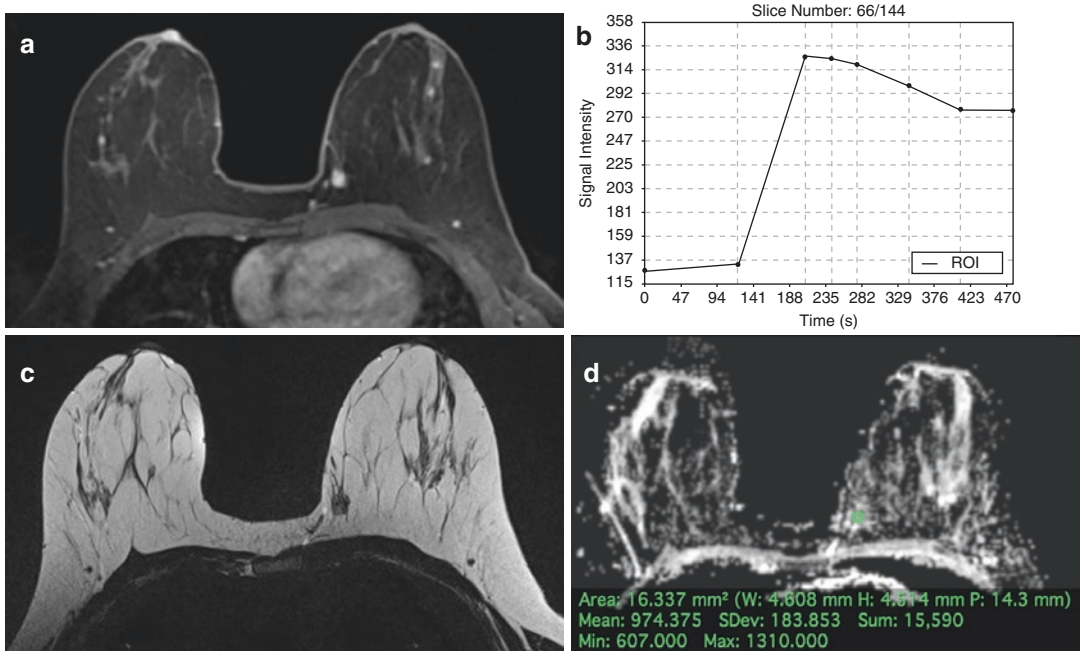


Fig. 8.3 HER2-enriched, HR-negative invasive ductal cancer grade 3 with a Ki-67 of 40% in a 48-year-old woman, medial in the left breast. (**a**) The irregular-shaped and spiculated mass demonstrated (**b**) a homogenous initial fast/wash-out contrast enhancement. (**c**) On T2-weighed images, the lesion is iso- to slightly hyperintense compared to normal fibroglandular tissue. On DWI, the lesion also showed a restricted diffusivity (**d**) with mean ADC values below the cut-off for malignancy (0.974×10^{-3} mm^2/s), which is additionally indicative of a malignant finding

often used interchangeably. However, *in the subset of TN breast cancers, which constitute up to 20% of breast cancers, all molecular subtypes exist, which show distinct differences in outcomes and responses to treatment* [16]. Therefore, a way to distinguish between basal-like and non-basal-like subtypes within TN breast cancer is highly desirable and has opened new avenues for advanced imaging.

Imaging phenotypes of TN breast cancers have been investigated in several studies. It was found that TN breast cancers tend to manifest as a mass with a relatively circumscribed margin and without calcifications. These women are also more likely to present with pure ductal carcinoma in situ or an in situ component adjacent to invasive cancers [31] and are more often associated with calcifications on mammography. [17]. On US, TN breast cancers often present as a mass with circumscribed margins and posterior acoustic enhancement. On MRI, TN breast cancers frequently present as a mass with high signal intensity on T2-weighted sequences and rim enhancement on T1-weighted images (example in Fig. 8.4) [18–20]. For the prediction of response to a treatment or the survival outcome of TN breast cancers, the presence of intratumoral necrosis and an irregular mass on DCE-

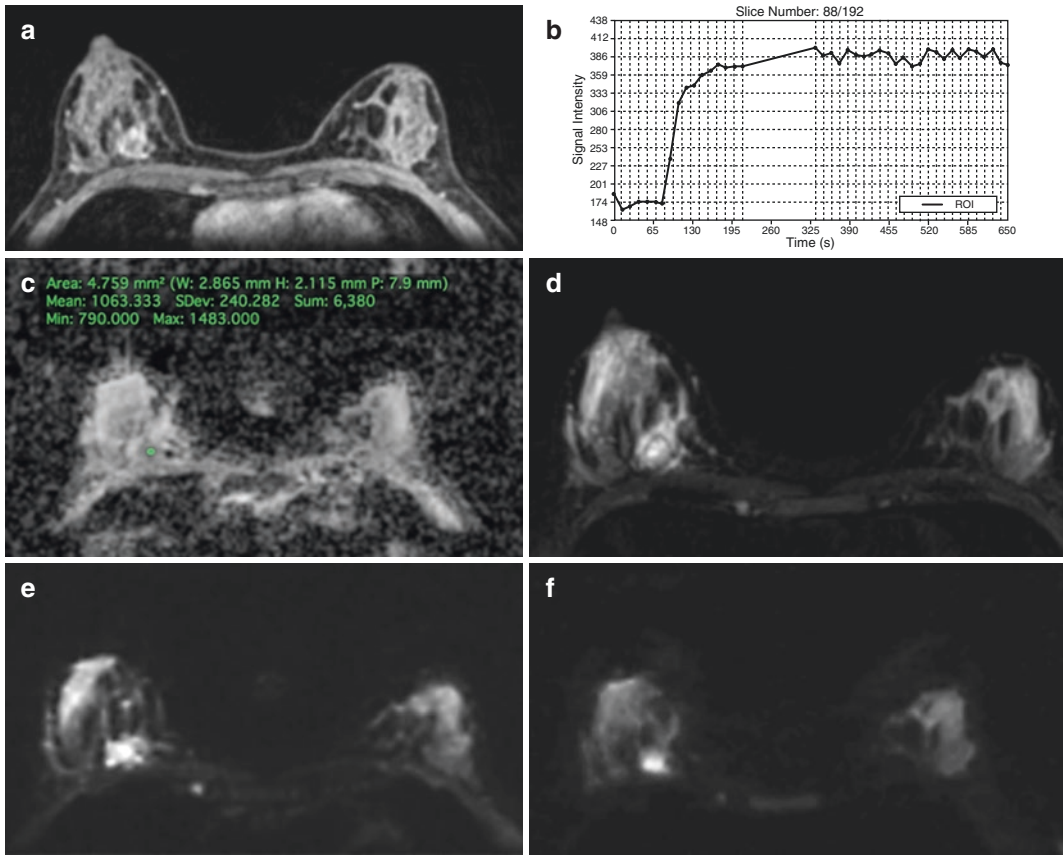


Fig. 8.4 Invasive ductal TN cancer with a Ki-67 of 90% in a 44-year-old woman, medial prepectoral in the right breast. On the contrast-enhanced fat-sat T1-weighted image (**a**), the lesion appears as an irregularly shaped inhomogeneous mass, with (**b**) an initial fast enhancement and a post-initial plateau curve. On the ADC map (**c**), the lesion showed a restricted diffusivity and a mean ADC value of (1.063×10^{-3} mm^2/s). Note the high signal on the T2-weighted STIR image (**d**), the similar appearance on DWI obtained with $b = 0$ s/mm^2 (**e**) and the high signal of the only inner part of the lesion on DWI obtained with b = 850 s/mm^2 (**f**). The high signal at the periphery of the lesion in D, E, and F could be attributed also to perilesional edema

MRI were reported to be associated with the treatment failure of neoadjuvant chemotherapy [21, 22], and the presence of a peri-tumoral edema on T2-weighted sequences has been associated with worse recurrence-free survival [23].

8.2.4 Breast Cancers in High-Risk Women

About 10% of all breast cancers are caused by a genetic predisposition. *BRCA1* and *BRCA2* are the most well-known genes whose pathogenic mutations can be responsible for an increased risk of developing breast cancer. Patients with "deleterious" *BRCA1* and *BRCA2* mutations have a 45–87% lifetime risk of developing breast cancer [24–27]. These breast cancers have distinct tumor characteristics, such as grade, and HR status, which differ according to specific *BRCA* mutation types [28, 29].

BRCA1 mutation carriers are more likely to develop invasive ductal carcinomas with a high nuclear and histological grade, particularly TN cancers (example in Fig. 8.5). These more aggressive tumors are more difficult to detect on mammography and often present with apparently benign features, such as a round or oval shape with a circumscribed margin, and are, therefore, also more likely to present as interval cancers. The benign appearance of these cancers is most likely due to a rapid growth rate, especially in TN cancers [30] whose imaging differentiation from benign entities, such as fibroadenomas, is often possible only with MRI, as these lesions do not present with non-enhancing septa and often exhibit intermediate or malignant enhancement kinetics.

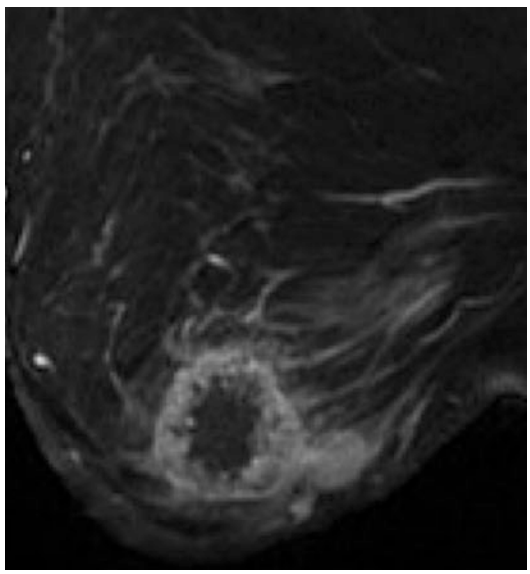


Fig. 8.5 Invasive ductal TN cancer in a *BRCA1* mutation carrier, caudal right breast. The round lesion had indistinct margins and demonstrated a rim enhancement. There was a round, circumscribed satellite lesion in the immediate vicinity, as well as skin thickening

Hormone receptor–positive tumors with a lower histological and nuclear grade are more frequently seen in *BRCA2* mutation carriers [28, 29]. These women are also more likely to present with pure ductal carcinoma in situ or an in situ component adjacent to invasive cancers [31], associated with calcifications on mammography. However, in general, *high-risk breast cancers are less likely to present with microcalcifications compared to the rate of these microcalcifications in the general population where they comprise up to 50% of breast cancers*.

Furthermore, benign enhancement kinetics with MRI have been described for breast cancers associated with both *BRCA1* and *BRCA2* mutations, which can complicate detection with MRI. One study reported a predilection for a prepectoral localization of these breast cancers in high-risk women [32], a finding indirectly confirmed by a study showing that triple-negative breast cancers are located significantly closer to the chest wall than non-triple negative breast cancers [33].

8.3 Radiogenomics and Radiomics of Breast Cancer

Personalized cancer therapy relies on diagnostic tests being equally multilayered and complex to identify the relevant genetic alterations that would render cancers susceptible to treatment. Such tests must extend beyond the identification of single oncogenic defects and, moreover,

should encompass the genomic and molecular complexities of neoplastic disease to support the precise prediction, guidance, and monitoring of a therapy. Medical imaging has always been an integral part of disease diagnosis and treatment decisions in oncology. With significant advances in imaging techniques and analysis as well as the development of high-throughput methods to extract and correlate multiple imaging parameters with genomic data, a new direction has emerged.

*Radiogenomics is a novel approach that aims to correlate imaging characteristics (*i.e.*, the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related characteristics of a given tumor* [34–38]. Radiogenomics is not to be equated with radiomics. Radiogenomics investigates relationships between imaging features and genomics, whereas radiomics refers to the methodology behind the conversion of digital medical images to higher-dimensional, mineable data, using computer classification algorithms, and correlating these features with various data of interest, including patient characteristics, outcomes, and 'omics' data for improved decision support [34, 36, 39, 40]. For a detailed review of the process of *radiomics*, i.e., image acquisition, volume of interest identification, segmentation, feature extraction and quantification, database building, classifier modeling, data sharing, and its challenges, refer to recent review articles by Gillies et al. [36] and Sala et al. [41].

The term "radiogenomics" was initially coined by radiation oncology specialists to describe the associations between patient genetics and variations of patient sensitivities to radiation treatment [42–44]. In contrast to the current use of radiogenomics, this area of research focuses on the identification of phenotypes that represent normal tissue radiation toxicity and will not be discussed in this chapter.

Radiogenomics represents the evolution of radiology-pathology correlation from the anatomical-histological to the cellular and subcellular level. It is designed to facilitate a deeper understanding of tumor biology and capture the intrinsic tumor heterogeneity. Ultimately, the goal of radiogenomics is to develop imaging biomarkers for outcome that incorporate both phenotypic and genotypic metrics. In a typical radiogenomics study, several qualitative and/or quantitative imaging features, such as signal intensity, shape, size, volume, or texture, are manually or semi-/automatically extracted and computed from an imaging dataset and are then correlated with individual gene expression profiles, genomic subtypes, or other molecular subtypes. This correlation provides useful bi-directional information: imaging parameters can be used to predict cancer genotypes, and imaging phenotypes can be predicted from gene signatures [34, 35, 45, 46].

In breast imaging, the field of radiogenomics is just emerging. The first papers were published in 2012 [47], and the number has been increasing ever since. To date, radiogenomics in breast imaging is almost exclusively dominated by MRI [48]. This is due to the characteristics of the test, intrinsically multiparametric. MRI gained an essential role in breast imaging, with multiple established indications, being the most sensitive test for breast cancer detection [49–51]. DCE-MRI provides morphological, as well as functional information, about neoangiogenesis as a tumor-specific feature [52, 53]. To overcome MRI limitations in specificity, functional parameters have been explored. While functional parameters, such as diffusion-weighted imaging (DWI), and, to some extent, proton MR spectroscopy (MRS), have been implemented in the clinical routine [54, 55], other promising MRI parameters, such as phosphorus MRS, chemical exchange saturation transfer (CEST), and sodium imaging are currently under investigation [56–60].

To date, a state-of-the-art MRI of the breast is usually performed as a multiparametric imaging protocol and comprises high-resolution DCE-MRI, T2-weighted imaging, and diffusion-weighted imaging (DWI). Thus far, MRI radiogenomics in the breast has mainly focused on DCE-MRI and the analyses of either individual genomic signatures, breast cancer molecular subtypes, or clinically used recurrence scores, with promising results. *Although no radiogenomics study has currently specifically focused on*

breast cancer in high-risk patients, the field of radiogenomics in breast cancer is rapidly evolving and it is only a matter of time before this topic will be addressed. In the following section, we will briefly explain the image extraction techniques and radiogenomic approaches, then we will review current applications and available results of radiogenomics in breast cancer, and finally we will address its challenges.

8.3.1 Image Extraction Techniques

The extraction of image information for breast radiogenomics can be performed with human input, semi-automatically, or fully automatically.

With *human feature extraction*, MRI images are typically reviewed by the reader to provide an assessment of specific variables. These variables are usually based on established descriptors used in routine breast imaging, such as enhancement type (mass versus non-mass), shape, margin, pattern, or enhancement kinetics, as defined in the BI-RADS MRI lexicon [50]. Although human-extracted features can be easily assessed without any sophisticated post-processing or software, they are hampered by suboptimal inter- and intra-observer variability, which may result in weaker correlations, and, depending on the number of measurements needed, can be time-consuming, which limits implementation in clinical practice [45]. With the respect to these limitations, semi- and fully automatic approaches for feature extraction are preferred.

Semi-automatic or automatic approaches use computer algorithms to analyze images and extract the features of interest. With *semi-automatic approaches*, there is still a degree of human input, such as delineation of the tumor or definition of a region of interest necessary to allow further analysis and feature extraction. In *fully automated approaches*, computer vision algorithms are used and no human input is required, eliminating this potential source of error. Computer vision algorithms and data mining can assess a multitude of textural and kinetic features that are beyond human perception.

Textural features are typically evaluated by texture analysis, which aims to quantify the internal morphology and the three-dimensional structure of the lesion in question. *Texture analysis* approaches usually address four major tasks: feature extraction; texture discrimination; texture classification; and, if necessary, shape reconstruction [61, 62]. In the first step of feature extraction, calculations are performed that generate a numerical value for a specific texture property. These calculations can be based on statistical, structural, model-based, signal processing, and transform methods. To date, there are already texture libraries publicly available, which provide such variables as the *MaZda features* [61] and *Haralick features* [63]. For texture discrimination, the images are then segmented and regions with similar texture features are grouped together. Consequently, these texture regions are matched with predefined variables, such as fat, fibroglandular, benign, or malignant tissue, and thus, the texture is classified. Figure 8.6 demonstrates a segmentation algorithm of a breast MRI with classification into fat and fibroglandular tissue. The derived textural information can be used to reconstruct three-dimensional shapes or models. Finally, the results of the texture analysis can be correlated with genomic or outcome variables.

In addition to the evaluation of textural features, *data mining* algorithms can also assess enhancement kinetics, which correlate with neoangiogenesis as a tumor-specific feature. Kinetic features quantify the enhancement of tumors over time on high temporal resolution, contrast-enhanced MRI. Kinetic variables that are commonly assessed are the rate of contrast enhancement on the first post-contrast sequences, the magnitude of the peak enhancement, or the slope of the late post-contrast sequences. In a study by Maciej A. Mazurowski and coworkers [10], a significant association was found between the luminal B subtype and a dynamic feature that quantifies the relationship between lesion enhancement and background parenchymal enhancement (BPE).

In contrast to human-extracted features, *computer vision algorithms* allow rapid throughput of

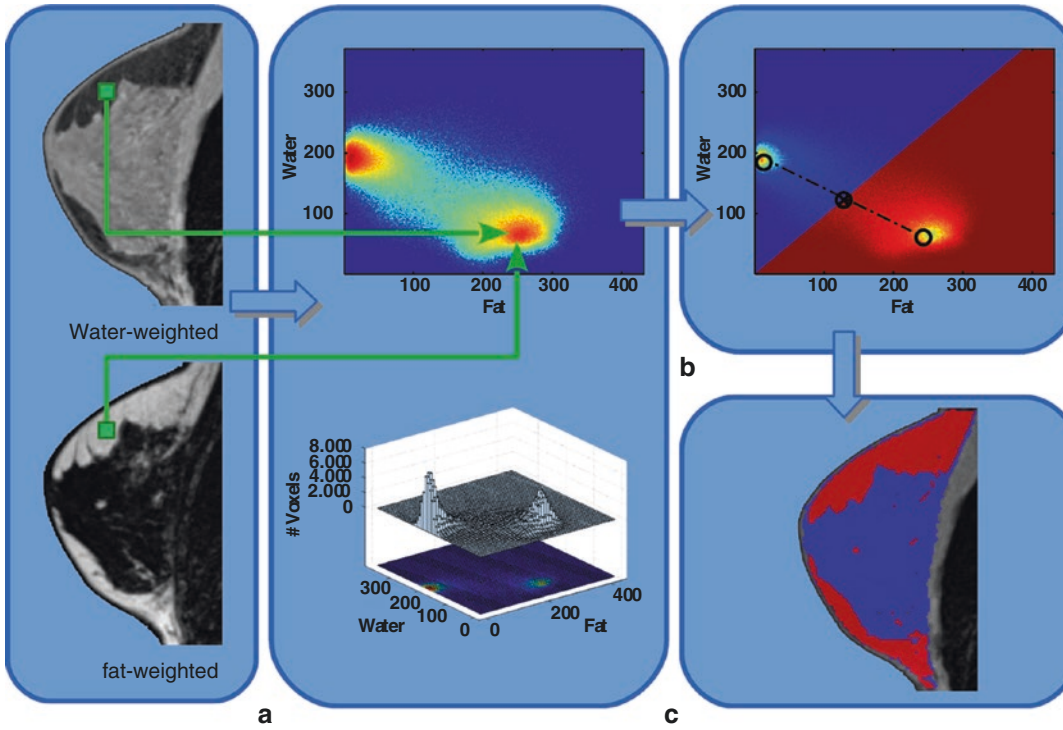


Fig. 8.6 Illustration of the process of fibroglandular tissue segmentation. (**a**) Joint histogram of fat- and water-weighted pixel intensities. *Top*, Heat-map illustration, where *red* indicates a high number of voxels sharing the specific combined fat-weighted and water-weighted values. *Bottom*, The 3D representation of the histogram. The *green* arrow shows at which position the selected voxel (*green square*) is located in the histogram, with a high value in the fat-weighted image and a low value in the water-weighted image. (**b**) The optimal separating line is determined by (1) detecting two cluster peaks that corresponded to the majority of the voxels containing the two different tissue types (*circle symbols*), (2) determining the line bisector between the peaks (symbol ⊗ in the diagram), and (3) by setting the threshold as a straight line from the diagram origin to ⊗], and dividing the histogram into fat tissue (*red*) and dense tissue (*blue*) area. (**c**) Illustration of the assignment of each voxel to either fat tissue (*red*) or dense tissue (*blue*) according to the SI values and the determined separating line. (Reprinted with permission from: Wengert GJ1, Helbich TH, Vogl WD, Baltzer P, Langs G, Weber M, Bogner W, Gruber S, Trattnig S, Pinker K. Introduction of an automated, user-independent, quantitative, volumetric magnetic resonance imaging breast density measurement system using the Dixon sequence: comparison with mammographic breast density assessment. Invest Radiol. 2015;50:73–80)

large image data volumes, are not reader-dependent, can provide information that is beyond human perception, and could theoretically be easily implemented into the clinical workflow. However, to date, the results of these computer vision algorithms are not readily reproducible due to a lack of image protocol and data extraction standardization. Before a seamless implementation into the clinical routine is possible, commercially available solutions must be developed.

8.3.2 Radiogenomics Approaches

Radiogenomics studies are categorized as either *exploratory* or *hypothesis-driven*. In the first category, a radiogenomics approach is used to test the extracted imaging features against a multitude of different genomic variables. In this approach, metrics, such as the *false discovery rate*, are often implemented to identify meaningful prospective variables in the setting of multiple hypotheses testing [48, 64, 65]. Another method

is *hierarchical clustering*, which is used to identify similarities in large genetic datasets. In this approach, individual data points that show similarities are clustered until the clustering process has established the relationship between all data points. The largest group at the top of the hierarchical clustering map is then used to define different groups within the dataset. A famous example of this approach is the original definition of the molecular subtypes of breast cancer by Charles M. Perou and coworkers [66].

In *hypothesis-driven radiogenomics*, research imaging phenotypes are correlated with specific genetic alterations or signatures [45], with several potential benefits for diagnostic and therapeutic interventions. *As currently no low-cost genetic testing is readily available, the development of accurate surrogates by means of radiogenomics with MRI would provide an attractive alternative*. Alternatively, radiogenomics might be used to develop imaging surrogates for specific genetic signatures to predict outcome variables, such as response to therapy or early metastases [67, 68].

8.4 Applications of Radiogenomics in Breast Cancer Management

8.4.1 Individual Genomic Signatures

The first radiogenomic breast MRI study was an exploratory analysis of the correlations of global gene expression characterization with DCE-MRI, which set the stage for the radiogenomic age in breast imaging. In this pilot study, Shota Yamamoto and coworkers [47] investigated ten patients with preoperative DCE-MRI and global gene expression analysis and presented a preliminary radiogenomic association map that linked MRI phenotypes to underlying global gene expression patterns in breast cancer. In this study, high-level analysis identified 21 imaging traits that were globally significantly correlated with 71% of the total genes measured in patients with breast cancer. Moreover, there were significant correlations between heterogeneous enhancement patterns and the interferon-rich breast cancer subtype (recently identified from ER-PR-HER2-tumors, showing overexpression of interferon-regulated genes). In addition, 12 imaging traits significantly correlated (false discovery rate <0.25) with breast cancer gene sets and 11 traits correlated (false discovery rate <0.25) with prognostic gene sets. In a more recent study, the same groups of authors [66] pursued these analyses and investigated the multiscale relationships among quantitative, computer vision-extracted DCE-MRI phenotypes, early metastasis, and long noncoding RNA (lncRNA) expression, using high-resolution, next-generation RNA sequencing. Radiogenomic analysis allowed the identification of eight lncRNAs that were significantly associated with the enhancing rim fraction (ERF) score. The ERF score is associated with early metastasis and the expression of *Homeobox transcript antisense intergenic RNA*, a known predictor of poor metastasis-free survival (Fig. 8.7).

8.4.2 Correlation with Molecular Breast Cancer Subtypes

Most data for breast MRI radiogenomics is derived from molecular breast cancer subtypes [69–72]. There is a strong demand for more accurate, non-invasive means of differentiating molecular breast cancer subtypes, and radiogenomics could, therefore, provide an attractive alternative.

Several authors [10, 73, 74] have investigated DCE-MRI enhancement kinetics and molecular breast cancer subtypes. Eric Blaschke and Hiroyuki Abe [74] used IHC surrogates of molecular breast cancer subtypes and found that HER2-positive cancers showed a more rapid initial phase enhancement than other subtypes. Maciej A. Mazurowski and coworkers [10], as already mentioned above, investigated DCE-MRI enhancement kinetics and molecular subtypes derived from formal genetic testing in 48 patients and found an increased ratio of tumor to background parenchymal enhancement in HER2-

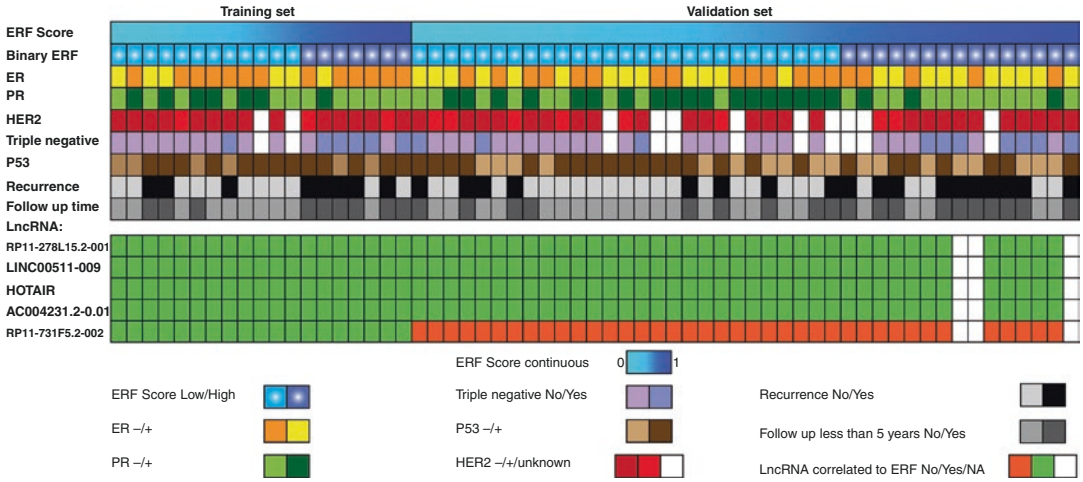


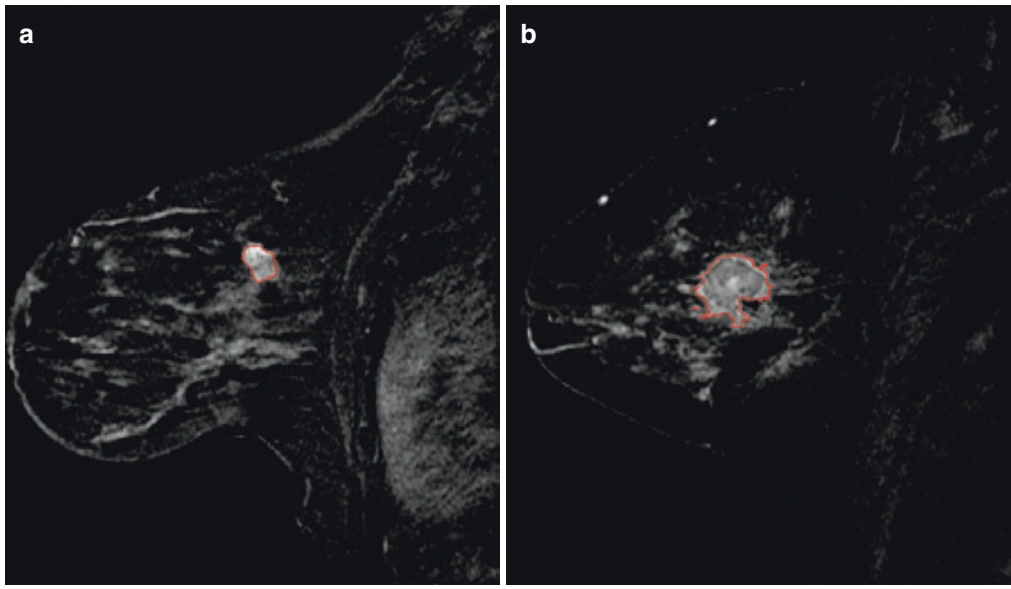
Fig. 8.7 Graph shows molecular characteristics of the enhancing rim fraction (ERF) score phenotype in training (n = 19) and validation (n = 42) sets. Continuous ERF scores for each patient are listed from low to high in the respective datasets. Status of estrogen receptor, progesterone receptor, epidermal growth factor receptor 2, triple negative receptors, tumor protein 53, and lncRNA expression are provided as labeled. Recurrence and follow-up data are also included. (Reprinted with permission from: Yamamoto S, Han W, Kim Y, Du L, Jamshidi N, Huang D, Kim JH, Kuo MD. Breast Cancer: Radiogenomic Biomarker Reveals Associations among Dynamic Contrast-enhanced MR Imaging, Long Noncoding RNA, and Metastasis. Radiology. 2015;275:384–392)

positive cancers. Both groups of authors attributed these findings to an increased tumor neoangiogenesis induced by HER2 overexpression. Ken Yamaguchi and coworkers [73] assessed the delayed phase of enhancement in 192 cancers and correlated these with the IHC surrogates of molecular breast cancer types. Luminal A and basal-like cancers demonstrated less washout on the delayed phase of enhancement, and the authors attributed these findings in luminal A cancers to the association with ductal carcinoma in situ in their study sample, and, in basal-like cancers, to the existence of tumor necrosis and central scarring.

Recently, other functional MRI parameters, such as those derived from DWI, have been implemented in the clinical routine. Several studies have demonstrated that apparent diffusion coefficient (ADC) mapping derived from DWI sequences improves diagnostic accuracy in breast cancer diagnosis [75–79]. In addition, DWI with ADC mapping has been assessed for correlations of ADC values and molecular breast cancer subtypes [80–82]. All studies independently showed that HER2-positive cancers had high ADC values, whereas luminal B cancers without HER2 overexpression had low ADC values. An explanation for this counterintuitive finding might be an increased tumor neo-angiogenesis, as HER2 overexpression induces vascular endothelial growth factor, which, in turn, leads to increased vessel diameters, vascular permeability, and extracellular fluid. These interesting findings indicate that functional parameters can significantly contribute to our understanding of tumor biology and highlight their potential for radiogenomics in breast cancer.

One of the main objectives of radiogenomics in breast imaging is to develop imaging biomarkers as surrogates for genetic testing, and three studies have thus far approached this task. Shelley A. Waugh and coworkers [83] explored texture analysis from 220 imaging features to identify molecular breast cancer subtypes, with limited success. They achieved a classification accuracy of 57.2%, with an AUC of 0.754. Lars J Grimm and coworkers [84] developed a model that incorporated 56 imaging features, including lesion morphology and texture, as well as kinetic features. On multivariate analysis, they

demonstrated a significant strong association between the collective imaging features and both luminal A and luminal B molecular breast cancer subtypes. In a study by Hui Li and coworkers [70], radiomics analysis was performed on 91 DCE-MRI datasets of biopsy-proven invasive breast cancers from the National Cancer Institute's multi-institutional TCGA/TCIA. The performance of a classifier model for molecular subtyping was evaluated using receiver operating characteristic analysis, and the computer-extracted tumor phenotypes were able to distinguish between molecular prognostic indicators (Fig. 8.8). The results indicate that computer-extracted image phenotypes show promise for high-throughput discrimination of



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	ER Positive Case (a)	ER Negative Case (b)
Cancer Subtype	Luminal A	HER2-enriched
MRI CEIP Size (Effective Diameter) Range [7.8 54.0]	12.9 mm	23.8 mm
MRI CEIP Shape (Irregularity) Range [0.40 0.84]	0.452	0.602
MRI CEIP Enhancement Texture (Entropy) Range [6.00 6.59]	6.30	6.46

Fig. 8.8 Illustration of the computer segmentation method in example cases of one estrogen receptor-positive tumor and one estrogen receptor-negative tumor. The tumor segmentation outlines are shown (**a**) ER-positive example; (**b**) ER-negative example, along with (**c**) computer-extracted image phenotype (CEIP) values (and ranges) for size, irregularity, and contrast enhancement heterogeneity. (Reprinted from: Li H, Zhu Y, Burnside ES, Huang E, Drukker K, Hoadley KA, Fan C, Conzen SD, Zuley M, Net JM, Sutton E, Whitman GJ, Morris E, Perou CM, Ji Y, Giger ML.Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set. NPJ Breast Cancer. 2016;2. pii: 16012)

breast cancer subtypes and may yield a quantitative, predictive signature for advancing *precision medicine*.

8.4.3 Recurrence Scores

MRI features of breast cancer have also been correlated with clinically available genomic assays (*OncotypeDx*, Genomic Health, CA; *MammaPrint*, Agendia, CA; *Mammostrat*, Clarient Diagnostic Services, CA; *PAM50/Prosigna*, NanoString, WA), which provide scores for the risk of recurrence and guide treatment decisions [68, 69, 72, 85, 86]. Ahmed B. Ashraf and coworkers [68, 87] investigated radiogenomics correlations of DCE-MRI features and the 21-gene recurrence score assay (OncotypeDx). They identified four dominant imaging phenotypes, two of which were exclusively associated with low- and medium-risk tumors. DCE-MRI kinetic features and imaging phenotypes were predictive of recurrence risk, with area under the curve at the ROC analysis of 0.82. Tumors with greater neo-angiogenesis were associated with an increased risk of recurrence. Lisabethe J. Sutton and coworkers [72] assessed the correlations of morphological and texture-based image features extracted from breast MRI with the OncotypeDx 21-gene recurrence score assay in 95 patients with a median Oncotype Dx recurrence score of 16 (range: 0–45). Thus, the authors developed a model using imaging and pathology information that correlated with the Oncotype Dx recurrence score (Fig. 8.9).

In a recent study, Hui Li and coworkers [69] investigated the relationships of computer-extracted breast MRI phenotypes with the currently clinically available multigene assays (*MammaPrint*, *Oncotype DX*, and *PAM50/Prosigna*) to assess the role of radiogenomics in detecting or predicting the risk of breast cancer recurrence. Significant associations were found between breast cancer MRI radiomics signatures and the multigene assay recurrence scores ($r = 0.5–0.56$, $p < 0.0001$). Results from multiple linear regression analyses indicated that tumors with a high risk of recurrence are larger with a more heterogeneous enhancement. Figure 8.10 shows a correlation heat map based on univariate linear regression analysis between each individual MR imaging phenotype and the MammaPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P risks of recurrence scores. Some phenotypes correlated similarly across the risk estimate models, whereas others did not.

8.4.4 Challenges

In radiogenomics, large datasets of genetic information, patient characteristics, and standardized images are needed. Breast imaging MRI is routinely performed for various indications, and thus, this data is often available for retrospective research. However, there is often a substantial inter- and intra-institutional heterogeneity of datasets because of different hardware, scan protocols, and post-processing which limits the generalizability of the results of individual studies. In contrast to imaging data, the acquisition of patient genetic information or the conducting of genetic testing is often a challenge and can be costly. A solution is the use of paired genetic and imaging repositories, such as the Cancer Genome Atlas and the Cancer Imaging Archive through the National Cancer Institute, which provide a collaborative source of genetic and imaging data [88]. However, to date, there are still limited patient numbers.

In some cases, IHC surrogates can be used, e.g., for the prediction of molecular subtypes. However, although these IHC surrogates can provide clinical guidance, there is variable agreement with formal genetic testing (41–100%) and IHC surrogate markers have been shown to be less robust in predicting patient outcomes [15, 74, 89]. In addition, for most genetic defects, such surrogates have not been identified.

To date, most of the available radiogenomics studies are retrospective and feature small patient cohorts (<100), which limit the conclusions that can be drawn to some extent [33, 45, 72]. Larger prospective studies are, therefore, warranted to define which radiogenomics associations can be meaningfully implemented in the clinical routine.

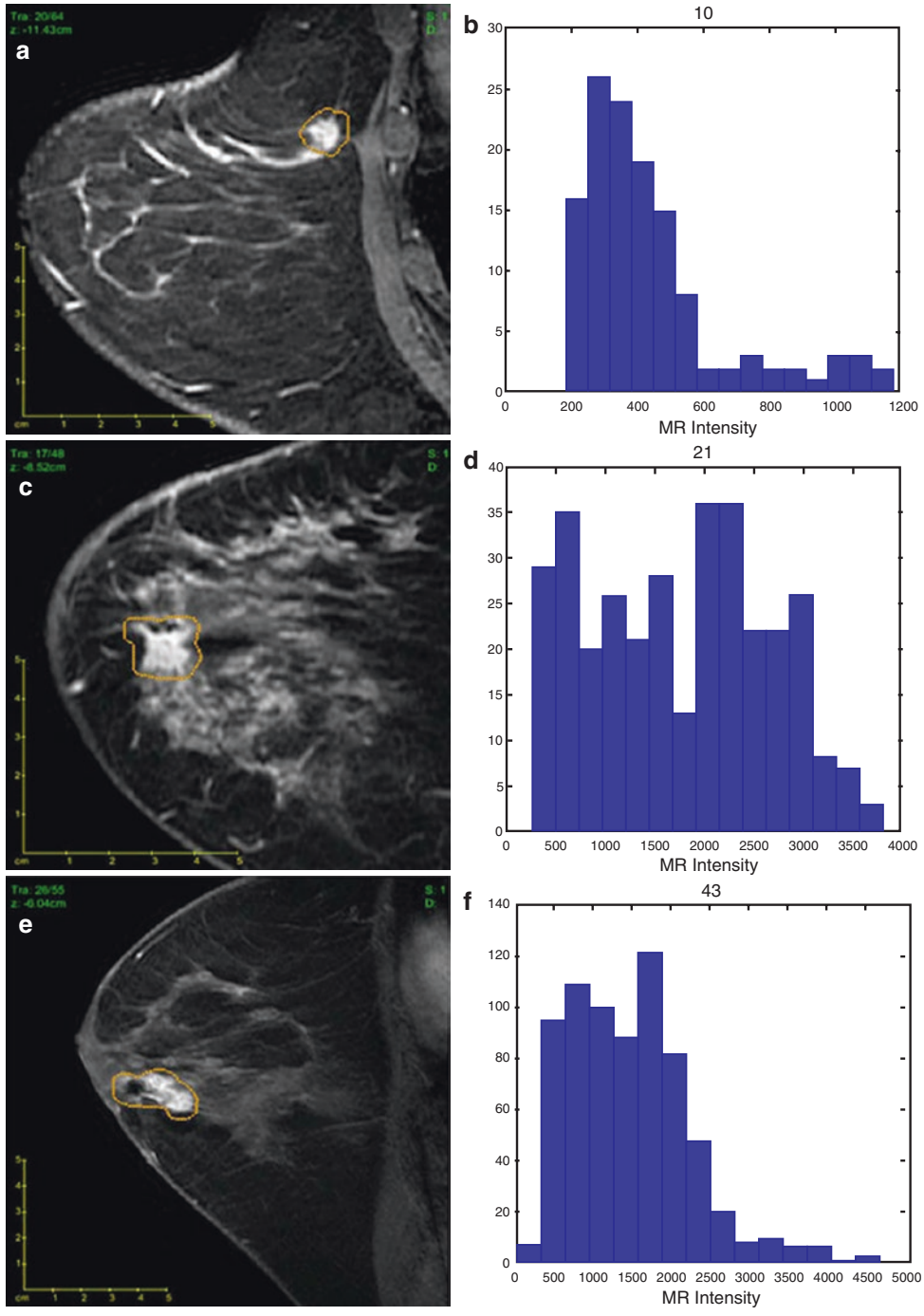

Fig. 8.9 The best-fit linear regression model allows imaging features to differentiate tumors with different Oncotype Dx Recurrence Scores (ODxRS). (**a**) Sagittal, T1-weighted, fat-suppressed, post-contrast MRI of an invasive, ductal, nuclear grade 1 carcinoma with an ODxRS of 10 and (**b**) corresponding kurtosis histogram, which demonstrates the frequency of MR intensity. (**c**) Sagittal, T1-weighted, fat-suppressed post-contrast MRI of an invasive ductal nuclear grade 2 carcinoma with an ODxRS of 21 and (**d**) corresponding kurtosis histogram. (**e**) Sagittal, T1-weighted, fat-suppressed post-contrast MRI of an invasive ductal nuclear grade 3 carcinoma with an ODxRS of 43 and (**f**) corresponding kurtosis histogram. (Reprinted by permission from: Sutton EJ, Oh JH, Dashevsky BZ, Veeraraghavan H, Apte AP, Thakur SB, Deasy JO, Morris EA. Breast cancer subtype intertumor heterogeneity: MRI-based features predict results of a genomic assay. J Magn Reson Imaging. 2015;42:1398–1406)

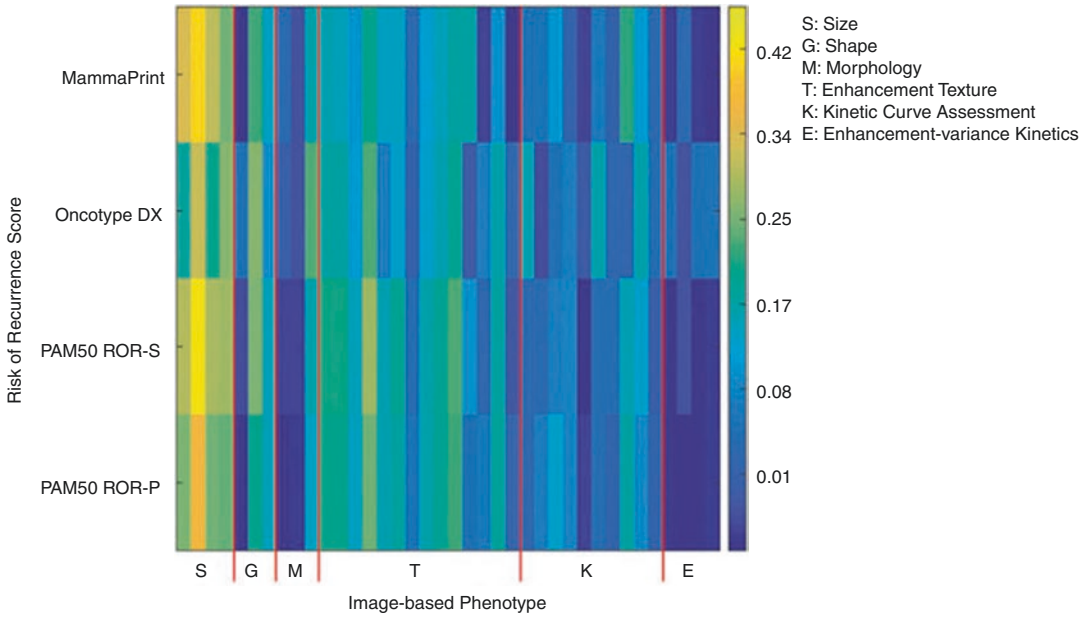

Fig. 8.10 Correlation heat map based on univariate linear regression analysis between each individual MR imaging phenotype and the recurrence predictor models of MammaPrint, Oncotype DX, PAM50 ROR-S, and PAM50 ROR-P. In this color scale, *yellow* indicates higher correlation compared to *blue*, and the different gene assays served as the "reference standard" in this study. Some phenotypes correlated similarly (i.e., similar color on the color scale) across the risk estimate models, while others did not. (Reprinted by permission from: Li H, Zhu Y, Burnside ES, Drukker K, Hoadley KA, Fan C, Conzen SD, Whitman GJ, Sutton EJ, Net JM, Ganott M, Huang E, Morris EA, Perou CM, Ji Y, Giger ML. MR Imaging Radiomics Signatures for Predicting the Risk of Breast Cancer Recurrence as Given by Research Versions of MammaPrint, Oncotype DX, and PAM50 Gene Assays. Radiology. 2016;281:382–391)

8.5 Conclusion

Radiogenomics investigates the correlations between imaging phenotypes and disease genomic characteristics to enable a deeper understanding of underlying pathologic processes. Due to the non-invasive nature of medical imaging and its ubiquitous use in clinical practice, the emerging field of radiogenomics offers many potential applications for cancer imaging and patient care. To date, radiogenomics in breast cancer has mainly investigated DCE-MRI as an imaging modality, but it can be expected that the exploration of additional functional imaging data, such as MR diffusion, perfusion, spectroscopy data as well as data from positron emission tomography (PET) will open new avenues of multi-dimensional radiogenomic research [53, 54].

However, additional efforts and rigorous standardization will be necessary to validate the already-described radiogenomic correlations, to discover new correlations, and to define clinically relevant imaging biomarkers to be translated into the clinical arena. In breast cancer, radiogenomics has thus far focused on the correlation of breast imaging phenotypes and individual genomic signatures, breast cancer molecular subtypes, or clinically used recurrence scores.

High-risk breast cancer presents with distinct imaging phenotypes and genetic alterations and thus represents an interesting topic for radiogenomics. However, to date, there is no study that has specifically focused on high-risk breast cancer with radiogenomics. Due to the large number of clinically relevant genetic variables in breast cancer and the continuous advancements in breast

imaging, more radiogenomic multi-dimensional studies will emerge and it is only a matter of time until they focus on high-risk patients.

Ideally, in the future, radiogenomics in breast cancer will span the whole spectrum of patient populations and combine multiple qualitative and quantitative parameters with genomic alterations to devise meaningful imaging biomarkers for *precision medicine* in breast cancer.

References

1. Huber KE, Carey LA, Wazer DE (2009) Breast cancer molecular subtypes in patients with locally advanced disease: impact on prognosis, patterns of recurrence, and response to therapy. Semin Radiat Oncol 19:204–210
2. Carey LA, Perou CM, Livasy CA et al (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492–2502
3. Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumours. Nature 490:61–70
4. Sørlie T, Perou CM, Tibshirani R et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869–10874
5. Parker JS, Mullins M, Cheang MC et al (2009) Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 27: 1160–1167
6. Goldhirsch A, Wood WC, Coates AS et al (2011) Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 22:1736–1747
7. Goldhirsch A, Winer EP, Coates AS et al (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24:2206–2223
8. Prat A, Pineda E, Adamo B et al (2015) Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast 24(Suppl 2):S26–S35
9. Prat A, Parker JS, Fan C et al (2012) Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann Oncol 23:2866–2873
10. Mazurowski MA, Zhang J, Grimm LJ, Yoon SC, Silber JI (2014) Radiogenomic analysis of breast cancer: luminal B molecular subtype is associated with enhancement dynamics at MR imaging. Radiology 273:365–372
11. Shin HJ, Kim HH, Huh MO et al (2011) Correlation between mammographic and sonographic findings and prognostic factors in patients with node-negative invasive breast cancer. Br J Radiol 84:19–30
12. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L (2011) Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol 9:16–32
13. Coates AS, Winer EP, Goldhirsch A et al (2015) Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 26:1533–1546
14. Elias SG, Adams A, Wisner DJ et al (2014) Imaging features of HER2 overexpression in breast cancer: a systematic review and meta-analysis. Cancer Epidemiol Biomark Prev 23:1464–1483
15. Grimm LJ, Johnson KS, Marcom PK, Baker JA, Soo MS (2015) Can breast cancer molecular subtype help to select patients for preoperative MR imaging? Radiology 274:352–358
16. Prat A, Adamo B, Cheang MC, Anders CK, Carey LA, Perou CM (2013) Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist 18:123–133
17. Dogan BE, Turnbull LW (2012) Imaging of triple-negative breast cancer. Ann Oncol 23(Suppl 6):vi23–vi29
18. Uematsu T (2011) MR imaging of triple-negative breast cancer. Breast Cancer 18:161–164
19. Uematsu T, Kasami M, Yuen S (2009) Triple-negative breast cancer: correlation between MR imaging and pathologic findings. Radiology 250:638–647
20. Luck AA, Evans AJ, James JJ et al (2008) Breast carcinoma with basal phenotype: mammographic findings. AJR Am J Roentgenol 191:346–351
21. Kawashima H, Inokuchi M, Furukawa H, Kitamura S (2011) Triple-negative breast cancer: are the imaging findings different between responders and nonresponders to neoadjuvant chemotherapy? Acad Radiol 18:963–969
22. Kawashima H (2011) Imaging findings of triple-negative breast cancer. Breast Cancer 18:145
23. Bae MS, Shin SU, Ryu HS et al (2016) Pretreatment MR imaging features of triple-negative breast cancer: association with response to neoadjuvant chemotherapy and recurrence-free survival. Radiology 281:392–400
24. Miki Y (2012) Cellular functions of BRCA genes - from basic science to therapeutics. Gan To Kagaku Ryoho 39:498–501
25. Wooster R, Bignell G, Lancaster J et al (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792
26. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER (2008) Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer 8:155
27. van der Kolk DM, de Bock GH, Leegte BK et al (2010) Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. Breast Cancer Res Treat 124:643–651

28. Atchley DP, Albarracin CT, Lopez A et al (2008) Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 26:4282–4288
29. Rakha EA, Reis-Filho JS, Ellis IO (2008) Basal-like breast cancer: a critical review. J Clin Oncol 26:2568–2581
30. Sung JS, Jochelson MS, Brennan S et al (2013) MR imaging features of triple-negative breast cancers. Breast J 19:643–649
31. Arun B, Vogel KJ, Lopez A et al (2009) High prevalence of preinvasive lesions adjacent to BRCA1/2-associated breast cancers. Cancer Prev Res (Phila) 2:122–127
32. Schrading S, Kuhl CK (2008) Mammographic, US, and MR imaging phenotypes of familial breast cancer. Radiology 246:58–70
33. Kim WH, Han W, Chang JM, Cho N, Park IA, Moon WK (2015) Location of triple-negative breast cancers: comparison with estrogen receptor-positive breast cancers on MR imaging. PLoS One 10(1):e011634433
34. Mazurowski MA (2015) Radiogenomics: what it is and why it is important. J Am Coll Radiol 12:862–866
35. Bai HX, Lee AM, Yang L (2016) Imaging genomics in cancer research: limitations and promises. Br J Radiol 89:20151030
36. Gillies RJ, Kinahan PE, Hricak H (2016) Radiomics: images are more than pictures, they are data. Radiology 278:563–577
37. Herold CJ, Lewin JS, Wibmer AG et al (2016) Imaging in the age of precision medicine: summary of the proceedings of the 10th biannual symposium of the International Society for Strategic Studies in Radiology. Radiology 279:226–238
38. Thrall JH (2015) Moreton Lecture: Imaging in the age of precision medicine. J Am Coll Radiol 12:1106–1111
39. Kumar V, Gu Y, Basu S, Berglund A et al (2012) Radiomics: the process and the challenges. Magn Reson Imaging 30:1234–1248
40. Lambin P, Rios-Velazquez E, Leijenaar R et al (2012) Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 48:441–446
41. Sala E, Mema E, Himoto Y et al (2017) Unravelling tumour heterogeneity using next-generation imaging: radiomics, radiogenomics, and habitat imaging. Clin Radiol 72:3–10
42. West C, Rosenstein BS, Alsner J et al (2010) Establishment of a Radiogenomics Consortium. Int J Radiat Oncol Biol Phys 76:1295–1296
43. Kerns SL, West CM, Andreassen CN et al (2014) Radiogenomics: the search for genetic predictors of radiotherapy response. Future Oncol 10:2391–2406
44. Rosenstein BS, West CM, Bentzen SM et al (2014) Radiogenomics: radiobiology enters the era of big data and team science. Int J Radiat Oncol Biol Phys 89:709–713
45. Kuo MD, Jamshidi N (2014) Behind the numbers: decoding molecular phenotypes with radiogenomics—guiding principles and technical considerations. Radiology 270:320–325
46. European Society of Radiology (2010) White paper on imaging biomarkers. Insights Imaging 1:42–45
47. Yamamoto S, Maki DD, Korn RL, Kuo MD (2012) Radiogenomic analysis of breast cancer using MRI: a preliminary study to define the landscape. AJR Am J Roentgenol 199:654–663
48. Grimm LJ (2016) Breast MRI radiogenomics: Current status and research implications. J Magn Reson Imaging 43:1269–1278
49. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
50. American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
51. Mann RM, Balleyguier C, Baltzer PA et al (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25(12):3669–3678
52. Preda A, Novikov V, Möglich M et al (2005) Magnetic resonance characterization of tumor microvessels in experimental breast tumors using a slow clearance blood pool contrast agent (carboxymethyldextran-A2-Gd-DOTA) with histopathological correlation. Eur Radiol 15:2268–2275
53. El Khouli RH, Macura KJ, Kamel IR, Jacobs MA, Bluemke DA (2011) 3-T dynamic contrast-enhanced MRI of the breast: pharmacokinetic parameters versus conventional kinetic curve analysis. AJR Am J Roentgenol 197:1498–1505
54. Pinker K, Helbich TH, Morris EA (2017) The potential of multiparametric MRI of the breast. Br J Radiol 90:20160715
55. Rahbar H, Partridge SC (2016) Multiparametric MR imaging of breast cancer. Magn Reson Imaging Clin N Am 24:223–238
56. Schmitt B, Zamecnik P, Zaiss M et al (2011) A new contrast in MR mammography by means of chemical exchange saturation transfer (CEST) imaging at 3 Tesla: preliminary results. RöFo 183:1030–1036
57. Klomp DW, van de Bank BL, Raaijmakers A et al (2011) 31P MRSI and 1H MRS at 7 T: initial results in human breast cancer. NMR Biomed 24:1337–1342
58. Wijnen JP, van der Kemp WJ, Luttje MP, Korteweg MA, Luijten PR, Klomp DW (2012) Quantitative (31) P magnetic resonance spectroscopy of the human breast at 7 T. Magn Reson Med 68:339–348
59. Schmitz AM, Veldhuis WB, Menke-Pluijmers MB et al (2015) Multiparametric MRI with dynamic contrast enhancement, diffusion-weighted imaging, and 31-phosphorus spectroscopy at 7 T for characterization of breast cancer. Investig Radiol 50: 766–771
60. Zaric O, Pinker K, Zbyn S et al (2016) Quantitative sodium MR imaging at 7 T: initial results and comparison with diffusion-weighted imaging in patients with breast tumors. Radiology 280:39–48
61. Szczypiński PM, Strzelecki M, Materka A, Klepaczko A (2009) MaZda—a software package for image texture analysis. Comput Methods Prog Biomed 94:66–76

62. Materka A (2004) Texture analysis methodologies for magnetic resonance imaging. Dialogues Clin Neurosci 6:243–250
63. Haralick RM, Shanmugam M, Dinstein IH (1973) Textural features for image classification. IEEE Trans Syst Man Cybernet 1973:610–621
64. Peterson CB, Bogomolov M, Benjamini Y, Sabatti C (2016) Many phenotypes without many false discoveries: error controlling strategies for multitrait association studies. Genet Epidemiol 40:45–56
65. Reiner A, Yekutieli D, Benjamini Y (2003) Identifying differentially expressed genes using false discovery rate controlling procedures. Bioinformatics 19:368–375
66. Perou CM, Sørlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752
67. Yamamoto S, Han W, Kim Y et al (2015) Breast Cancer: radiogenomic biomarker reveals associations among dynamic contrast-enhanced MR imaging, long noncoding RNA, and metastasis. Radiology 275:384–392
68. Ashraf AB, Daye D, Gavenonis S et al (2014) Identification of intrinsic imaging phenotypes for breast cancer tumors: preliminary associations with gene expression profiles. Radiology 272:374–384
69. Li H, Zhu Y, Burnside ES et al (2016) MR imaging radiomics signatures for predicting the risk of breast cancer recurrence as given by research versions of MammaPrint, Oncotype DX, and PAM50 gene assays. Radiology 281:382–391
70. Li H, Zhu Y, Burnside ES et al (2016) Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set. NPJ Breast Cancer 2:16012
71. Sutton EJ, Dashevsky BZ, Oh JH et al (2016) Breast cancer molecular subtype classifier that incorporates MRI features. J Magn Reson Imaging 44: 122–129
72. Sutton EJ, Oh JH, Dashevsky BZ et al (2015) Breast cancer subtype intertumor heterogeneity: MRI-based features predict results of a genomic assay. J Magn Reson Imaging 42:1398–1406
73. Yamaguchi K, Abe H, Newstead GM et al (2015) Intratumoral heterogeneity of the distribution of kinetic parameters in breast cancer: comparison based on the molecular subtypes of invasive breast cancer. Breast Cancer 22:496–502
74. Blaschke E, Abe H (2015) MRI phenotype of breast cancer: kinetic assessment for molecular subtypes. J Magn Reson Imaging 42:920–924
75. Dijkstra H, Dorrius MD, Wielema M, Pijnappel RM, Oudkerk M, Sijens PE (2016) Quantitative DWI implemented after DCE-MRI yields increased specificity for BI-RADS 3 and 4 breast lesions. J Magn Reson Imaging 44:1642–1649
76. Dorrius MD, Dijkstra H, Oudkerk M, Sijens PE (2014) Effect of b value and pre-admission of contrast on diagnostic accuracy of 1.5-T breast DWI: a systematic review and meta-analysis. Eur Radiol 24:2835–2847
77. Bogner W, Pinker-Domenig K, Bickel H et al (2012) Readout-segmented echo-planar imaging improves the diagnostic performance of diffusion-weighted MR breast examinations at 3.0 T. Radiology 263:64–76
78. Pinker K, Bickel H, Helbich TH et al (2013) Combined contrast-enhanced magnetic resonance and diffusion-weighted imaging reading adapted to the "Breast Imaging Reporting and Data System" for multiparametric 3-T imaging of breast lesions. Eur Radiol 23:1791–1802
79. Partridge SC, McDonald ES (2013) Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. Magn Reson Imaging Clin N Am 21:601–624
80. Kim EJ, Kim SH, Park GE et al (2015) Histogram analysis of apparent diffusion coefficient at 3.0T: Correlation with prognostic factors and subtypes of invasive ductal carcinoma. J Magn Reson Imaging 42:1666–1678
81. Park SH, Choi HY, Hahn SY (2015) Correlations between apparent diffusion coefficient values of invasive ductal carcinoma and pathologic factors on diffusion-weighted MRI at 3.0 Tesla. J Magn Reson Imaging 41:175–182
82. Martincich L, Deantoni V, Bertotto I et al (2012) Correlations between diffusion-weighted imaging and breast cancer biomarkers. Eur Radiol 22:1519–1528
83. Waugh SA, Purdie CA, Jordan LB et al (2016) Magnetic resonance imaging texture analysis classification of primary breast cancer. Eur Radiol 26:322–330
84. Grimm LJ, Zhang J, Mazurowski MA (2015) Computational approach to radiogenomics of breast cancer: Luminal A and luminal B molecular subtypes are associated with imaging features on routine breast MRI extracted using computer vision algorithms. J Magn Reson Imaging 42(4):902–907
85. Mahrooghy M, Ashraf AB, Daye D et al (2015) Pharmacokinetic tumor heterogeneity as a prognostic biomarker for classifying breast cancer recurrence risk. IEEE Trans Biomed Eng 62:1585–1594
86. Mahrooghy M, Ashraf AB, Daye D et al (2013) Heterogeneity wavelet kinetics from DCE-MRI for classifying gene expression based breast cancer recurrence risk. Med Image Comput Comput Assist Interv 16(Pt 2):295–302
87. Ashraf AB, Gavenonis SC, Daye D et al (2013) A multichannel Markov random field framework for tumor segmentation with an application to classification of gene expression-based breast cancer recurrence risk. IEEE Trans Med Imaging 32: 637–648
88. Clark K, Vendt B, Smith K et al (2013) The Cancer Imaging Archive (TCIA): maintaining and operating a public information repository. J Digit Imaging 26:1045–1057
89. Guiu S, Michiels S, André F et al (2012) Molecular subclasses of breast cancer: how do we define them? The IMPAKT 2012 Working Group Statement. Ann Oncol 23:2997–3006

9 Primary Studies on Breast MRI Screening of High-Risk Women

Francesco Sardanelli and Franca Podo

Abbreviations

ACS	American Cancer Society
AUC	Area under the curve
BC	Breast cancer
CBE	Clinical breast examination
CE-MRI	Contrast-enhanced magnetic resonance imaging
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
EBM	Evidence-based medicine
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
LTR	Lifetime risk
MRI	Magnetic resonance imaging
PPV	Positive predictive value
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
US	Ultrasound

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9.1 Introduction

Evidence-based medicine (EBM) [1] is generally adopted as a method for guiding clinicians as well as governmental bodies so that we should be able to define the best evidence-based medical practices. The EBM principles are increasingly applied to radiology [2], where a specific safety criterion regards the reduction of radiation exposure to a level defined *as low as reasonably achievable* (ALARA) [3].

The Oxford center for EBM [4] clearly distinguishes between diagnostic tests and screening tests.[1] For example, the definition of the disease size (or extent, at large) is a diagnostic task for which tests can be validated by cohort studies with reference standards independent of the test and applied blindly or objectively to all patients. This means that non-randomized prospective (especially intra-individual) studies enable us to choose the test with the best sensitivity/specificity, without needing randomized controlled trials (RCTs). Conversely, screening tests should be demonstrated to be effective in terms of patient outcome (i.e., overall or disease-specific survival, disease-free or metastasis-free survival, etc.) by RCTs before being implemented in practice [4], a rule also affirmed in 2002 by a European Guideline [5].

[1] See also Chap. 11 (in particular Table 11.1) on this matter.

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As already outlined in Chap. 1, during the 1990s, the availability of both *BRCA* genetic testing and contrast-enhanced (CE) breast MRI determined the conditions for studies aimed at comparing MRI with conventional imaging, i.e., mammography and ultrasound (US), for the detection of breast cancers (BCs) in *BRCA* mutation carriers, in their first-degree relatives as well as in women with family history implying a high risk of hereditary BC predisposition. Thus, an intra-individual design was adopted to firstly demonstrate the diagnostic performance of MRI, characterized by a superior sensitivity coupled with an acceptable specificity. This was the aim of the studies that initially reported on MRI versus mammography/US for screening women at high BC risk [6–12].

The gap in sensitivity between MRI and mammography, the standard BC screening tool, was so high that the ideal second phase, i.e., RCTs, to demonstrate that high-risk women screened with MRI have an advantage in terms of patient outcome became ethically unfeasible. This unfeasibility was due to the combination of the high MRI sensitivity with the high probability of BC in a high-risk population: the BC diagnosis anticipated by MRI was considered as more likely positively impacting survival than determining a negative effect in terms of overdiagnosis and overtreatment. The known effect of mortality reduction by early BC detection through screening mammography in the general population was translated to MRI in the high-risk population.

In this chapter, after an overview of the general context given by screening mammography in the general female population, we describe the main results obtained by intra-individual studies comparing MRI with conventional imaging for screening women at high BC risk.

9.2 The Context: Secondary Prevention of BC by Screening Mammography

In the last 50 years, the context of secondary prevention of BC in the general female population has been the kingdom of screening mammography, notwithstanding its intrinsic limitations in terms of sensitivity and specificity. Mammography evolved from the screen-film to the digital technique, demonstrated to be more sensitive in women under 50, those with dense breasts, or in premenopausal or perimenopausal age [13]. Although substantial differences do exist in terms of organizational matters and testing performance between organized population-based mass screening in most European countries and spontaneous screening in the United States (mainly consisting in a higher false-positive recall rate in the latter modality [14]), the general issue characterizing the debate on screening mammography in the last two decades is the effectiveness of screening mammography in reducing the BC mortality and the harm-to-benefit balance.

This debate has been dominated by a never-ending discussion on *overdiagnosis*, i.e., the screening diagnosis of a cancer that would not become clinically evident during the woman's lifetime in the absence of the screening participation. The harm of overdiagnosis is not only the psychological effect of the diagnosis but mainly the *overtreatment* that follows the overdiagnosis. It is clear that the final judgment on the harm-to-benefit balance of screening mammography is dependent on the extent of this phenomenon in relation to the mortality reduction. A review [15] recently highlighted the huge variability in the ratio between the estimated overdiagnosis and the estimated mortality reduction in eight studies. A 25-fold variation (from 0.4 to 10) was found to strongly correlate with the "attitude" of the corresponding authors to the screening, which could mean that being either in favor or against screening mammography influences the results. We do not enter here in the highly complex statistical issues regarding the estimation of overdiagnosis. We only note that the discussion is hot and probably will continue in the next years.

What is more relevant is the other side of the dilemma, i.e., the general question about the role of early (preclinical) detection in determining a mortality reduction. A basic argument against screening mammography is the following: *the more effective the treatments, the less favorable is the harm-to-benefit balance of screening mam-*

mography [16]. Considering that therapies (especially adjuvant treatment and radiation therapy) strongly improved in the last 20 years, a fundamental question is: did we reach the break-even point where the T stage of the tumor is no longer impacting patients' outcome? If yes, there would be no reason to organize any screening, independently of the preferred estimation of overdiagnosis. If no, to screen for detecting smaller cancers than those we would encounter waiting for their clinical appearance should remain a major goal of preventive medicine.

In 2005, Donald A. Berry and coworkers [17] estimated the changes in the rate of deaths from BC (the number of deaths/100,000 women) from the 1970s to 2000, showing that only the combination of screening and adjuvant therapy explained the reduction of this rate from a peak near to 50 BC deaths/100,000 women to about 35 in 2000. The proportion in this reduction attributed to screening mammography varied from 28% to 65% in seven models considered (median 46%), the remaining proportion being attributed to adjuvant therapy. Thus at that time, the authors described a near 50%-to-50% contribution of screening mammography and adjuvant therapy in determining the decline of BC mortality.

Today, the crucial question is the following: *is early detection still relevant for BC patient outcome in the era of modern powerful systemic therapies including targeted biological treatments?* The answer is yes. This has been demonstrated by a population-based study from the Netherlands Cancer Registry [18], evaluating more than 170,000 patients: although the rate of those receiving neoadjuvant/adjuvant therapy from 1995–2005 to 2006–2012 increased from 53% to 60%, the mortality in 2006–2012 still increased with progressing tumor stage, significantly for T1c versus T1a (hazard ratio [HR] 1.54), and independently of the nodal status. Moreover, we must consider that screening mammography has a relevant role in making neoadjuvant treatment more effective, as shown by its ability to downscale the clinico-pathological features of invasive BCs and reducing the need for loco-regional and adjuvant treatments [19–22].

In 2015, the International Agency for Research on Cancer (IARC) summarized the evidence for screening mammography [23], contributing to clarify a so hotly discussed matter [24]. The estimated reduction in BC mortality has been estimated to be 23% for all women aged 50–69 invited to be screened (i.e., also including those not accepting the invitation) and 40% for women aged 50–69 who are screened. A *limited evidence* was reported for mortality reduction in women aged 40–49 (*less pronounced* mortality reduction) and 70–74 (*substantial* mortality reduction). The IARC working group also reported the overdiagnosis rate to be from 1% to 10% or from 4% to 11%, according to different estimation methods, substantially confirming the estimates provided in 2012 by the EUROSCREEN working group [25].

The EUROSCREEN working group [26] also presented their estimate of the harm-to-benefit balance of screening mammography using natural frequencies, a method that allows for a better understanding by the public. They say that for every 1,000 women that have biennial mammography in a European population-based screening program from 50 to 69 years of age and are followed up to 79 years of age, we observe:

- 8 women with a screen-detected BC, treated for the disease, who survived thanks to the screening
- Other 47 women diagnosed with a BC, treated and survived
- 4 women with BC overdiagnosis (and overtreatment)
- 12 women who died for BC
- 30 women who underwent image-guided needle biopsy for benign findings
- 170 women who underwent further imaging (during the recall session) for benign findings
- 729 women, never recalled, reassured on the absence of cancer in their breasts

This means that the risk for a false-positive recall is limited to 20% for women aged 50–69 who have ten screens in 20 years; 15% of recalled women have an invasive procedure, which results in a probability during the 20 years of 3%. The

probability of overdiagnosis is half the probability to have the life saved. Notably, *overdetection*, a radiological issue, should be considered as a quite different topic from *overdiagnosis* [27], which implies also an essential role of pathologists, with their suboptimal reproducibility, especially in the case of differential diagnosis between atypical ductal hyperplasia and ductal carcinoma in situ [DCIS] [28, 29], where a second opinion may be beneficial [29, 30], while more efforts should be directly dedicated to the reduction of *overtreatment*.

However, one weak point of population-based screening programs is the *one size fits all* general principle: in Europe, mammography every 2 years (every 3 years in the United Kingdom) from 49 to 69 years. Some changes mainly regarded the invitation of women from 40 or, more frequently, from 45 to 49 to get a mammogram every year. All in all, organizational issues and other factors worked against the idea to stratify the screening strategy according to the risk level and breast density. The latter factor is relevant: even though density as an independent risk factor is commonly overestimated [31], its masking effect results in a relevant reduction in mammography sensitivity [32], as also discussed in Chap. 20 of this book. An organized screening strategy tailored for the woman's individual risk, also considering breast density, is a hope for the future.

Coming to the crucial point, in the late 1990s and the early 2000s, the current recommendations for *BRCA* mutation carriers were to undergo breast surveillance from age 25 years onward with annual mammography and clinical breast examination (CBE) every 6 months [33, 34]. It was clear that screening mammography in high-risk women was inadequate. Its sensitivity ranged from 29% to 50%, interval cancer rate from 35% to 50%, and metastatic nodal involvement at diagnosis from 20% to 56% [35].

A new strategy to be implemented had to consider three crucial needs:

1. To start very early in the life of high-risk women, accounting for the high probability of an early onset of BC
2. To perform screening events every year or closer, accounting for the fast BC growth in these women
3. To warrant independence of the screening tool from breast density, accounting for the woman's young age and for the higher breast density in high-risk women

In addition, the possibility of avoiding ionizing radiation exposure is an important issue, accounting for the higher susceptibility to radiation of *BRCA* mutation carriers, as extensively discussed in Chap. 12 of this book.

This was the context when the first MRI-including screening studies were reported, during the first decade of 2000. As mentioned above, mammography had moved from screen-film to digital but no impact from this transition was expected for high-risk women.

9.3 High-Risk Screening with MRI: From a *Mission Impossible* to the First Evidence (2000–2006)

To explore the diagnostic power of breast MRI in a screening setting was initially considered as a *mission impossible*. The typical criticism, especially from epidemiologists, was: *MRI specificity is too low, and you will be flooded by a deluge of false positives*. The reasons for this view are extensively explained in Chap. 2 of this book.

Several breast imaging research groups started to verify the hypothesis that CE-MRI could be useful for BC screening in women at increased BC risk, especially those with hereditary predisposition. This was also a way to begin to discuss, from the side of high risk, the *one size fits all* principle. Breast radiologists had to get at least basic knowledge about familial/genetic predisposition to BC. In 2010, we summarized this knowledge as follows [36]:

- Autosomal dominant inherited BCs are only 5% of all BCs (one third of all familial BCs).
- *BRCA1/2* mutations account for only about 40% of autosomal dominant inherited BCs

and other known genes explain about 10%, while the remaining 50% has no gene mutation clearly identified. *BRCA1/2* deleterious mutations confer to the carrier an over 40–50% of lifetime risk (LTR).[2]

- Most BCs in very young women are associated with a *BRCA1* mutation, a condition that may also show association with ovarian cancer.
- In women carrying a *BRCA2* mutation, the risk profile is shifted to a slightly more advanced age, while BCs in males are commonly associated with this type of mutation.

More detailed information on this topic can be found in Chap. 3 of this book.

This basic knowledge allowed radiologists to identify those women whose family history indicates the possibility of an inherited BC predisposition. Since 2004–2005, software could be used for a preliminary risk evaluation, such as that based on the Tyrer-Cuzick model [37, 38] (BC risk modeling is extensively treated in Chap. 20 of this book). However, *radiologists (and other professionals who suspected a BC genetic predisposition) had to refer the woman suspected to be at high-risk to a specialized department/center for genetic and psycho-oncology counseling to define the possibility of genetic testing*. Importantly, radiologists learned that in the case of strong family history of BC and/or ovarian cancer without identification of known gene mutations in the family, genetic testing had to be defined as *inconclusive* and the case had to be labeled as BRCAX [39]. Finally, it was important to know that for different reasons, including unsuitable psycho-oncologic condition, women with strong family history often prefer not to perform any genetic testing.

The first pilot study was reported by Christiane K. Kuhl in 2000 [6]. In 192 asymptomatic women proven or suspected to be carriers of a BC susceptibility gene mutation included in this report (which also included 6 symptomatic cases, here not considered), 9 BCs were detected at the University of Bonn Medical Center in 293 screening events. Sensitivity was 33% for mammography, 33% for US (44% for mammography and US combined), and 100% for MRI; the positive predictive value (PPV) was 30% for mammography, 14% for US, and 64% for MRI. The authors concluded that *the accuracy of MRI was significantly higher than that of conventional imaging in screening high-risk women*. These data were later included in the final report published in 2005 [12].

Thereafter, several cohort prospective single- or multi-center studies on asymptomatic high-risk women followed, building a robust body of evidence in favor of breast MRI screening in this population. We will now focus on these studies for which reports were published up to 2017. To present the historical pathway that led to the acceptance of MRI in this setting, we firstly describe the results of the studies on which the American Cancer Society (ACS) based the 2007 guidelines [40] in favor of MRI screening for women at high risk, which represented a turning point in this story. In the next section we will describe the results of the prospective studies published after the publication of the ACS guideline.

In 2002, we reported [7] the preliminary results of the first phase (21 months) of the High Breast Cancer Risk Italian (HIBCRIT-1) study. At that time, 105 asymptomatic women (mean/median age 46/51 years; range 25–77 years) had been enrolled in 12 centers in Italy, under the coordination of the Istituto Superiore di Sanità, Roma. They either were proven *BRCA1* or *BRCA2* mutation carriers, or had a 1:2 probability of being *BRCA* mutation carriers, or had a high record of first- and/or second-degree relatives at very high incidence of breast cancer. Importantly, 40 of 105 (38%) had a previous personal history of BC. The study protocol included yearly mammography, US, and MRI, independently interpreted.[3] During this first phase of the study (119 screening events), 8 BCs were detected (2 invasive ductal; 2 invasive lobular; 1 invasive mixed ductal/lobular; 2 multi-

[2]Unless differently specified, in this chapter, with LTR we mean *cumulative* LTR.

[3]Data on clinical breast examination will be illustrated below, with the final results of the HIBCRIT-1 study.

focal DCIS; 1 DCIS associated with lobular carcinoma in situ). All study-detected BCs (8/8) were identified by MRI, while mammography and US correctly classified only one. MRI had one false-positive case, mammography and US none. Of 7 BCs detected on MRI-only (4 invasive, 3 DCIS), 2 occurred in premenopausal women, 5 in postmenopausal women. Despite the still preliminary nature of these data, we confirmed that MRI is a very useful tool to screen subjects at high genetic risk for breast carcinoma, not only in premenopausal but also in postmenopausal age, with a low probability of false-positive cases. We also estimated that the cost per MRI-only detected BC in the high-risk setting was substantially lower than that of a screen-detected cancer in the general female population undergoing screening mammography.

The general trends were already clear:

1. High BC prevalence due to the eligibility criteria
2. An overall very large gap in sensitivity between MRI and conventional imaging, i.e., not only mammography but also US
3. Lower sensitivity of mammography also in postmenopausal high-risk women
4. Absence of data suggesting high frequency of false positives, low specificity, and low PPV

In 2004, Mieke Kriege and coworkers [8] reported the results of the Magnetic Resonance Imaging Screening (MRISC) study carried out in six centers in the Netherlands comparing clinical breast examination (CBE), performed every 6 months, MRI and mammography (both of them performed yearly) in women with a cumulative LTR for BC ≥15%. They screened 1,909 women, including 358 carriers of germ-line mutations. A total of 51 malignant lesions (44 invasive cancers, 6 DCIS, 1 lymphoma) and 1 lobular carcinoma in situ were diagnosed in a total of 5,249 woman-years at risk. The sensitivity for detecting invasive BCs was 18% for CBE, 33% for mammography, and 80% for MRI; specificity was 98%, 95%, and 90%, respectively. The reported sensitivity values for al BCs (invasive or DCIS) were 18% for CBE, 40% for mammography, and 71% for MRI. The overall diagnostic power of MRI (area under the curve [AUC] at receiver operator characteristics [ROC] analysis 0.83) was significantly higher than that of mammography (AUC 0.69).

The authors also compared their results with those obtained in two control groups external to the study, matched for age with the patients in the study group. The first control group was derived from all women diagnosed with BC in 1998 in the Netherlands (data from the National Cancer Registry). The second control group consisted of patients diagnosed with primary BC in Leiden or Rotterdam from 1996 to 2002, participating in a prospective study of the prevalence of gene mutations. The second control group included all the unscreened patients with 25–60 years of age and cumulative LTR for BC higher than 15% on the basis of the family history. The proportion of invasive tumors ≤10 mm in diameter was significantly greater in the study group (43%) than in either control group (14% and 13%, respectively). In the study, 21% invasive cancers had positive axillary nodes or micrometastases, while this rate was significantly higher in the two control groups (52% and 56%, respectively). The straightforward conclusion was: *MRI appears to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to BC* [8].

In 2004, Ellen Warner and coworkers [9] compared the sensitivity and specificity of CBE, mammography, US, and MRI for screening in high-risk women. A total of 236 Canadian women aged 25 to 65 years being *BRCA1* or *BRCA2* mutation carriers underwent 1–3 annual screening events (for a total of 457 screening events) at the Sunnybrook and Women's College Health Sciences Centre and University of Toronto. CBE was performed on the day of imaging examinations and at 6-month intervals. Twenty-two cancers were detected (16 invasive and 6 DCIS). The sensitivity and specificity (based on biopsy rates) were 77% and 95.4% for MRI, 36% and 99.8% for mammography, 33% and 96% for US, and 9.1% and 99.3% for CBE, respectively. All screening modalities combined had a sensitivity of 95% (1 interval cancer) to be compared with

45% for mammography and CBE combined. The authors concluded that in *BRCA* mutation carriers, *MRI is more sensitive for detecting breast cancers than mammography, US, or CBE alone*, and noted that the possibility of MRI to reduce BC mortality in high-risk women *required further investigation*.

The year after, in 2005, Martin O. Leach and coworkers [10] published the results of a prospective cohort study (Magnetic Resonance Imaging Breast Screening, MARIBS) performed in 22 centers in the United Kingdom. A total of 649 women aged 35–49 years with a strong family history of BC or a high probability of a *BRCA1*, *BRCA2*, or *TP53* mutation underwent annual screening with CE MRI and mammography for 2–7 years. Thirty-five BCs were diagnosed during 1,881 screening events, 19 by CE-MRI only, 6 by mammography only, and 8 by both, with two interval cancers. The sensitivity of MRI (77%) was significantly higher than that of mammography (40%), reaching 94% when combining both of them. The specificity of mammography (93%) was significantly higher than that of MRI (81%), and 77% when combining both modalities. The authors noted that the difference in sensitivity between MRI and mammography was very high in *BRCA1* mutation carriers (92% versus 23%, respectively, on a total of 13 cancers). Again, the authors concluded that in this population, MRI was more sensitive than mammography for cancer detection and that specificity for both procedures was acceptable, also noting that, despite a high proportion of grade 3 cancers, tumors were small, with few cases of nodal involvement. They suggested the combined use of MRI and mammography for screening this high-risk group.

In the same year (2005), Constance D. Lehman and coworkers of the International Breast MRI Consortium Working Group [11] compared the performance of mammography versus MRI for screening genetically high-risk women through a prospective study carried out in 13 centers in the United States and Canada. They were eligible from the age of 25 years, even if they had a personal BC history (contralateral screening when they had been diagnosed within 5 years; bilateral screening if they had been diagnosed more than 5 years previously). A total of 367 women completed (only once) all examinations in 13 centers, under the coordination of the University of Washington, Seattle Cancer Care Alliance, Seattle, United States. Imaging evaluations recommended 38 biopsies, 27 of them being performed, resulting in 4 cancers diagnosed; MRI detected all cancers, mammography only one. The biopsy recommendation rate was 8.5% for MRI and 2.2% for mammography. The conclusion, based on a lower BC incidence if compared to the other studies, was that screening MRI in high-risk women was capable of detecting mammographically and clinically occult BC with a tradeoff in terms of false positives causing a 5% rate of benign biopsy.

Finally, still in 2005, Christiane K. Kuhl and coworkers [12] reported on the final results of the single-center study whose preliminary results we mentioned earlier [6]. They compared mammography, US, and MRI for screening women with a lifetime risk ≥20%. The surveillance cohort study, carried out at the University of Bonn, enrolled 529 asymptomatic women suspected or proven to be *BRCA* mutation carriers. A total of 1,542 annual rounds were completed. A total of 43 BCs cancers were identified during the study (34 invasive, 9 DCIS). The sensitivity of mammography (33%) and ultrasound (40%) or the combination of both (49%) was significantly lower than that of MRI (91%). The overall node-positive rate was 16%. The specificity of MRI (97.2%) was equivalent to that of mammography (96.8%). The authors concluded that mammography, even when combined with US, was insufficient for early BC diagnosis in women at increased familial risk and that screening MRI allowed for BC diagnosis in this population with a significantly higher sensitivity and at a more favorable stage.

Thus, by 2005, 7 prospective studies on a total of 3,794 women undergoing multimodality screening and 172 cancers diagnosed in a total of 9,614 annual screening events showed that MRI emerged as a breast imaging modality with a sen-

sitivity ranging from 77% to 100%, always by far superior to that of mammography or US (not over 50% even when combined), with a variable but substantially acceptable specificity, as also judged by the group from the United Kingdom [10], where a long tradition of BC screening with mammography should be considered a reliable testing bench for evaluating a new screening modality.

9.4 The American Cancer Society 2007 Guidelines

What we have described was the basis of evidence available to the panel of experts of the ACS Breast Cancer Advisory Group who, in 2007, published the new *guidelines for breast screening with MRI as an adjunct to mammography* [40]. Their conclusions were as follows:

> Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography. Diagnostic uses of MRI were not considered to be within the scope of this review. [40]

The panel recommended MRI screening (as an adjunct to mammography) on the basis of *evidence from nonrandomized screening trials and observational studies* (those we have described above) in:

- *BRCA* mutation carriers
- First-degree relative of *BRCA* mutation carriers, but untested
- All women with a modeled cumulative LTR of ~20% to 25% or greater

Conversely, the panel also recommended MRI screening (as an adjunct to mammography) on the basis of *expert consensus opinion* taking into consideration only the evidence for LTR for BC in the case of:

- Radiation to chest between age 10 and 30 years
- Li-Fraumeni syndrome (*TP53* mutation carriers) and first-degree relatives
- Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives

As we will see, the evidence subsequently accumulated reinforced the indication of MRI screening for women at hereditary high risk (see the following paragraphs of this Chapter and also Chaps. 10 and 11) and offered a new basis of evidence for the indication to MRI screening for women with previous chest radiation therapy (see Chap. 14). As outlined in Chap. 16, the thresholds for LTR to recommend MRI was already a matter for discussion, as demonstrated by the choice of the ACS Breast Cancer Advisory Group that defined a threshold as a range of 20–25% of LTR, which implies to offer (when the cutoff is 20%) or not to offer screening MRI (when the cutoff is 25%) to thousands and thousands of women in Europe or North America. Recent reviews highlighted the role of MRI surveillance for *TP53* mutation carriers [41] and more generally in the era of next-generation sequencing and moderate-risk genetic mutations, anyway defined as associated with a LTR of 20% or higher, such as ATM, CHEK2, and PALB2 [42].[4]

The new paradigm launched by the ACS was *MRI as an adjunct to mammography*. The subsequent body of evidence will work for reverting this scheme opening the discussion about whether and when mammography should be used as an adjunct to MRI.

9.5 High-Risk Screening with MRI: More Evidence from Prospective Studies (2007–2017)

A number of studies followed and the body of evidence have grown up in the 10 years after the ACS 2007 guidelines publication. The general trend for a huge difference in diagnostic power, especially in sensitivity, between MRI and conventional imag-

[4] See also Chap. 3 on this matter.

ing modalities was largely confirmed. The list of all the studies published in the period from 2000 to 2015, with their main results, is reported in Table 9.1, grouping together the results of subsequent phases of individual projects [6–12, 43–50].

In 2007, Anne I. Hagen and coworkers [43] described their results obtained offering breast MRI screening besides conventional imaging (mammography ± US) to 445 *BRCA1* and 46 *BRCA2* mutation carriers at five centers in Norway (total of 867 screening events). They observed a total of 25 BCs (including 21 invasive and 4 DCIS), 5 of them (20%) as interval cancers. At the time of diagnosis, sensitivity was 19/22 (86%) for MRI and 12/24 (50%) for mammography. Among 21 cancers that were examined by both methods (in 19/21 *BRCA* mutation carriers), the sensitivity of mammography was 10/21 (48%) and that of MRI was 18/21 (86%). Furthermore, the authors noted that MRI had a higher sensitivity than mammography to diagnose all BCs staged less than pT2, which was a major conclusion of their study.

In the same year (2007), Christopher C. Riedl and coworkers [44] reported preliminary results obtained at the Medical University of Vienna by multimodality BC screening in 327 high-risk women (*BRCA* mutation carriers and women with a familial LTR higher than 20%) who underwent 672 complete annual rounds. Of a total of 28 BCs diagnosed, sensitivities were 50% for mammography, 43% for US, and 86% for MRI (the sensitivity of MRI was higher than that of conventional imaging also for the DCIS subgroup), specificities 98%, 98%, and 92%, respectively. Of 101 false-positive findings, 35 (35%) were atypical ductal hyperplasias, 9 (26%) detected by mammography, 2 (6%) by US, and 32 (91%) by MRI. They concluded that MRI improves the detection of invasive and preinvasive BCs as well as premalignant lesions in a high-risk population.

The results of this study were updated in 2015 [45] for 559 women (including 156 *BRCA1*/*BRCA2* mutation cariers) with 1,365 complete rounds. The sensitivity of MRI (90%) was significantly higher than that of mammography (38%) and ultrasound (38%). Of 40 cancers, 18 (45.0%) were detected by MRI alone, 2 cancers were found by mammography alone (a DCIS with microinvasion and a DCIS with less than 10-mm invasive areas), without a significant increase in sensitivity compared to MRI alone. No BCs were detected by US alone. Of 14 DCIS, all were detected by MRI, whereas mammography and US each detected 5 DCIS (36%). The authors also noted that age, mutation status, and breast density did not influence MRI sensitivity, confirming the MRI superiority over mammography and US under these different conditions. They concluded that MRI allows early detection of familial breast cancer regardless of patient age, breast density, or risk status. In addition, they noted that in this setting US provides no additional value, mammography only a limited one.

Still in 2007, we published the mid-term results of the HIBCRIT Italian study [46] for 278 *BRCA1* or *BRCA2* mutation carriers, first-degree relatives of *BRCA1* or *BRCA2* mutation carriers, or women enrolled because of a strong family history of breast or ovarian cancer for a total of 377 rounds: the criteria for enrolling women on the only basis of family history were: three or more events in first- or second-degree relatives in either maternal or paternal line; these included breast cancer in women younger than 60 years, ovarian cancer at any age, and male breast cancer at any age. Of 18 BCs diagnosed, 6 (33%) were detected only with MRI. Sensitivity was 50% for CBE, 59% for mammography, 65% for US, 94% for MRI; PPV3 (i.e., based on performed biopsy) was 82%, 77%, 65%, and 63%, respectively.

We updated these data as final results in 2011 [47] for 501 high-risk women enrolled in 18 centers in Italy. Considering a total of 1,592 rounds (3.2 rounds/woman), 49 screen-detected and 3 interval BCs were diagnosed: 8 DCIS and 44 invasive; 4 pT2 stage and 32 G3 grade. Twenty-eight of 39 patients explored for nodal status (72%) were negative. The incidence per year-woman resulted 3.3% overall, significantly lower (2.1%) under 50 years of age than over 50 (5.4%), significantly higher (4.3%) in women with previous personal BC than in those without (2.5%). MRI was significantly more sensitive (91%) than CBE (18%), mammography (50%), US (52%), or mammography plus US (63%). Specificity ranged from 97% to 99%, PPV from 56% to

Table 9.1 Prospective studies on MRI-including screening of asymptomatic women with hereditary predisposition to BC

First author(s) and year of publication(s), [Reference(s)], name of the study (if any), country[a]	Enrollment (cumulative lifetime risk)	Women analyzed	Rounds	BCs diagnosed during the study					Mammography		Ultrasound		Mammography + ultrasound		MRI	
				All	Invasive/ all	DCIS/ all	Invasive G3/all invasive	N^+/ invasive	Sens %	Spec %	Sens %	Spec %	Sens %	Spec %	Sens %	Spec %
Kuhl 2000 [6], Kuhl 2005 [12], Germany	Fam + Mut (≥20%)	529	1,542	43	34/43 (79%)	9/43 (21%)	11/24[b] (46%)	5/31[b] (16%)	33	97	40	91	49	89	91	97
Podo 2002 [7], Sardanelli 2007 [46], Sardanelli 2011 [47], HIBCRIT, Italy	Fam + Mut (>30%)[c]	501	1,592	52	44/52 (85%)	8/52 (15%)	28/44 (64%)	11/39 (28%)	50	99	52	98	63	98	91	97
Kriege 2004 [8], Rijnsburger 2010 [49], MRISC, The Netherlands[d]	Fam + Mut (≥15%)	2,157	8,760	97	78/97 (80%)	19/97 (20%)	28/74 (38%)	22/74 (30%)	41	95	NR	NR	NR	NR	71	90
Warner 2004 [9], Canada	Mut (>40%)[c]	236	457	22	16/22 (73%)	6/22 (27%)	NR	2/15 (13%)	36	100	33	96	NR	NR	77	95
Leach 2005 [10], MARIBS, United Kingdom	Fam + Mut (≥30%)[c]	649	1,881	35	29/35 (83%)	6/35 (17%)	19/29 (66%)	5/26 (19%)	40	93	NR	NR	NR	NR	77	81
Lehman 2005 [11], United States	Fam + Mut (>25%)	367	367	4	3/4 (75%)	1/4 (25%)	N/R	0/3 (0%)	25	99	NR	NR	NR	NR	100	94
Hagen 2007 [43], Norway	Mut (>40%)[c]	491	867	25	21/25 (84%)	4/25 (16%)	13/21 (62%)	6/20 (30%)	57[e]	NR	NR	NR	NR	NR	86[e]	NR
Riedl 2007 [44], Riedl 2015 [45], Austria	Fam + Mut (>20%)	559	1,365	40	26/40 (65%)	14/40 (35%)	12/25 (48%)	(3/25) (12%)	38	97	38	97	50	96	90	89

First author(s) and year of publication(s), [Reference(s)], name of the study (if any), country[a]	Enrollment (cumulative lifetime risk)	Women analyzed	Rounds	BCs diagnosed during the study					Mammography		Ultrasound		Mammography + ultrasound		MRI	
				All	Invasive/ all	DCIS/ all	Invasive G3/all invasive	N^+/ invasive	Sens %	Spec %	Sens %	Spec %	Sens %	Spec %	Sens %	Spec %
Kuhl 2010 [48], EVA Trial, Germany	Fam + Mut (≥20%)	687	1,679	27	16/27 (59%)	11/27 (41%)	6/16 (38%)	NR	33	99	37	98	48	98	93	98
Trop 2010 [50], Canada	Fam + Mut (>30%)[c]	184	387	12	9/12 (75%)	3/12 (25%)	2/9 (22%)	1/8 (13%)	58	96	42	94[f]	67	91[f]	83	94
Total or interval	Fam + Mut or Mut (from ≥15% to >40%)	6,360	18,897	357	276/357 (77%)	81/357 (23%)	119/242 (49%)	55/241 (23%)	25–58	93–100	33–52	91–98	48–67	89–98	71–100	81–98

MRI magnetic resonance imaging, *BC* breast cancer, *DCIS* ductal carcinoma in situ, *G* histological grade, *Fam* women enrolled for being at elevated familial risk of breast cancer, *Mut* women enrolled for being proven carriers of deleterious mutation in a breast cancer susceptibility gene, *NR* not reported, *Sens* sensitivity (%), *Spec* specificity (%)

[a]Prospective screening studies from 2000 to 2015 are listed in order of publication; when more than one report was published (*e.g.*, preliminary, mid-term, final results) the Table reports the final results. The study by T Huzarsky and coworkers (2017), due to the specific enrollment criteria, has been mentioned and commented in the text

[b]Computed for 31 primary BCs diagnosed during the study period in women without personal history of BC (24 invasive, 7 intraductal)

[c]Estimated

[d]In 2014, from the database of this study, I-M Obdeijn and coworkers extracted and published a retrospective analysis, that was used as control set for the screening project (see Sect. 9.7 of this chapter)

[e]Sensitivities at the time of diagnosis for patients who underwent both mammography and MRI

[f]Biannual (instead of annual) US *plus* CBE sessions

71%, positive likelihood ratio from 25 to 50, without significant differences. MRI showed a significantly better negative predictive value (99.6%) and negative likelihood ratio (0.09) than those of the other modalities. At ROC analysis, the AUC of MRI (0.97) was significantly higher than that of mammography (0.83) or US (0.82) and not significantly increased when MRI was combined with mammography and/or US (examples in Fig. 9.1; Table 9.2). Of 52 BCs, 16 (31%) were diagnosed only by MRI, 8 of 21 (38%) in women <50, and 8 of 31 (26%) in women ≥50 years of age. A subanalysis distinguishing screen-film from digital mammography did not find any increase in sensitivity. We concluded that MRI largely outperformed mammography, US, and their combination for screening high-risk women below and over 50.

In 2010, Christiane K. Kuhl and coworkers [48] published the results of the EVA observational cohort study, conducted at four academic centers in Germany. They enrolled 687 asymptomatic women with familial LTR ≥ 20% who underwent 1,679 annual rounds with CBE, mammography, US, and MRI; 371 women had additional half-yearly US and CBE during 869 rounds. A total of 27 BCs were diagnosed: 11 DCIS (41%) and 16 invasive BCs (59%); 3/27 (11%) with positive nodal status. No interval cancers; no cancers detected with half-yearly US. The BC yield of US (6.0/1,000) and mammography (5.4/1,000) was equivalent, not significantly increased when mammography and US were combined (7.7/1,000). BC yield by MRI alone (14.9/1,000) was significantly higher than that of mammography, US, or their combination and was not significantly improved by adding mammography or US; PPV was 39% for mammography, 36% for US, and 48% for MRI. The authors concluded that in women at elevated familial risk, MRI screening shifts the distribution of screen-detected BCs toward the

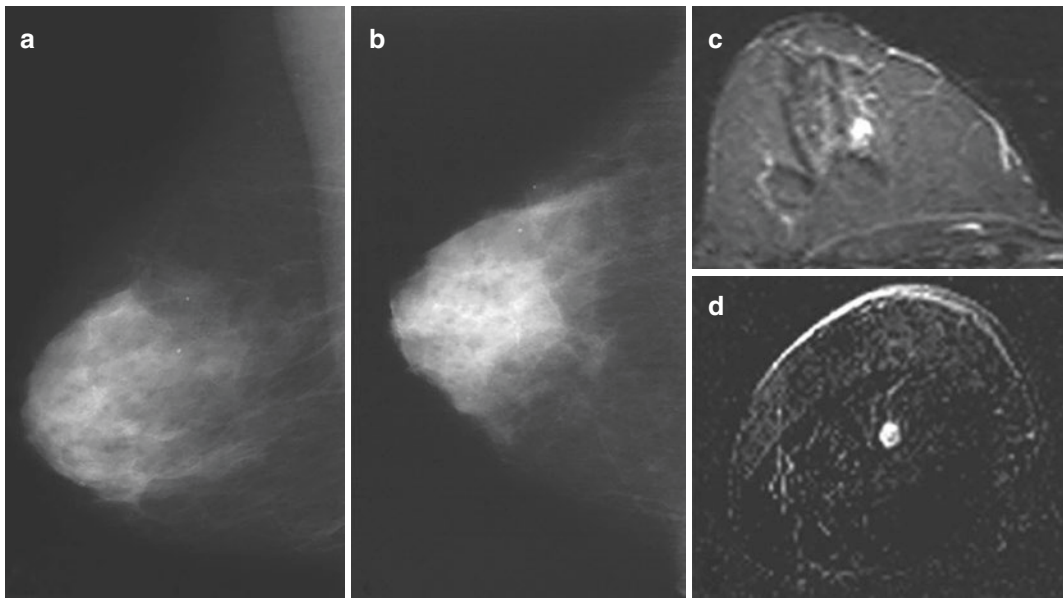

Fig. 9.1 A case from the HIBCRIT study. A 53-year-old *BRCA1* mutation carrier, already treated for an invasive ductal cancer of the left breast at 33 years of age, underwent multimodal screening including clinical breast examination (CBE), mammography, US, and MRI. The left breast only showed minimal signs of the previous treatment at each screening modality (not shown). Mammography of the right breast showed a negative dense breast (**a** and **b**). Also CBE and US (not shown) were negative; at MRI the unenhanced T2-weighted axial short-tau inversion recovery sequence (**c**) showed a small hyperintense mass, confirmed at the subtracted (contrast-enhanced minus unenhanced T1-weighted gradient echo) coronal image (**d**). Final diagnosis: node-negative invasive ductal carcinoma (6 mm in diameter). From Podo et al. (2016) Clin Cancer Res 22:895–904

Table 9.2 Diagnostic performance of the different modalities in the HIBCRIT-1 study

Modality	Sensitivity %	Specificity %	PPV %	NPV %	LR^+	LR^-
Clinical breast examination	17.6	99.3	56.3	96.1	26.4	0.83
Mammography	50.0	99.0	71.4	97.6	52.3	0.50
Ultrasound	52.0	98.4	61.9	97.7	33.0	0.49
MRI	91.3	96.7	56.0	99.6	27.6	0.09
Mammography + ultrasound	62.5	97.6	55.6	98.2	26.0	0.38
MRI + mammography	93.2	96.3	53.2	99.7	25.4	0.07
MRI + ultrasound	93.3	96.0	52.5	99.7	23.6	0.07

PPV positive predictive value, *NPV* negative predictive value, LR^+ positive likelihood ratio, LR^- negative likelihood ratio, *MRI* contrast-enhanced magnetic resonance imaging. From Sardanelli F et al. [47]

pre-invasive stage, while neither mammography, nor annual or half-yearly ultrasound or CBE significantly increase BC detection over MRI alone.

In the same year (2010), Adriana J. Rijnsburger and coworkers [49] updated the results of the Dutch MRISC study, which had enrolled women with LTR for BC ≥ 15%, screened with biannual CBE and annual mammography and MRI [8]. Considering 2,157 eligible women, 599 of them being mutation carriers, 97 primary BCs were diagnosed. The MRI overall sensitivity was significantly higher than that of mammography for invasive cancer (77% versus 36%), but not for DCIS. Mammography sensitivity was only 25.0% in the *BRCA1* group, 62% in the *BRCA2* group, 46% in the high-risk group (with a 30–50% LTR), and 47% in the moderate-risk groups (with a 15–30% LTR). Results in the *BRCA1* group were also worse compared with the *BRCA2* group, high- and moderate-risk group regarding tumor size ≤1 cm at diagnosis (21%, 62%, 41%, and 64%, respectively); proportion of DCIS (7%, 19%, 15%, and 31.3%); and interval cancers (32%, 6%, 4%, and 6%). The authors also reported on cumulative distant metastasis-free and overall survival at 6 years for invasive BCs, which were 84% and 93%, respectively, in 42 *BRCA* mutation carriers with invasive BC and 100% in 43 women of familial groups. They concluded that screening results were somewhat worse in *BRCA1* mutation carriers, but the 6-year survival was high in all groups.

Still in 2010, Isabelle Trop and coworkers [50] reported results obtained at the Université de Montréal, Canada. They enrolled 184 asymptomatic women being *BRCA1/2* mutation carriers or with >30% probability of being *BRCA1/2* mutation carriers as estimated by BRCAPRO. During 387 rounds, 12 BCs were detected (9 invasive, 3 DCIS), for an overall yield of 6.5%; 7/9 invasive cancers were smaller than 2 cm in diameter; only 1 case of positive nodal status was observed; all BCs were negative to the human epidermal growth factor receptor 2 (HER2). Sensitivity was 10/12 for MRI (83%), 7/12 (58%) for mammography; US did not detect any additional cancers. The recall rate was 22% for MRI, 16% for mammography, and 11% for US. Importantly, the authors noted that recall rates declined with successive screening rounds. In total, 45 biopsies were performed: 21 due to US, 17 due to MRI, and 7 due to mammography. The authors concluded that MRI offers to high-risk women the best sensitivity for BC screening and that the combination of yearly MRI and mammography reached a negative predictive value of 100%.

In 2012, Wendy D. Berg and coworkers [51] reported on the results of a subproject of ACRIN 6666 multicenter study to determine supplemental cancer detection yield of US and MRI in women at elevated BC risk. Women were eligible if being asymptomatic, having heterogeneously dense or extremely dense breast tissue, and also having at least one of other risk factors. A total of 2,809 women at 21 sites had annual independent screens with mammography and US in randomized order; after three rounds of both screenings, 612 women underwent MRI and had complete data. A total of 2,662 women underwent 7,473 mammogram and US screenings, 110 of whom had 111 BCs diagnosed: 33 detected by mammography only, 32 by US only,

26 by both, and 9 by MRI after mammography + US; 11 were not detected by any imaging modality. Supplemental US identified additional BCs in 3.7/1,000 screens. Sensitivity for mammography + US was 76%, specificity 84%, and PPV3 (i.e., based on performed biopsy) 16%. For mammography alone, sensitivity was 52%, specificity 91%, and PPV3 38%. Of the MRI participants, 16 women (2.6%) had a BC diagnosed. The supplemental yield of MRI was 14.7/1,000. Sensitivity for MRI and mammography plus US was 100%, specificity was 65%, and PPV3 19%. For mammography and US, sensitivity was 44%, specificity 84%, and PPV3 18%. The number of screens needed to detect one cancer was 127 for mammography, 234 for supplemental US, and 68 for MRI after negative mammography and US. The authors concluded that the addition of screening US or MRI to mammography in women at increased risk of breast cancer resulted in a higher cancer detection yield, but also an increase in false-positive findings. The study has a particular interest: it shows the additional diagnostic power of each breast imaging technique when applied sequentially, with MRI associated with the lowest number of screens needed for detecting one cancer (68) as third examination versus mammography (127) at the beginning of the sequence, and US (234) in between. However, the study design does not allow an intra-individual comparative analysis. Data are not comparable with those of the other prospective studies. For this reason, we did not include this study in Table 9.1.

Finally, in 2014, Anna M. Chiarelli and coworkers [52] reported on the results obtained by the Ontario Breast Screening Program which in July 2011 started to screen women at high BC risk from 30 to 69 years of age with annual MRI and digital mammography in 28 centers. Eligibility was based on the following criteria: known *BRCA1* or *BRCA2* mutation or other gene mutations associated with high BC risk; untested first-degree relative of a mutation carrier; family history consistent with hereditary BC syndrome and estimated personal LTR ≥ 25%; or chest radiation therapy (before age 30 and ≥8 years previously). These results have a particular relevance, for being the first screening program for high-risk women organized on a regional base. Thirty-five BCs were diagnosed (16.3/1,000), none of them by mammography alone, 23 (66%) by MRI alone (10.7/1,000); 25/35 BCs (71%) were detected among mutation carriers (30.8/1,000). The recall rate was significantly higher in the cases of positive MRI alone (15.1%) than with mammography alone (6.4%); PPV was highest for detection based on both mammography and MRI (12.4%). The authors concluded that screening with annual MRI and mammography has the potential to be implemented into an organized breast screening program for women at high risk for breast cancer.

To summarize, in 10 years after the ACS guidelines, different prospective studies performed in Europe and in North America increased the body of knowledge on BC screening in high-risk women (see Table 9.1), showing that:

1. The higher sensitivity of MRI versus mammography (combined with acceptable MRI specificity and PPV values) was confirmed on a larger basis.
2. The transition from screen-film to digital technique did not provide an increase in BC detection by mammography.
3. When performed, the additional value of US appeared very low, if any, also with a 6-month interval.
4. The additional value of mammography also appeared open for debate, due to the low number of cases diagnosed by mammography only, mostly of them being DCIS.
5. A higher diagnostic power of MRI was also reported in postmenopausal women.
6. The value of MRI screening was also shown in high-risk women already treated for BC.

Points 1, 2, and 3 above were reinforced by the ROC analysis curves from the HIBCRIT-1 study [47, 53] (Fig. 9.2); also the EVA trial [48] gave similar results.

Lastly, we wish to mention the multicenter study by Tomasz Huzarski and coworkers [54]

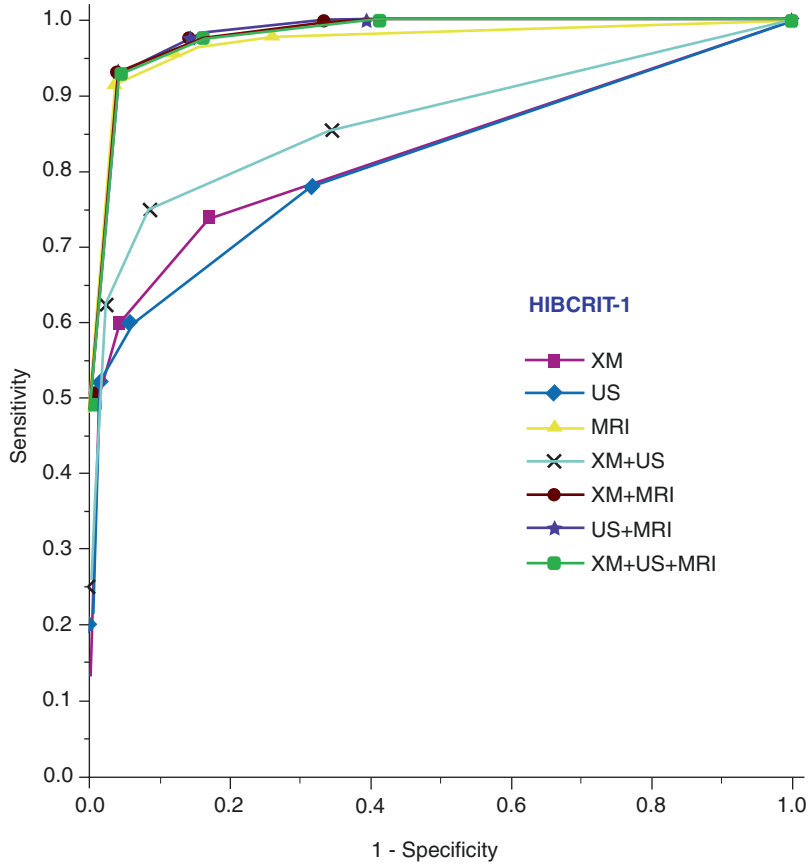

Fig. 9.2 ROC analysis of diagnostic performance of annual mammography (XM), US, MRI, and their combinations for screening high-risk women in the HIBCRIT-1 study. The MRI AUC was significantly higher than that of mammography, US, or their combination, without a significant increase in diagnostic power when mammography and/or US were combined with MRI. With permission, from Sardanelli F, Podo F [53]

from the Polish Hereditary Breast Cancer Study Group, investigating the role of MRI for screening women at average or intermediate risk, hence being outside our focus on high risk. However, their results can be useful to a general reasoning. They enrolled 2,995 women aged 40–65, without previous BC history: 356 (12%) with a CHEK2 mutation, 370 (12%) with a first-degree relative with BC but without CHEK2 mutation, and 2,269 (76%) without any risk factor. These women underwent two rounds of MRI, US, and mammography, 1 year apart and were followed for 3 years. During the 4-year time frame, 27 invasive cancers, 6 DCIS, and 1 angiosarcoma were diagnosed. Of the 27 cancers, 20 were screen-detected, 2 interval, and five during follow-up. For invasive cancers, sensitivity was 86% for MRI, 59% for US, and 50% for mammography; of the 19 invasive cancers detected by MRI, 17 (89%) were also detected by US or mammography. MRI prompted 156 biopsies, US 57, mammography 35. The authors concluded that MRI sensitivity was only slightly better than that of mammography/US and that, also considering costs, MRI screening is probably not warranted outside of high-risk populations. In Chaps. 21 and 22, the reader can find an extensive explanation of the limited evidence for using MRI in intermediate-risk population. Anyway, this study shows how the application of MRI screening to a mixed population composed of average-risk women for over three quarters does not seem to

provide relevant results in terms of additional cancer yield.

Of note, after 2007, studies also offered a basis of evidence in favor of MRI screening in women who underwent chest radiation therapy, even though with lower sensitivity than for women with hereditary BC predisposition. *Mammography as adjunct to MRI* has been suggested for women of this BC risk category, in consideration of the relatively higher probability of DCIS with microcalcifications and low angiogenesis [55]. This topic is extensively treated in Chap. 14.

9.6 Other Guidelines and the Ten Key Points from EUSOMA Recommendations

After 2007, many other national and international bodies issued guidelines and recommendations for MRI screening of women at high BC risk, among them, the American College of Radiology [56], the European Society of Breast Imaging [57, 58], or the multidisciplinary European Society of Breast Cancer Specialists (EUSOMA) [59], but also governmental bodies such as the National Comprehensive Cancer Network [60] in the United States and the National Institute for Health and Care Excellence [61] in the United Kingdom. Differences exist among guidelines, especially for the threshold of LTR to define the indication to MRI, lower (20–25%) in guidelines from the United States (where the ACR recently recommended screening MRI also in lower risk categories [62]), higher (30% or more) in some European guidelines. However, in all guidelines MRI is proposed for screening high-risk women. In Chap. 16, the reader can find an extensive review of these and other guidelines.

In this paragraph, we only wish to reserve a special mention to the EUSOMA recommendations published in 2010 [59] for their characteristic of having been provided by a multisciplinary panel, with a list of ten key points for breast MRI screening in high-risk women that we still consider useful today (Table 9.3).

9.7 Rethinking of the Relative Role of Mammography versus MRI for Screening High-Risk Women

During the last two decades, also retrospective studies on breast MRI screening of high-risk women were published. We did not mention them earlier because of the lower value that a retrospective study design implies in this context. However, some of them, recently published, deserve in our opinion a particular consideration.

In particular, three retrospective studies provided further contribution to rethinking the role of mammography for screening high-risk women.

In 2014, Inge-Marie Obdeijn and coworkers [63] reported specifically on 93 cases of BC in *BRCA1* mutation carriers who underwent screening with MRI and digital mammography at the Erasmus Medical Center in Rotterdam, the Antoni van Leeuwenhoek Hospital in Amsterdam, and at the University Medical Center in Nijmegen: 82 invasive cancers and 12 DCIS. Screening sensitivity was 90/94 (96%) overall, significantly higher for MRI (88/94, 94%) than for mammography (48/94, 51%). While 42/94 malignancies (45%) were detected only by MRI, only 2 DCIS (2/94, 2%) were detected only with mammography (one G3 DCIS in a 50-year-old patient and one G2 in a 67-year-old patient). All the 4 interval cancers (4/94, 4%) were G3 triple-negative invasive ductal carcinomas. The authors concluded that digital mammography added only 2% to the breast cancer detection in *BRCA1* patients, without any benefit of additional mammography under 40 years of age. They proposed that, given the potential risk of radiation-induced breast cancer in young mutation carriers, *BRCA1* mutation carriers could be screened yearly with MRI from age 25 onward and with mammography not earlier than age 40.

In 2017, Lo and coworkers [64] reviewed the prospective database of 3,934 screening studies (1,977 MRI and 1,957 mammography examinations) performed on 1,249 high-risk women at three academic hospitals in Canada. A total of 45 cancers (33 invasive and 12 DCIS) were diagnosed, 43 of them seen with MRI and 14 with both mam-

Table 9.3 Ten key points on screening women with an increased BC risk from EUSOMA recommendations

1. Women with a family history suspicious for inherited BC predisposition should have their risk assessed by an appropriately trained professional group (genetic counseling); LTR thresholds for including women in surveillance programs with annual MRI may be selected on the basis of regional or national considerations
2. High-risk screening including MRI should be conducted only at a nationally/regionally approved and audited service or as part of an ethically approved research study. Periodical audit should be undertaken to ensure that high sensitivity is achieved and recall rate (MRI more frequently than annual) is less than 10%, and to monitor detection rate, needle biopsy rate and interval cancers
3. Annual MRI screening should be available starting from the age of 30. Starting screening before 30 may be possible for *BRCA1/2* mutation carriers (from 25 to 29) and TP53 (from 20)
4. Annual MRI screening should be offered to: *BRCA1*, *BRCA2*, and *TP53* mutation carriers; women at 50% risk for *BRCA1*, *BRCA2*, or *TP53* mutation in their family (first-degree relatives of mutation carriers); women from families not tested or inconclusively tested for *BRCA* mutation with a 20–30% LTR or greater
5. MRI-including screening should be offered also to high-risk women previously treated for BC.
6. Screening mammography should not be performed in high-risk women below 35. In *TP53* mutation carriers of any age annual mammography can be avoided based on discussion on risks and benefits from radiation exposure
7. Annual mammography may be considered for high-risk women from age 35
8. If annual MRI is performed, screening whole breast using US and clinical breast examination are not necessary. They are recommended in women under 35 who do not tolerate or have contraindication to MRI or to Gd-based contrast material administration
9. Cases requiring workup after MRI should be initially assessed with conventional imaging (re-evaluation of mammograms, targeted US). In case of only MRI-detected suspicious findings, MR-guided biopsy/localization should be performed
10. Risk factors such as heterogeneously or extremely dense breasts, previous diagnosis of breast invasive cancer or ductal carcinoma in situ, atypical ductal hyperplasia, lobular intraepithelial neoplasia, when not associated with other risk factors, do not confer an increased risk that justifies screening MRI

BC breast cancer, *LTR* lifetime risk, *MRI* contrast-enhanced magnetic resonance imaging, *US* ultrasound. From Sardanelli et al. [59], modified. Notably, the EUSOMA recommendations include also women who underwent chest radiation therapy, discussed in Chap. 14

mography and MRI. Additional tests (further imaging and/or biopsy) were recommended in 461 screening MRI (recall rate, 23%) while mammography recalled 217 (recall rate, 11%). The detection rate was significantly higher for MRI (21.8/1,000) than for mammography (7.2/1,000). The sensitivity of MRI (96%) was significantly higher than that of mammography (31%); the specificity of MRI (78%) was significantly lower than that of mammography (89%); the PPV1 (i.e., for recalls) of MRI (9.3%) was higher, but not significantly, than that of mammography (6.5%). The authors concluded that mammography did not have an added value for BC detection in high-risk women undergoing MRI screening. As a consequence, they said that routine mammography in women undergoing screening MRI imaging warrants reconsideration.

Lastly, Suzan Vreeman and coworkers [65] from Radboud University Medical Center, Nijmegen, investigated the added value of mammography in different age-groups of women with and without *BRCA* mutation screened with breast MRI, based on 6,553 rounds in 2,026 women at increased BC risk of breast cancer (1 January 2003–1 January 2014). Of a total of 125 screen-detected cancers, 112 were detected by MRI and 66 by mammography: 13 cancers were detected only by mammography, 8 of them being DCIS. Cancer detected only by mammography were 3/61 (5%) in *BRCA* mutation carriers, and 10/64 (16%) in non-*BRCA* mutation carriers. While 77% of mammography-only cancers were detected in women ≥50 years of age, mammography also added more to the false-positive recalls in these women. Below 50 years of age, the number of mammographic examinations needed to find an MRI-occult cancer was 1,427. The authors concluded that the benefit of mammography appears slightly larger in women over 50 years of age without *BRCA* mutation, associated with a substantial increase in false-positive recalls.

Conversely, two recent retrospective reports focused on missed BCs in high-risk screening, in particular on MRI false negative cases.

Antony J Maxwell and coworkers [66] from Nightingale Centre, University Hospital of South Manchester, Manchester, reported on 32 high-risk women who had undergone screening MRI and had been diagnosed with breast cancer within 2 years after a negative MRI. For 23 cases, MRI images were available for review. Fourteen were diagnosed at MRI, 4 at interim mammography, two symptomatically, one incidentally on US, and two at risk-reducing mastectomy. Ten of the 23 women (43%) had a potentially avoidable delayed diagnosis. The preceding MRIs were classified as false-negative screens in five women (one prevalent, four incident), false-negative assessment in seven, and minimal signs in three (three women were assigned dual classifications). Reasons for the diagnostic delay mostly were small overlooked enhancing masses, areas of non-mass enhancement showing little, if any, change between screens, false reassurance from normal conventional imaging at assessment, and overreliance on repeat MRI at short-interval. The authors concluded recommending double reading of both screening and assessment examinations, ready access to MRI biopsy, and limited use of short-interval repeat MRI only for areas likely to be benign glandular enhancement. They also recommend annual mammography in these women.

Suzan Vreemann and coworkers by the Nijmegen group [67] investigated the same issue for a larger case series of 131 missed BCs for which negative prior MRI was available. Overall, visible findings on prior negative MRI were observed in 31% of cases, minimal signs in 34%, no signs in 35%. These visible findings were significantly less frequent in *BRCA* mutation carriers (19%) than in non-carriers (46%). Less than perfect image quality significantly increased the probability of visible findings and minimal signs in the negative prior MRI. The author concluded that almost one-third of cancers detected in a high-risk screening program are already visible at the last negative MRI scan, and even more so in women without *BRCA* mutations, so that regular auditing and double reading for breast MRI are warranted.

Finally, the same group from Nijmegen [68] reported on real-life performance of a large screening program for women with different categories of increased risk in their academic hospital. They analyzed 8,818 MRI and 6,245 mammography examinations performed in 2,463 women. On a total of 170 cancers, 129 were screen-detected cancers, 16 interval, and 25 found at prophylactic mastectomy. Overall sensitivity was 76% including cancers from prophylactic mastectomy and 90% excluding them. Sensitivity was lowest for carriers of the *BRCA1* mutation (66 and 81%, respectively). Specificity was higher at follow-up (96%) than in first rounds (85%) and was high for both MRI (97%) and mammography (99%); PPV of recall and of biopsy were lowest in women with only family BC history. The authors' conclusions were that screening performance was dependent on risk category, with lowest sensitivity in *BRCA1* mutation carriers, and that specificity improved at follow-up rounds.

9.8 Conclusions and Open Issues

As the readers can understand, a general agreement for recommending breast MRI annual screening in women at high risk does exist on the basis of a large body of evidence provided by a dozen of prospective studies including 6,360 women, about 18,900 rounds, and 357 BCs diagnosed. However, a number of issues deserve attention and, for them, we refer the reader to other Chapters in this book.

First, systematic reviews and meta-analyses have explored interesting aspects, especially allowing for subgroup analyses that the power of original studies would not have permitted. The reader can find these results in Chap. 11.

Second, the possibility of using *MRI alone* for screening at least certain categories at high-risk women should be considered, not only for the low contribution of mammography and US to the screening sensitivity, but also for their increase in false-positive recalls rate, a topic extensively treated in Chap. 10. In addition, also radioprotection considerations may play in favor of avoiding mammography [69] (and other radiation exposure of the chest, including computed tomogra-

phy!), especially in *BRCA* mutation carriers, a topic extensively treated in Chap. 12.

Third, the top sensitivity of breast MRI in high-risk women should determine positive effects in terms of patient outcome, i.e., at least disease-specific and disease-free survival. The reader can find the illustration of the results already available in the absence of randomized controlled trials in Chap. 13.

At any rate, due to the very low, if any, contribution of US and the low contribution of mammography when compared to MRI for screening a high-risk population, we can propose the following simple recommendations [53]:

1. MRI alone up to 35 years of age for all high-risk women
2. MRI alone for *BRCA1* and *TP53* mutation carriers without age limitations
3. Mammography as an adjunct to MRI for *BRCA2* mutation carriers after 35 years of age and to women who had previous chest radiation therapy

Thus, the paradigm "MRI as an adjunct to mammography" has been reverted into its contrary. When "mammography as an adjunct to MRI" is under consideration for high-risk women, a good conservative approach has been suggested, consisting of performing only one projection, the mediolateral oblique one [70].

About two decades after the start of the first prospective studies on breast MRI screening in high-risk women, the efforts of several research groups in Europe and North America have opened an efficient way of surveillance as an alternative to prophylactic mastectomy to be offered to these women. Much work still needs to be done but one important step forward has been done.

References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996) Evidence based medicine: what it is and what it isn't. BMJ 312:71–72
2. Sardanelli F, Hunink MG, Gilbert FJ, Di Leo G, Krestin GP (2010) Evidence-based radiology: why and how? Eur Radiol 20:1–15
3. Prasad KN, Cole WC, Haase GM (2004) Radiation protection in humans: extending the concept of as low as reasonably achievable (ALARA) from dose to biological damage. Br J Radiol 77:97–99
4. Oxford Centre for Evidence-based Medicine (2009) Levels of Evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 30 Jun 2020
5. The Council of the European Union (2003) Council recommendation of 2 December 2003 on cancer screening (2003/878/EC). https://ec.europa.eu/jrc/sites/jrcsh/files/2_December_2003%20cancer%20screening.pdf. Accessed 30 Jun 2020
6. Kuhl CK, Schmutzler RK, Leutner CC et al (2000) Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 215:267–279
7. Podo F, Sardanelli F, Canese R et al (2002) The Italian multi-centre project on evaluation of MRI and other imaging modalities in early detection of breast cancer in subjects at high genetic risk. J Exp Clin Cancer Res 21(3 Suppl):115–124
8. Kriege M, Brekelmans CT, Boetes C et al; Magnetic Resonance Imaging Screening Study Group (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427–437
9. Warner E, Plewes DB, Hill KA et al (2004) Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317–1325
10. Leach MO, Boggis CR, Dixon AK et al (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
11. Lehman CD, Blume JD, Weatherall P et al; International Breast MRI Consortium Working Group (2005) Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer 103:1898–1905
12. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
13. Pisano ED, Gatsonis C, Hendrick E et al; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group (2005) Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 353:1773–1783
14. Kemp Jacobsen K, Abraham L, Buist DS et al (2015) Comparison of cumulative false-positive risk of screening mammography in the United States and Denmark. Cancer Epidemiol 39:656–663
15. Hofmann B (2018) Fake facts and alternative truths in medical research. BMC Med Ethics 19:4

16. Autier P, Boniol M (2018) Mammography screening: a major issue in medicine. Eur J Cancer 90:34–62
17. Berry DA, Cronin KA, Plevritis SK et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792
18. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM (2015) Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. BMJ 351:h4901
19. Hofvind S, Sørum R, Thoresen S (2008) Incidence and tumor characteristics of breast cancer diagnosed before and after implementation of a population-based screening-program. Acta Oncol 47:225–231
20. Cutuli B, Dalenc F, Cottu PH et al (2015) Impact of screening on clinicopathological features and treatment for invasive breast cancer: results of two national surveys. Cancer Radiother 19:295–302
21. Dong W, Berry DA, Bevers TB et al (2008) Prognostic role of detection method and its relationship with tumor biomarkers in breast cancer: the university of Texas M.D. Anderson Cancer Center experience. Cancer Epidemiol Biomark Prev 17:1096–1103
22. Nagtegaal ID, Allgood PC, Duffy SW et al (2011) Prognosis and pathology of screen-detected carcinomas: how different are they? Cancer 117:1360–1368
23. Lauby-Secretan B, Scoccianti C, Loomis D et al; International Agency for Research on Cancer Handbook Working Group (2015) Breast cancer screening—viewpoint of the IARC working group. N Engl J Med 372:2353–2358
24. Sardanelli F (2015) Screening mammography: a clear statement by the IARC handbook. Epidemiol Prev 39:149–150
25. Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M, Paci E; EUROSCREEN Working Group (2012) Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. J Med Screen 19(Suppl 1):42–56
26. Paci E; EUROSCREEN Working Group (2012) Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. J Med Screen 19(Suppl 1):5–13
27. Colin C, Devouassoux-Shisheboran M, Sardanelli F (2014) Is breast cancer overdiagnosis also nested in pathologic misclassification? Radiology 273: 652–655
28. Elmore JG, Longton GM, Carney PA et al (2015) Diagnostic concordance among pathologists interpreting breast biopsy specimens. JAMA 313:1122–1132
29. Tosteson ANA, Yang Q, Nelson HD et al (2018) Second opinion strategies in breast pathology: a decision analysis addressing over-treatment, under-treatment, and care costs. Breast Cancer Res Treat 167:195–203
30. Sardanelli F, Trimboli RM, Tot T (2018) Expert review of breast pathology in borderline lesions: a chance to reduce overdiagnosis and overtreatment? JAMA Oncol 4:1325–1326
31. Colin C, Schott AM, Valette PJ (2014) Mammographic density is not a worthwhile examination to distinguish high cancer risk women in screening. Eur Radiol 24:2412–2416
32. Freer PE (2015) Mammographic breast density: impact on breast cancer risk and implications for screening. Radiographics 35:302–315
33. Burke W, Daly M, Garber J et al (1997) Recommendations for follow-up care of individuals with an inherited predisposition to cancer II BRCA1 and BRCA2: Cancer genetics studies consortium. JAMA 277:997–1003
34. Daly MB and coworkers (2003) The NCCN 2003 genetic/familial high-risk assessment clinical practice guidelines in oncology, version 1. https://www2.trikobe.org/nccn/guideline/gynecological/english/genetic_familial.pdf. Accessed 30 Jun 2020
35. Dent R, Warner E (2007) Screening for hereditary breast cancer. Semin Oncol 34:392–400
36. Sardanelli F, Carbonaro LA, Santoro F, Podo F (2010) Sorveglianza RM nelle donne ad alto rischio di carcinoma mammario. In: Ragozzino A (ed) Imaging RM nella donna. Idelson-Gnocchi, Napoli, pp 47–72. isbn:978-88-7947-521-1
37. Tyrer J, Duffy SW, Cuzick J (2004) A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 23:1111–1130
38. International Breast Cancer Intervention Study (IBIS). https://www.fairfaxradiology.com/services/exams/IBIS-Tool.php. Accessed 30 Jun 2020
39. Hedenfalk I, Ringner M, Ben-Dor A et al (2003) Molecular classification of familial non-BRCA1/BRCA2 breast cancer. Proc Natl Acad Sci USA 100:2532–2537
40. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
41. Schon K, Tischkowitz M Clinical implications of germline mutations in breast cancer: TP53. Breast Cancer Res Treat 167:417–423
42. Macklin S, Gass J, Mitri G, Atwal PS, Hines S (2018) The role of screening MRI in the era of next generation sequencing and moderate-risk genetic mutations. Familial Cancer 17:167–173
43. Hagen AI, Kvistad KA, Maehle L et al (2007) Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast 16:367–374
44. Riedl CC, Ponhold L, Flöry D et al (2007) Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. Clin Cancer Res 13:6144–6152
45. Riedl CC, Luft N, Bernhart C, et al (2015) Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 33:1128–1135
46. Sardanelli F, Podo F, D'Agnolo G et al (2007) Multicenter comparative multimodality surveillance

of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 242:698–715
47. Sardanelli F, Podo F, Santoro F, et al for the High Breast Cancer Risk Italian 1 (HIBCRIT-1) Study (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Investig Radiol 46:94–105
48. Kuhl C, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
49. Rijnsburger AJ, Obdeijn IM, Kaas R et al (2010) BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol 28:5265–5273
50. Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D (2010) Multimodality breast cancer screening in women with a familial or genetic predisposition. Curr Oncol 17:28–36
51. Berg WA1, Zhang Z, Lehrer D et al; ACRIN 6666 Investigators (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
52. Chiarelli AM, Prummel MV, Muradali D et al (2014) Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario high risk breast screening program. J Clin Oncol 32:2224–2230
53. Sardanelli F, Podo F (2017) Radiological screening of breast cancer: evolution. High-risk population. In: Veronesi U, Goldhirsch A (eds) Breast cancer. Innovations in research and management. Springer, Cham, pp 189–203
54. Huzarski T, Górecka-Szyld B, Huzarska J et al (2017) Screening with magnetic resonance imaging, mammography and ultrasound in women at average and intermediate risk of breast cancer. Hered Cancer Clin Pract 15:4
55. Mariscotti G, Belli P, Bernardi D et al (2016) Mammography and MRI for screening women who underwent chest radiation therapy (lymphoma survivors). Recommendations for surveillance from the Italian College of Breast Radiologists by SIRM. Radiol Med 121:834–837
56. American College of Radiology practice parameter for the performance of contrast-enhanced MRI of the breast. http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/MRI_Breast.pdf. Accessed 30 Jun 2020
57. Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 18:1307–1318
58. Mann RM, Balleyguier C, Baltzer PA, et al; European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678
59. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
60. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
61. National Institute for Health and Care Excellence (NICE). Protocols for the surveillance of women at higher risk of developing breast cancer. Version 4. Updated NICE guidance on women with a familial history of breast cancer. NHSBSP Publication no. 74—June 2013
62. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA (2018) Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol 15(3 Pt A):408–414
63. Obdeijn IM, Winter-Warnars GA, Mann RM, Hooning MJ, Hunink MG (2014) Tilanus-Linthorst MM. Should we screen BRCA1 mutation carriers only with MRI? A multicenter study. Breast Cancer Res Treat 144:577–582
64. Lo G, Scaranelo AM, Aboras H et al (2017) Evaluation of the utility of screening mammography for high-risk women undergoing screening breast MR imaging. Radiology 285:36–43
65. Vreemann S, van Zelst JCM, Schlooz-Vries M et al (2018) The added value of mammography in different age-groups of women with and without BRCA mutation screened with breast MRI. Breast Cancer Res 20:84
66. Maxwell AJ, Lim YY, Hurley E, Evans DG, Howell A, Gadde S (2017) False-negative MRI breast screening in high-risk women. Clin Radiol 72:207–216
67. Vreemann S, Gubern-Merida A, Lardenoije S et al (2018) The frequency of missed breast cancers in women participating in a high-risk MRI screening program. Breast Cancer Res Treat 169:323–331
68. Vreemann S, Gubern-Mérida A, Schlooz-Vries MS et al (2018) Influence of risk category and screening round on the performance of an MR imaging and mammography screening program in carriers of the BRCA mutation and other women at increased risk. Radiology 286:443–451
69. Sardanelli F, Podo F (2007) Management of an inherited predisposition to breast cancer. N Engl J Med 357:1663
70. Colin C, Foray N (2012) DNA damage induced by mammography in high family risk patients: only one single view in screening. Breast 21:409–410

10 Genetic/Familial High-Risk Screening: MRI Alone?

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Abbreviations

DWI	Diffusion-weighted imaging
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
MRI	Magnetic resonance imaging
PR	Progesterone receptor
US	Ultrasonography, ultrasound

10.1 Introduction

Women who carry a *BRCA1* or *BRCA2* deleterious mutation have approximately a 3% risk of developing breast cancer before the age of 30 years, a risk of almost 50% at 50, and up to 80% at 70 years of age [1]. It is assumed that there are other hereditary conditions increasing the risk of breast cancer. Thus, women with a strong family history of breast and/or ovarian cancer, even if non-tested or tested negative for *BRCA1* or *BRCA2* deleterious mutations, should be regarded as having a substantial increase in breast cancer risk [2–5]. For high-risk women, in particular for *BRCA1/2* mutation carriers, also options such as prophylactic bilateral mastectomy and oophorectomy, allowing a reduction of breast cancer risk up to 90%, are available [6, 7].

Alternatively, these women can join screening programs, mostly preferred by these patients [8–10]. International and national medical societies as well as governmental bodies have established guidelines for breast cancer screening in individuals with a known or suspected genetic predisposition. However, no consensus has been reached on several aspects and the regimen of the various screening programs differs widely throughout Europe and the United States [4, 11–20]. The reader can find a detailed analysis of guidelines in Chap. 16.

The combined use of mammography, ultrasonography (US), and magnetic resonance imaging (MRI) has the best diagnostic performance and yields the highest detection rates. Nevertheless, the triple-modality approach increases the number of false-positive findings and increases costs [21–24]. In several prospective high-risk screening studies, MRI has widely proven its high sen-

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sitivity, outperforming other breast imaging techniques, such as mammography and/or US [25, 26]. Therefore, experts currently recommend annual MRI screening from age 25 years onward, and additional mammography from age 30 years for women at high-risk [12, 27].

This chapter aims to provide a comprehensive overview of the current possibilities in screening women with a genetic/familial high risk. The role of the different breast imaging screening modalities, together with clinical breast examination, will be reviewed, particularly, to determine whether MRI can be used as a single modality in women at genetic/familial high risk. In addition, we will discuss the impact of screening on survival rates of the genetic/familial high-risk women and we will provide insights into the cost-benefit aspects.

10.2 Mammography in High-Risk Women

Randomized controlled trials have shown that screening with mammography can reduce breast cancer mortality by 30–50% [28–30]. Although these findings have been repeatedly disputed [31, 32], there is currently a consensus among clinicians that mammographic screening is effective, especially in women at an average risk for breast cancer and between 50 and 70 years of age [30, 33–35].

Compared to women at an average risk, high-risk women present with an earlier onset of disease and often with more aggressive tumor types [36–41]. Thus, in these women screening programs must begin at a young age, 30 years or earlier, to be effective. Furthermore, the screening method of choice must be able to detect small lesions at an early stage.

Based on the available evidence regarding the effectiveness of mammography in the general population, screening mammography was also suggested as a screening tool in high-risk women [13, 42, 43]. Several studies analyzed the effectiveness of performing screening mammography every year starting from 30–35 years of age in women with a known mutation and/or at high-risk of developing breast cancer [19, 20, 26, 44–47]. The sensitivity of mammography only ranged from 30% to 58% [20, 26, 48] (Table 10.1).

Although it has a low sensitivity, mammography maintains a very high specificity in high-risk women, up to 95–99% (Table 10.1) [20, 26, 44, 47]. As a consequence, mammography is the method that ensures a low recall rate ranging from 1.9% to 6.4% [19, 46].

Relevant drawbacks of mammography are related to the reduced sensitivity of this modality in high-risk women, including:

- Dense breast tissue, particularly in young patients participating in the surveillance programs [54–56]
- Rapid tumor growth [57]
- Atypical imaging features of breast cancers [58, 59]
- Cumulative effect of radiation from yearly mammograms [60, 61]

Breast cancers in high-risk women, particularly in women with a *BRCA1* deleterious mutation, present with imaging features that might be difficult to identify and characterize on mammography [36, 37, 39, 41, 58]. An example of prepectoral location of a triple negative breast cancer in *BRCA1* mutation carriers is given in Fig. 10.1. In addition, the incidence of cancers presenting with microcalcifications is lower compared to that in the general population [62, 63]. Based on the low incidence of calcified lesions, the subtle features of cancer in *BRCA1* mutation carriers, and the young age at cancer onset, MRI of the breast has been suggested as a single screening modality in these groups of women [47, 64], as we will see below. An example of simultaneous positivity of mammography, US and MRI is given Fig. 10.2, while Fig. 10.3 shows a case of an MRI-only detected cancer, with positive targeted (second-look) US.

A further issue should be considered: Women with *BRCA1* and *BRCA2* mutations carry mutations in genes involved in the DNA-damage repair pathway. These women are thus more prone to radiation-induced DNA damage and to radiation-induced breast cancer [65–67]. Exposing the breasts of these women to radiation annually, despite the small doses delivered,

Table 10.1 Sensitivity and specificity of mammography, US, MRI, and their combinations according to various studies

First author, year [reference]	Women	Mammography alone		US alone		Mammography and US		MRI alone		MRI and mammography		MRI and US	
		SN %	SP %	SN %	SP %	SN %	SP %	SN %	SP %	SN %	SP %	SN %	SP %
Warner (2004) [74][a]	236	38.0	99.6.	25.0	95.0	NA	NA	85.0	93.0	NA	NA	NA	NA
Kuhl (2005) [18]	529	32.6	96.8	39.5	90.5	48.8	89.0	90.7	97.2	93.0	96.1	NA	NA
Leach (2005) [19][b]	649	40.0	93.0	NA	NA	NA	NA	77.0	81.0	94.0	77.0	NA	NA
Weinstein (2009) [49]	609	39.0	91.0	17.0	88.0	NA	NA	71.0	79.0	NA	NA	NA	NA
Kuhl (2010) [20]	687	33.3	99.1	37.0	98.0	48.1	98.3	92.6	98.4	100.0	97.6	92.6	98.5
Rijnsburger (2010) [50]	2,157	41.3	94.6	NA	NA	NA	NA	70.7	89.7	NA	NA	NA	NA
Trop (2010) [51]	184	58.0	95.4	42.0	93.9	67.0[c]	90.3[c]	83.0	93.6	NA	NA	NA	NA
Sardanelli (2011) [26]	501	50.0	99.0	52.0	98.4	62.5	97.6	91.3	96.7	93.2	96.3	93.3	96.0
Obdeijn (2014) [52]	93	51.1	NA	NA	NA	NA	NA	93.6	NA	NA	NA	NA	NA
Chiarelli (2014) [46][d]	2,150	0.0[e]	93.5[e]	NA	NA	NA	NA	65.7	85.8	??[e]	??[e]	NA	NA
Riedl (2015) [47]	559	37.5	97.1	37.5	96.9	50.0	95.7	90.0	88.9	95.0	88.2	90.0	87.8
Lo (2017) [53]	1,249	31.0	89.4	NA	NA	NA	NA	95.6	78.4	NA	NA	NA	NA

SN sensitivity, *SP* specificity, *NA* not available
[a]Data for the first year of screening are shown
[b]Data on digital mammography are shown
[c]Also considering clinical breast examination
[d]Data extracted from the paper
[e]On 2080 that underwent mammography

might also affect their risk of developing cancer. The reader can find more details on this topic in Chap. 12.

10.3 Ultrasonography and Clinical Breast Examination in High-Risk Women

Ultrasonography was suggested early as a possible adjunct modality in order to increase breast cancer detection in cases in which mammography has limited sensitivity [55, 68–71]. Several analyses confirmed the usefulness of breast US, by showing that it was able to significantly increase the detection of node-negative invasive breast cancers in women with dense breasts [72–74]. Compared to other imaging modalities, such as MRI, US is more widely available, less expensive, and better tolerated by women [75].

Ultrasonography has been found to be able to increase cancer detection in high-risk women by 3.7 per 1,000 [75]. The sensitivity of US alone is not significantly different from that of mammography alone, ranging from 33% to 58% [18, 26, 47, 76] (Table 10.1). The addition of US to mammography can increase sensitivity up to 48–76% [20, 26, 47, 75]. However, *in the studies considering the diagnostic performance of mammography, US, and MRI, almost none of the cancers was detected by US only*.

There are several drawbacks when considering US as a screening tool. The most relevant is the increase in recall rates and unnecessary biopsies [75]. It is not infrequent, when per-

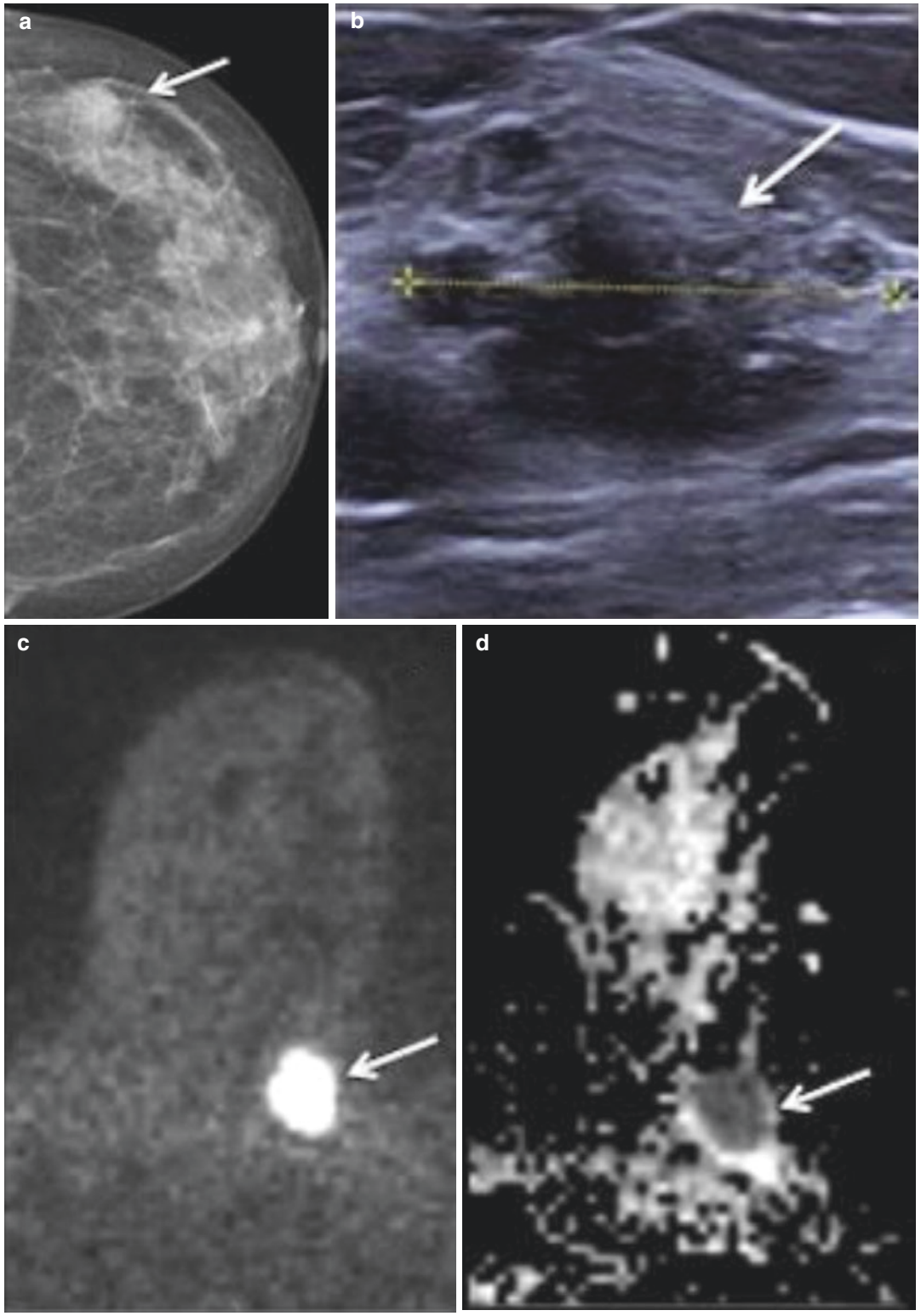
a
b
c
d

Fig. 10.1 A 36-year-old patient with a *BRCA1* mutation. (**a**) Seventh round of screening mammography, left craniocaudal projection. The breast is heterogeneously dense (ACR-BI-RADS density class *c*). An oval mass with obscured margins and a density equal to that of the parenchyma is seen on the left side (BI-RADS 5). (**b**) US shows a 20 mm irregular-shaped mass and indistinct margins, with parallel orientation at 11 o'clock (BI-RADS 5, highly suggestive of malignancy). (**c**, **d**) Diffusion-weighted imaging (DWI), axial plane; (**d**) Apparent diffusion coefficient (ADC) map. The oval-shaped mass with irregular margins is visible in the DWI images ($b = 1{,}000$) as a hyper-intense mass (**c**), with restricted diffusivity (1×10^{-3} mm^2/s) corresponding to a dark lesion on the quantitative ADC map (**d**), highly suggestive for malignancy (BI-RADS 5). Invasive ductal cancer, estrogen receptor negative (ER−), progesterone receptor negative (PR−), human epidermal growth factor receptor 2 negative (HER2−), G3. Note the prepectoral location of breast cancer, reported as more frequent in *BRCA* mutation carriers and high-risk women [58]

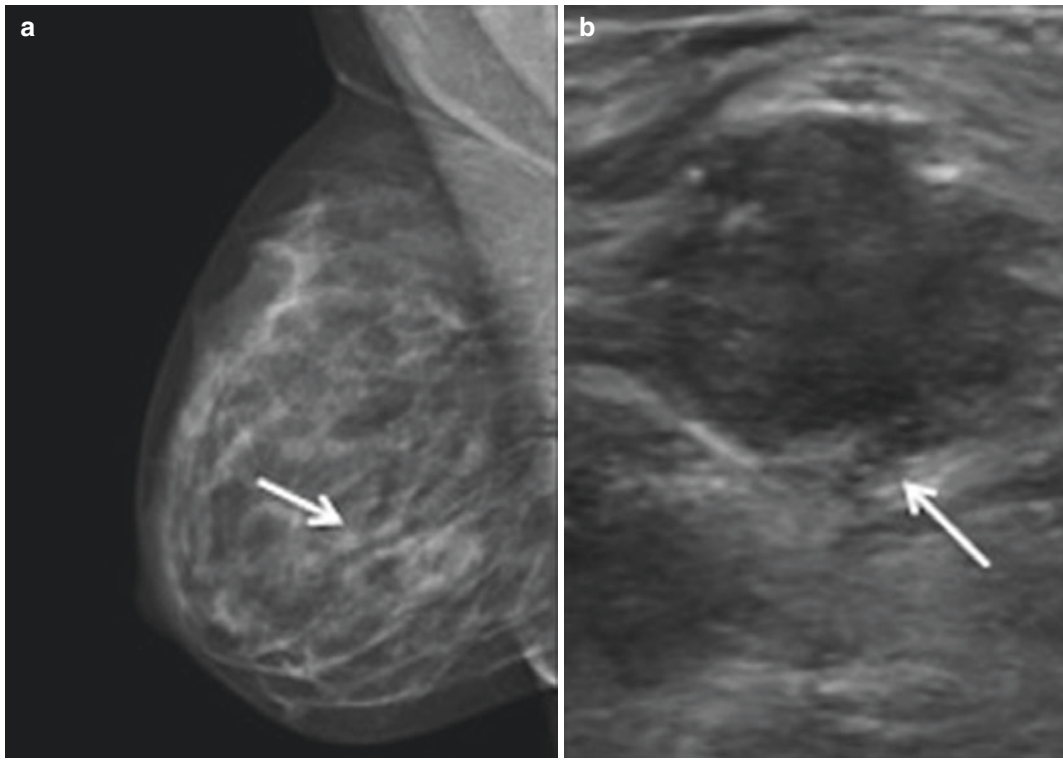

Fig. 10.2 A 37-year-old patient with a *BRCA2* mutation. (**a**) First round of screening mammography: right mediolateral oblique projection. The breast is heterogeneously dense (ACR-BI-RADS density class *c*), demonstrating a non-circumscribed oval lesion on the lower quadrant of the right breast (BI-RADS 4b). (**b**) US shows a 23-mm irregular-shaped mass with microlobulated margins and parallel orientation at 7 o'clock (BI-RADS 5). (**c**, **d**) MRI. (**c**) T2-weighted turbo spin-echo axial image. (**d**) Three-dimensional T1-weighted gradient-echo subtraction image of the delayed phase (6 min). The irregular-shaped mass with irregular margins is visible in the contrast-enhanced subtracted image, with heterogeneous enhancement, wash-out in the delayed phase, and hypointense correlation in the T2-weighted image (BI-RADS 5). Invasive ductal cancer, ER+, PR+, HER2−, G3

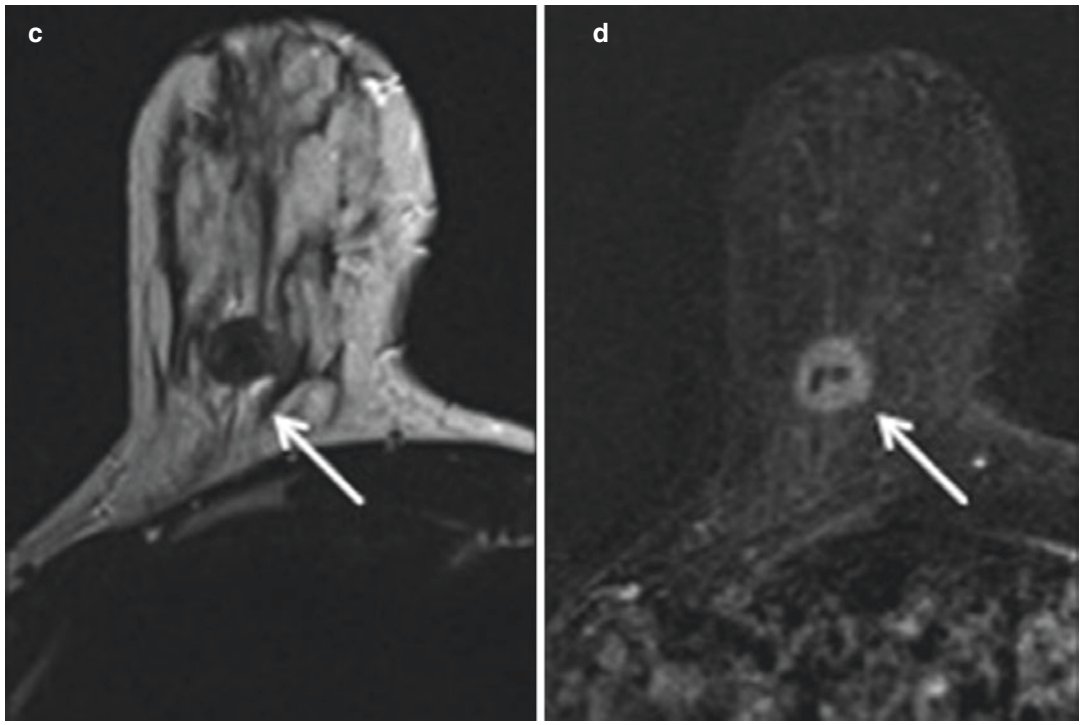

Fig. 10.2 (continued)

forming US, to detect uncharacteristic imaging findings that are classified as suspicious and require a histological verification to exclude malignancy. Thus, the specificity of mammography is decreased by the addition of US and ranges from 74% to 98% [20, 26, 47, 75, 76]. Specificity increased with screening rounds [26, 76], but the overall performance of US remains inferior compared to that of MRI (see below) [20, 26, 47], even when performed every 6 months [20]. *Considering the excellent results of MRI* [20, 21, 26, 47, 76]*, US should no longer be offered as a screening tool in high-risk women*.

Clinical breast examination (CBE) was proposed as an adjunct screening modality also in high-risk women [42]. Currently, there is no evidence of its usefulness. Studies have shown that it has a very low sensitivity in high-risk women, ranging from 7% to 20% [26, 44, 77]. CBE is of limited use in young women with dense breast parenchyma, who often present with cysts or other benign lesions, which, in several cases, might mimic or hide suspicious findings. However, CBE usually detects palpable lesions that indicate a rather advanced stage of disease. Thus, this method of screening was soon found to be ineffective in high-risk women [37].

10.4 Breast MRI in High-Risk Women

As mentioned above, over the past decade, a number of studies have investigated the effectiveness of breast MRI alone and in combination with different imaging breast modalities, namely, mammography and US, for an intensified surveillance in women at genetic/familial risk of developing breast cancer [18, 19, 22–24, 26, 50, 78, 79]. These studies have been prompted by the discouraging results of screening mammography for women at high risk, with interval cancer rates of up to 55% [20, 39, 49, 58, 80].

As widely reported, MRI has been shown to be highly sensitive for the identification of breast cancer, even in dense breasts [12, 27, 51]. Findings of several prospective studies have boosted the role of MRI alone as an excellent screening tool that may benefit women at high risk (Table 10.1).

Ellen Warner and coworkers [76] compared the sensitivity and specificity of four methods of breast cancer surveillance (mammography, US, MRI, and clinical breast examination) in 236 Canadian women 25–65 years of age with *BRCA1* or *BRCA2* mutations, who underwent one to three annual screening examinations. Sensitivity and specificity (based on biopsy rates) were 77 and 95% for MRI, 36% and 99.8% for mammography, 33% and 96% for US, and 9% and 99% for clinical breast examination. Thus, these results confirmed that MRI outperformed the other modalities, in terms of sensitivity for detecting breast cancers.

In a surveillance cohort study, Christiane Kuhl and coworkers [18, 49] investigated the effectiveness of mammography, US, and MRI in 529 asymptomatic women at genetic/familial high risk for breast cancer. The authors found a sensitivity of 91% for MRI alone versus 34% for mammography and 42% for US and concluded

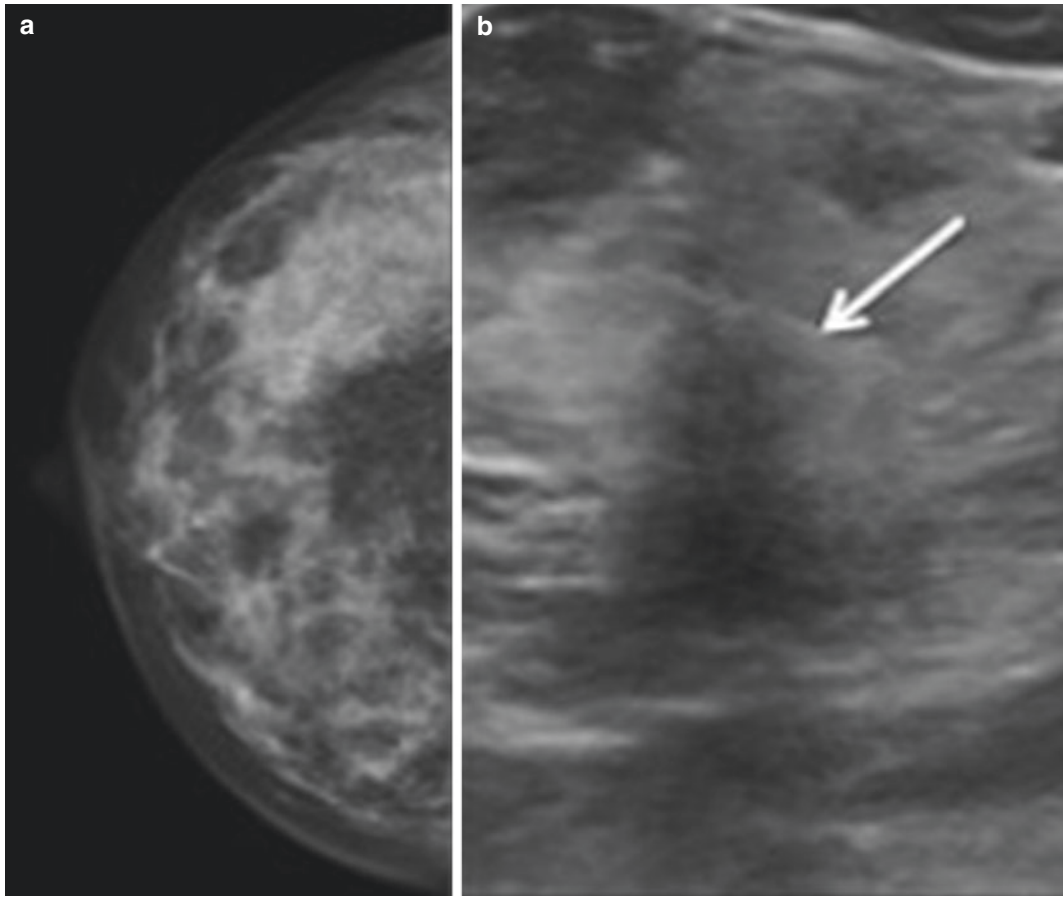

Fig. 10.3 A 41-year-old patient with a positive family history. (**a**) Third round of screening mammography: right craniocaudal projection. The breast is heterogeneously dense (ACR-BI-RADS density class *c*). No lesions are seen (BI-RADS 1). First-look US was negative (not shown). (**c**, **d**) DWI, axial plane. An irregular-shaped mass with spiculated margins is visible in the DWI image (b = 1,000) as an hyper-intense mass (**c**), with restricted diffusivity (1×10^{-3} mm^2/s) and dark signal on the quantitative ADC map (**d**) (BI-RADS 5). (**b**) Targeted (second-look) US shows a 7-mm irregular-shaped mass with indistinct margins, with vertical (non-parallel) orientation, at 1 o'clock, in the right breast (BI-RADS 5). Invasive ductal carcinoma, ER+, PR+, HER2−, G2. Only MRI allowed detecting the cancer

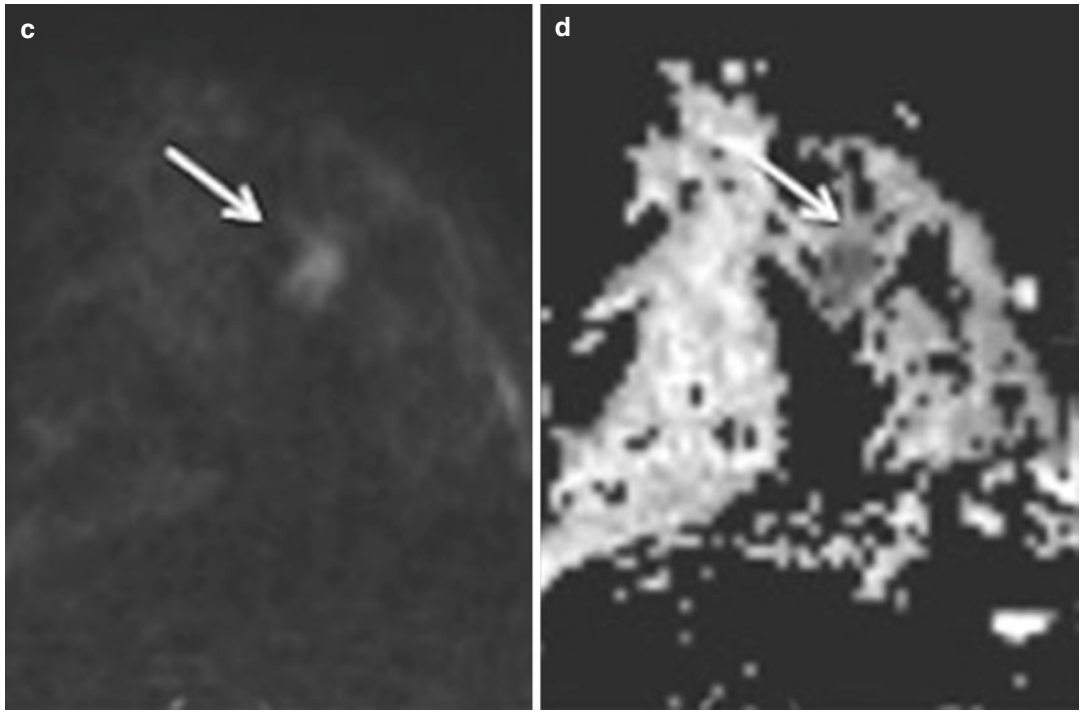

Fig. 10.3 (continued)

that MRI has the highest sensitivity, specificity, and positive predictive value for the detection of both invasive and intra-ductal cancers. Moreover, previously reported data suggested that the multimodality approach, i.e., the combination of two or more breast imaging techniques, has the highest diagnostic performance and yields the highest detection rates in the screening setting.

The MARIBS trial [19] demonstrated a significantly higher sensitivity (77%) of MRI than mammography (40%) in 649 women 35–49 years of age with a strong family history of breast cancer or a high probability of a *BRCA1*, *BRCA2*, or *TP53* mutation. Furthermore, when both methods were used, the sensitivity in breast cancer detection reached up to 94%. Specificity was 93% for mammography, 81% for MRI, and 77% (range 75–79%) with both methods.

The Italian multicenter screening study HIBCRIT [50] reported a sensitivity of 59% for mammography, 65% for US, and 94% for MRI, in 278 high-risk women screened between 2000 and 2007. The final report of this study extended to 501 enrolled women [26] maintained for MRI the highest sensitivity value (91% versus 50% for mammography, 52% for US, and 18% for clinical breast examination) associated with a specificity of 97% and a PPV of 56%, leading to the conclusion that the addition of MRI to screening programs for high-risk women may enable the detection of otherwise unsuspected breast cancers.

In a prospective study from Austria, Christopher C. Riedl and colleagues [21] elucidated the value of MRI compared to conventional imaging techniques, mammography, and US, in the surveillance setting on 327 women at high risk. In accordance with the previously mentioned publications, the authors found that MRI had a superior sensitivity, up to 86%, in the detection of breast cancers compared with mammography (50%) and US (50%). With regard to the specificity, the authors found a trend of an increased specificity for MRI in the follow-up rounds (from 90 to 95%) compared to the first round of surveillance screening (92%). Finally, the results of the study showed that MRI of the breast also improves

the detection of ductal carcinoma in situ and premalignant lesions such as atypical ductal hyperplasia with an alleged positive effect, in terms of saved years.

Based on these data, international guidelines recommend screening high-risk women with yearly MRI from age 25 years onward, and additional mammography from age 30 years [12, 19, 25, 27]. Yet, a number of issues remain. One of the main concerns about MRI as a modality for breast cancer screening is its relatively low positive predictive value, which ranges from 24% to 71% [19, 21, 23, 39, 76]. Moreover, when MRI is used in combination with other modalities, this leads to a trade-off between a very high detection rate and a relatively high false-positive rate. Thus, additional examinations, including repeated MRI scans, targeted US, and unnecessary breast biopsies [44, 81], are performed. As a consequence, the costs predictably increase [82].

In a single-center prospective study from Austria, Christopher C. Riedl and colleagues [47] analyzed a screening population of 559 women with 1,365 complete imaging rounds to evaluate the risks and benefits of the various breast screening modalities alone and in combination. MRI alone found almost half of all cancers (45%), whereas the added value of mammography was limited, and there was no added value for US.

In a retrospective cohort study, Narayan and colleagues [83] tested the cancer detection rate of adding mammography to breast MRI screening compared to breast MRI screening alone in patient at high risk less than 40 years. They found that the cancer detection rate of mammography in this setting is 0% whereas breast MRI screening alone yielded a cancer detection rate of 11.7/1,000. Therefore, the authors suggested than MRI alone may be useful in women at high risk under 40 years of age.

Similar conclusions were reached in a recently published individual patient data meta-analysis. Xuan-Anh Phi an coworkers [64] investigated the improved diagnostic accuracy of the screening programs that combined MRI and mammography in *BRCA1* and *BRCA2* mutation carriers. By analyzing findings from six prospective MRI screening studies, the authors found a limited contribution of mammography for *BRCA1*-mutated patients. Thus, in *BRCA1* mutation carriers, mammography could be no longer recommended as a screening tool, if MRI is performed. This might outweigh the possible disadvantages of mammography, such as false-positive results and the cumulative effects of radiations. However, the authors underlined the role of mammography for screening *BRCA2* mutation carriers, emphasizing the need for different screening recommendations for these two groups of women carrying different *BRCA* mutations.

10.5 Survival Rates and Cost-Effectiveness of High-Risk Screening

To be considered effective, a screening program must have several characteristics: it must be widely available; it must be accepted by the target population; it must not be excessively expensive; and it must be able to influence the natural history of the disease. This means that a screening program is only justified when it is cost-effective and able to reduce the disease-specific mortality. While this has been proven to be true for mammography screening applied to the general female population aged 50–69 years, there are only limited data available about the survival of high-risk women after screening with breast MRI. The lack of data has several causes: first, many of the studies that showed the superiority of breast MRI in cancer detection in high-risk women were not powered to perform a survival analysis. Indeed, many of the studies included a limited number of patients, thus limiting the results. Furthermore, many of these studies are relatively recent. This means that we still do not have sufficient follow-up to prove the benefits of MRI screening in high-risk women with regard to survival, although some initial data are already available. We summarized here some of the studies reporting results on survival rates of high-risk patients enrolled by MRI-including screening studies. The reader can find a more extensive analysis on the complex topic of high-risk patients' outcome in Chap. 13.

D. Gareth Evans and coworkers [84] analyzed the 10-year survival of three different groups of high-risk women. One underwent screening MRI and mammography, one group mammography only, and one group did not undergo screening. The results showed a significantly higher survival at 10 years for women screened with MRI and mammography (95% no deaths among the 21 *BRCA2* mutation carriers) compared to those not screened (74%). No significant difference was found between screening with MRI and mammography versus mammography alone. However, we should consider that these three groups were neither randomized nor concurrent in the same time period. In particular, the MRI-including screening was performed in the period 1997–2013 and compared to unscreened high-risk women diagnosed for breast cancer after 1990 and identified as *BRCA1/BRCA2* mutation carriers in the years following diagnosis. Thus, the high MRI sensitivity can partly explain the difference in 10-year survival. However, the evolution of therapeutic protocols applied to high-risk patients after the discovery of *BRCA* mutations in 1995–1997 could also have contributed to the observed difference in the survival of these two groups [85].

In the frame of a national surveillance program activated in Norway, Pål Møller and coworkers [86] focused their attention on women with a *BRCA1* mutation screened with MRI and mammography. For these patients they reported a breast cancer–specific survival of 75% at 5 years and 69% at 10 year. The authors commented that these survival rates were "less than anticipated." Of note, at multivariable analysis, tumor size resulted to be the only variable associated with survival.

In a recent report, Franca Podo and coworkers [87] reported high survival rates from the HIBCRIT study, showing a 5-year survival for triple negative breast cancers (86%), not significantly different from that of non-triple negative breast cancers (93%). The authors commented that in high-risk women, by combining an MRI-including annual screening with adequate treatment, the usual reported gap in outcome between TNBCs and non-TNBCs could be reduced.

At any rate, every screening program, even in a high-risk population, has to consider costs. Screening mammography has been shown to be cost-effective, also when beginning at 40 [85]. Compared to mammography and US, MRI is certainly more expensive due to the required highly trained personnel and costly facilities and consumables, including contrast agent to be administered. Moreover, false positives from MRI imply additional costs and short-term follow-up investigations.

Only a few studies have examined the cost-effectiveness of MRI breast cancer screening, alone or in combination with mammography.

Ingolf Griebsch and coworkers [88] used the data from the MARIBS study to evaluate the cost-effectiveness of mammography and MRI for high-risk women aged 35–49 years with a strong family history of breast cancer or with tested *BRCA1*, *BRCA2*, or *TP53* mutation or with a 50% risk of having inherited such a mutation. The authors found that the combination of MRI with mammography is potentially cost-effective, particularly for the *BRCA1* and *BRCA2* groups. For all women, the incremental cost per cancer detected with the combination MRI and mammography was £ 28,284 compared to mammography alone. When considering only *BRCA/2* mutation carriers, this incremental cost was reduced to £ 11,731 (MRI versus mammography) and £ 15,302 (MRI and mammography versus mammography alone).

Sylvia K. Plevitris and coworkers [89] led a similar analysis and concluded that breast MRI screening is more cost-effective for *BRCA1* than *BRCA2* mutation carriers, due to the greater risk of *BRCA1* mutation carriers for developing more aggressive breast cancer and at a younger age than *BRCA2* mutation carriers. The authors also suggested that the cost-effectiveness of MRI screening varies greatly by age.

Charu Taneja et al. [82] supported previous data and found that screening with MRI, alone or in combination with mammography, in women with *BRCA1/2* mutations is cost-effective compared to mammography alone. In addition, in women with other high-risk characteristics, MRI screening may be cost-effective, depending on

the expected prevalence of undiagnosed breast cancer at the time of screening.

Allison W. Kurian and coworkers [9] developed a Monte Carlo model for comparing, in 25-year-old *BRCA1/2* mutation carriers, annual mammography combined with MRI from ages 25 to 69 years, prophylactic mastectomy at various ages, and/or prophylactic oophorectomy at ages 40 or 50 years. In the case of no intervention, survival probability by age 70 resulted in 53% for *BRCA1* and 71% for *BRCA2* mutation carriers. Prophylactic oophorectomy at age 40 resulted in the most effective single intervention for *BRCA1* mutation carriers (15% survival gain). Prophylactic mastectomy at age 40 resulted in the most effective single intervention for *BRCA2* mutation carriers (7% survival gain). Combining prophylactic mastectomy and oophorectomy at age 40 improves survival more than any single intervention, giving *BRCA1* mutation carriers a 24% survival gain and *BRCA2* mutation carriers a 11% survival gain). Interestingly, the authors noted that anticipating prophylactic mastectomy at age 25 would offer a minimal incremental benefit (1–2%) and that substituting MRI and mammography screening for prophylactic mastectomy would yield a similarly minimal decrement in survival (2–3%). They concluded highlighting that "substituting mammography plus MRI screening for prophylactic mastectomy seems to offer comparable survival."

10.6 Conclusions

A body of evidence plays in favor of the following affirmations regarding screening strategies in high-risk women:

1. MRI is much more sensitive than mammography and/or US in detecting breast cancers (this evidence has been the basis for guidelines worldwide [4, 5, 12, 25, 27, 34, 82]).
2. The incremental detection rate of US, if any, is negligible.
3. The contribution of mammography alone in cancer detection is low, especially when considering *BRCA1* mutation carriers.

If we take into account cost-effective considerations and the higher sensitivity to ionizing radiation of *BRCA* or *TP53* mutation carriers (see in particular Chap. 12), the possibility of using MRI alone for screening high-risk women has to be evaluated. This strategy may simplify organizational issues and reduce costs and women's anxiety (only one test, only one visit!). Future research in this direction is certainly needed.

References

1. DeVita VT (2012) Cancer: Principles & Practice of Oncology: Primer of the Molecular Biology of Cancer (Kindle Locations 11542–11543). Lippincot (Wolters Kluwer Health). Kindle Edition
2. (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. The Lancet 358:1389–1399
3. Riedl CC, Ponhold L, Gruber R et al (2010) New information on high risk breast screening. Radiologe 50:955–956, 958–963
4. Singer CF, Tea M-K, Pristauz G et al (2012) Guideline for the prevention and early detection of breast and ovarian cancer in high risk patients, particularly in women from HBOC (hereditary breast and ovarian cancer) families. Wien Klin Wochenschr 124:334–339
5. Singer CF, Tea MK, Pristauz G et al (2015) Clinical practice guideline for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families. Wien Klin Wochenschr 127:981–986
6. Metcalfe K, Lynch HT, Ghadirian P et al (2004) Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 22:2328–2335
7. Metcalfe K, Gershman S, Lynch HT et al (2011) Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 104:1384–1392
8. van Dijk S, van Roosmalen MS, Otten W, Stalmeier PFM (2008) Decision making regarding prophylactic mastectomy: stability of preferences and the impact of anticipated feelings of regret. J Clin Oncol 26:2358–2363
9. Kurian AW, Sigal BM, Plevritis SK (2010) Survival analysis of Cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol 28:222–231
10. Heemskerk-Gerritsen BAM, Menke-Pluijmers MBE, Jager A et al (2013) Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis. Ann Oncol 24:2029–2035

11. Eccles DM, Evans DG, Mackay J (2000) Guidelines for a genetic risk based approach to advising women with a family history of breast cancer. UK Cancer family study group (UKCFSG). J Med Genet 37:203–209
12. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
13. Vasen HF, Haites NE, Evans DG et al (1998) Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European family cancer clinics. European familial breast Cancer collaborative group. Eur J Cancer 34:1922–1926
14. Evans DGR, Lalloo F (2002) Risk assessment and management of high risk familial breast cancer. J Med Genet 39:865–871
15. Eisinger F, Alby N, Bremond A et al (1998) Recommendations for medical management of hereditary breast and ovarian cancer: the French National ad hoc Committee. Ann Oncol 9: 939–950
16. Warner E, Heisey RE, Goel V et al (1999) Hereditary breast cancer. Risk assessment of patients with a family history of breast cancer. Can Fam Physician 45:104–112
17. Møller P, Evans G, Haites N et al (1999) Guidelines for follow-up of women at high risk for inherited breast cancer: consensus statement from the biomed 2 demonstration programme on inherited breast Cancer. Dis Markers 15:207–211
18. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
19. Leach MO, Boggis CRM, Dixon AK et al (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
20. Kuhl C, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
21. Riedl CC, Ponhold L, Flöry D et al (2007) Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. Clin Cancer Res 13:6144–6152
22. Tilanus-Linthorst MM, Obdeijn IM, Bartels KC et al (2000) First experiences in screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat 63:53–60
23. Stoutjesdijk MJ, Boetes C, Jager GJ et al (2001) Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 93:1095–1102
24. Warner E, Plewes DB, Shumak RS et al (2001) Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 19:3524–3531
25. Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol 18:1307–1318
26. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Investig Radiol 46:94–105
27. Mann RM, Balleyguier C, Baltzer PA, et al (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678
28. Brenner H (2002) Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet 360:1131–1135
29. Tabár L, Vitak B, Chen TH-H et al (2011) Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 260:658–663
30. Feig SA (2014) Screening mammography benefit controversies: sorting the evidence. Radiol Clin N Am 52:455–480
31. Miller AB, Wall C, Baines CJ et al (2014) Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. BMJ 348:g366
32. Welch HG, Prorok PC, O'Malley AJ, Kramer BS (2016) Breast-Cancer tumor size, Overdiagnosis, and mammography screening effectiveness. New Engl J Med 375:1438–1447
33. Otto SJ, Fracheboud J, Looman CWN et al (2003) Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 361:1411–1417
34. Lauby-Secretan B, Scoccianti C, Loomis D et al (2015) Breast-cancer screening--viewpoint of the IARC working group. New Engl J Med 372:2353–2358
35. Nelson HD, Cantor A, Humphrey L, et al (2016) Screening for Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Agency for Healthcare Research and Quality, Rockville, MD, USA
36. Kerlikowske K, Grady D, Barclay J et al (1993) Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 270:2444–2450
37. Brekelmans CT, Seynaeve C, Bartels CC et al (2001) Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924–930
38. Huo Z, Giger ML, Olopade OI et al (2002) Computerized analysis of digitized mammograms of BRCA1 and BRCA2 gene mutation carriers. Radiology 225:519–526
39. Tilanus-Linthorst M, Verhoog L, Obdeijn I-M et al (2002) A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently

contribute to a frequent false-negative mammography. Int J Cancer 102:91–95
40. Adem C, Reynolds C, Soderberg CL et al (2003) Pathologic characteristics of breast parenchyma in patients with hereditary breast carcinoma, including BRCA1 and BRCA2 mutation carriers. Cancer 97:1–11
41. Komenaka IK, Ditkoff B-A, Joseph K-A et al (2004) The development of interval breast malignancies in patients with BRCA mutations. Cancer 100:2079–2083
42. Burke W, Daly M, Garber J et al (1997) Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer genetics studies consortium. JAMA 277:997–1003
43. Pichert G, Bolliger B, Buser K et al (2003) Evidence-based management options for women at increased breast/ovarian cancer risk. Ann Oncol 14:9–19
44. Kriege M, Brekelmans CTM, Boetes C et al (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. New Engl J Med 351:427–437
45. Elmore JG, Reisch LM, Barton MB et al (2005) Efficacy of breast cancer screening in the community according to risk level. J Natl Cancer Inst 97:1035–1043
46. Chiarelli AM, Prummel MV, Muradali D et al (2014) Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario high risk breast screening program. J Clin Oncol 32:2224–2230
47. Riedl CC, Luft N, Bernhart C et al (2015) Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 33: 1128–1135
48. Hagen AI, Kvistad KA, Maehle L et al (2007) Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast 16:367–374
49. Kuhl CK, Schmutzler RK, Leutner CC et al (2000) Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 215:267–279
50. Sardanelli F, Podo F, D'Agnolo G et al (2007) Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 242:698–715
51. for the European Society of Breast Imaging (EUSOBI), Sardanelli F, Helbich TH (2012) Mammography: EUSOBI recommendations for women's information. Insights Imaging 3:7–10
52. Obdeijn I-M, Winter-Warnars GAO, Mann RM et al (2014) Should we screen BRCA1 mutation carriers only with MRI? A multicenter study. Breast Cancer Res Treat 144:577–582
53. Lo G, Scaranelo AM, Aboras H et al (2017) Evaluation of the utility of screening mammography for high-risk women undergoing screening breast MR imaging. Radiology 285:36–43
54. Mandelson MT, Oestreicher N, Porter PL et al (2000) Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 92:1081–1087
55. Kolb TM, Lichy J, Newhouse JH (2002) Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 225:165–175
56. Olsen AH, Bihrmann K, Jensen M-B et al (2009) Breast density and outcome of mammography screening: a cohort study. Br J Cancer 100:1205–1208
57. Tilanus-Linthorst MMA, Kriege M, Boetes C et al (2005) Hereditary breast cancer growth rates and its impact on screening policy. Eur J Cancer 41:1610–1617
58. Schrading S, Kuhl CK (2008) Mammographic, US, and MR imaging phenotypes of familial breast cancer. Radiology 246:58–70
59. Veltman J, Mann R, Kok T et al (2008) Breast tumor characteristics of BRCA1 and BRCA2 gene mutation carriers on MRI. Eur Radiol 18:931–938
60. Powell SN, Kachnic LA (2003) Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. Oncogene 22:5784–5791
61. Jansen-van der Weide MC, Greuter MJW, Jansen L et al (2010) Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. Eur Radiol 20:2547–2556
62. Lakhani SR, Jacquemier J, Sloane JP et al (1998) Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90: 1138–1145
63. Armes JE, Venter DJ (2002) The pathology of inherited breast cancer. Pathology 34:309–314
64. Phi X-A, Saadatmand S, De Bock GH et al (2016) Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 114:631–637
65. Preston DL, Mattsson A, Holmberg E et al (2002) Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 158:220–235
66. Andrieu N, Easton DF, Chang-Claude J et al (2006) Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS collaborators' group. J Clin Oncol 24: 3361–3366
67. Broeks A, Braaf LM, Huseinovic A et al (2007) Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. Breast Cancer Res 9:R26

68. Buchberger W, Niehoff A, Obrist P et al (2000) Clinically and mammographically occult breast lesions: detection and classification with high-resolution sonography. Semin Ultrasound CT MR 21:325–336
69. Kaplan SS (2001) Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. Radiology 221:641–649
70. Crystal P, Strano SD, Shcharynski S, Koretz MJ (2003) Using sonography to screen women with mammographically dense breasts. AJR Am J Roentgenol 181:177–182
71. Leconte I, Feger C, Galant C et al (2003) Mammography and subsequent whole-breast sonography of nonpalpable breast cancers: the importance of radiologic breast density. AJR Am J Roentgenol 180:1675–1679
72. Berg WA, Blume JD, Cormack JB et al (2008) Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 299:2151–2163
73. Tohno E, Ueno E, Watanabe H (2009) Ultrasound screening of breast cancer. Breast Cancer 16:18–22
74. Corsetti V, Houssami N, Ghirardi M et al (2011) Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: interval breast cancers at 1 year follow-up. Eur J Cancer 47:1021–1026
75. Berg WA, Zhang Z, Lehrer D et al (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
76. Warner E, Plewes DB, Hill KA et al (2004) Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317–1325
77. Rijnsburger AJ, Obdeijn I-M, Kaas R et al (2010) BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol 28:5265–5273
78. Narod SA, Lubinski J, Ghadirian P et al (2006) Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 7:402–406
79. Morrow M, Waters J, Morris E (2011) MRI for breast cancer screening, diagnosis, and treatment. Lancet 378:1804–1811
80. Murday V, Pears R, Ball J et al (2004) An audit of screening for familial breast cancer before 50 years in the South Thames region—have we got it right? Familial Cancer 3:29–34
81. Morris EA, Liberman L, Ballon DJ et al (2003) MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol 181:619–626
82. Taneja C, Edelsberg J, Weycker D et al (2009) Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol 6:171–179
83. Narayan AK, Visvanathan K, Harvey SC (2016) Comparative effectiveness of breast MRI and mammography in screening young women with elevated risk of developing breast cancer: a retrospective cohort study. Breast Cancer Res Treat 158:583–589
84. Evans DG, Gareth ED, Kesavan N et al (2014) MRI breast screening in high-risk women: cancer detection and survival analysis. Breast Cancer Res Treat 145:663–672
85. Rosenquist CJ, Lindfors KK (1998) Screening mammography beginning at age 40 years: a reappraisal of cost-effectiveness. Cancer 82:2235–2240
86. Møller P, Stormorken A, Jonsrud C et al (2013) Survival of patients with BRCA1-associated breast cancer diagnosed in an MRI-based surveillance program. Breast Cancer Res Treat 139:155–161
87. Podo F, Santoro F, Di Leo G et al (2016) Triple-negative versus non-triple-negative breast cancers in high-risk women: phenotype features and survival from the HIBCRIT-1 MRI-including screening study. Clin Cancer Res 22:895–904
88. Griebsch I, Brown J, Boggis C et al (2006) Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. Br J Cancer 95:801–810
89. Plevritis SK, Kurian AW, Sigal BM et al (2006) Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA 295:2374–2384

11 Systematic Reviews, Meta-Analyses, and Cost-Effective Analyses on Breast MRI Screening of High-Risk Women

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Abbreviations

AD	Aggregate data
AUC	Area under the curve
BC	Breast cancer
CBE	Clinical breast examination
CEA	Cost-effectiveness analysis
CI	Confidence interval
EBM	Evidence-based medicine
HTA	Health technology assessment
IPD	Individual patient data
LTR	Lifetime risk
MA	Meta-analysis
MRI	Magnetic resonance imaging
NLR	Negative likelihood ratio
NSN	Number of screens needed
PLR	Positive likelihood ratio
PPV	Positive predictive value
QALYs	Quality-adjusted life years
ROC	Receiver operating characteristics
SR	Systematic review
US	Ultrasonography, Ultrasound

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11.1 Introduction

Science is a cooperative, interdependent enterprise. This is the first sentence opening the book *Research Synthesis and Meta-Analysis* by Harris M. Cooper [1]. There are many ways of cooperation in science and, in particular, in medical research. The first one relies on the obvious consideration that not any physician or basic scientist is able, alone, to produce new results enhancing the basic biologic or physiopathological knowledge or increasing the quality of healthcare. Whatever the biological discovery, drug, or device, it is always the effect of the efforts of many people or—better to say—of many teams working on a coordinated project at the same time or providing results that lead, step-by-step, to a common goal. This is increasingly true in the last decades, when every new knowledge is based on the use of technologies that other people made available to allow the new advancement.

Another way of cooperation in science is the combination of data obtained in different studies, as retrieved by researchers who review the amount of knowledge already available on a

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given topic. This approach deals with the *intrinsically cumulative nature of science*. Almost two decades ago, Ian Chalmers, Larry V. Edges, and Harris M. Cooper [2] highlighted the following contradiction:

> Science is supposed to be cumulative, but scientists only rarely cumulate evidence scientifically. This means that users of research evidence have to cope with a plethora of reports of individual studies with no systematic attempt made to present new results in the context of similar studies.

This manner to solve the problem consists of performing a *systematic review* (SR). Instead of conducting a new *primary study* enrolling patients to provide *primary evidence*, researchers can perform a *secondary analysis* "enrolling" primary studies to provide, when possible, *secondary evidence*. This last step is a new result, based on a number of patients and events larger than that of each of the individual primary studies. It is a synthesis obtained by means of a *meta-analysis* (MA), i.e., of special statistical techniques developed in the last decades, to address this specific aim. When not only the process of retrieval and selection of previous studies but also the new synthesis is carried out, we have the so-called *systematic review and meta-analysis* (SR&MA) [3, 4].[1] In the larger context of the evaluation process of medical technology, called *health technology assessment* (HTA),[2] a different kind of analysis integrating scientific evidence for benefit versus harms with economic issues is named cost-effectiveness analysis (CEA) [5].

Notably, the use of breast magnetic resonance imaging (MRI) for screening high-risk women has been investigated by SR&MAs. These secondary studies substantially contributed to the worldwide acceptance of this tool as a highly sensitive method to be offered to high-risk women. In some cases, SR&MAs not only gave more precise estimates of the diagnostic performance of breast MRI in this setting, but also provided deeper insights by means of the subgroup analysis or of a special approach named *individual patient (or participant) data MA* (IPD-MA).

Taking into consideration the relevance that SR&MAs are progressively acquiring for the definition of guidelines for evidence-based practice, we dedicate the first part of this Chapter to a brief explanation of general methodological issues regarding these particular studies.

Thus, the aims of this Chapter are the following: (1) to define the central role of SR&MAs in the context of contemporary medicine and the practice of healthcare systems; (2) to provide a brief history of SRs; (3) to present an overview of the methods of SRs and of MAs, summarizing their advantages and limitations; (4) to present the results of SR&MAs performed on breast MRI for screening high-risk women, looking not only at reinforced knowledge about the capability of MRI but also at new knowledge acquired through MA that the original individual primary studies were not able to provide; and (5) to examine the contributions on this topic from CEA.

11.2 The Key Role of Systematic Reviews in Contemporary Medicine

In the last two decades, SR&MAs gained a prominent position in the theory and practice of contemporary medicine. Practically, medical innovations that gain a relevant clinical role in the healthcare systems almost always are evaluated looking at the evidence available in the literature using this approach. SR&MAs were increasingly adopted as a key evidence synthesis, on which recommendations and guidelines from medical and governmental bodies are based.

In fact, in the hierarchy of *evidence-based medicine* (EBM) [6], the highest level of evidence (level 1a) for all the fields of application, is given by *SRs with homogeneity* (i.e., free of worrisome variations in the direction and magnitude of results among individual studies)

[1] There are cases when the systematic review (and the selection of published papers) cannot generate data suitable for a new synthesis. In these circumstances, we will have the systematic review with the description of the available data, without the meta-analysis.

[2] Note that in this context the term *technology* refers to any medical or surgical practice as well as to any medicines or devices.

(Table 11.1). However, we must note that the current trend is in favor of the acceptance of heterogeneity as long as sources of such heterogeneity are considered and explored, especially in SR&MAs of diagnostic performance, as we will see below in Sect. 11.4.

This means that the way for getting the best evidence for prevention and therapy, diagnosis, differential diagnosis, prognosis, and economic and decision analysis is given by SRs of different types of primary studies: randomized controlled trials for prevention and therapy; high-quality

Table 11.1 Levels of evidence according to the Oxford Centre for Evidence-Based Medicine

L	Diagnosis	Differential diagnosis/symptom prevalence study	Therapy/prevention, etiology/harm	Prognosis	Economic and decision analyses
1a	SR (with homogeneity[a]) of L1 diagnostic studies; CDR[b] with 1b studies from different clinical centers	SR (with homogeneity[a]) of prospective cohort studies	SR (with homogeneity[a]) of RCTs	SR (with homogeneity[a]) of inception cohort studies; CDR[b] Validated in different populations	SR (with homogeneity[a]) of L1 economic studies
1b	Validating[c] cohort study with good[e] reference standards; or CDR[b] tested within one clinical center	Prospective cohort study with good follow-up[f]	Individual RCT (with narrow CI)[d]	Individual inception cohort study with >80% follow-up; CDR[b] validated in a single population	Analysis based on clinically sensible costs or alternatives; SR of the evidence; and including multi-way sensitivity analyses
1c	Absolute *SPins* and *SnNouts*[g]	All or none[h] case-series	All or none[h]	All or none case-series	Absolute better-value or worse-value analyses[i]
2a	SR (with homogeneity[a]) of $L > 2$ diagnostic studies	SR (with homogeneity[a]) of 2b and better studies	SR (with homogeneity[a]) of cohort studies	SR (with homogeneity[a]) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity[a]) of $L > 2$ economic studies
2b	Exploratory[d] cohort study with good[e] reference standards; CDR[b] after derivation, or validated only on split-sample[j] or databases	Retrospective cohort study, or poor follow-up	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample[j] only	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c		Ecological studies	*Outcomes* research; ecological studies	*Outcomes* research	Audit or outcomes research
3a	SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of case-control studies		SR (with homogeneity[a]) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Individual case-control study		Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.

(continued)

Table 11.1 (continued)

L	Diagnosis	Differential diagnosis/symptom prevalence study	Therapy/prevention, etiology/harm	Prognosis	Economic and decision analyses
4	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Case-series (and poor quality cohort and case-control studies[k])	Case-series (and poor quality prognostic cohort studies[l])	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or *first principles*	Expert opinion without explicit critical appraisal, or based on physiology, bench research or *first principles*	Expert opinion without explicit critical appraisal, or based on physiology, bench research or *first principles*	Expert opinion without explicit critical appraisal, or based on physiology, bench research or *first principles*	Expert opinion without explicit critical appraisal, or based on economic theory or *first principles*

Slightly modified from https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/, Accessed 30 June 2020. Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick, March 2009

L level, *SR* systematic review, *CDR* clinical decision rules, *RCT* randomized controlled trial, *CI* confidence interval

Users can add a minus-sign (−) to denote the level of that fails to provide a conclusive answer because EITHER a single result with a wide CI OR a SR with troublesome heterogeneity. Such evidence is inconclusive and therefore can only generate Grade D recommendations

[a]A SR with homogeneity should be free of worrisome variations (heterogeneity) in the directions and magnitude of results among individual studies. Not all SR with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. SR displaying worrisome heterogeneity should be tagged with a "–" at the end of their designated level

[b]Clinical decision rules *are* algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category

[c]Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g., using a regression analysis) to find which factors are *significant*

[d]Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. The use of a non-independent reference standard (where the "test" is included in the "reference," or where the "testing" affects the "reference") implies a L4 study

[e]Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1–6 months acute, 1–5 years chronic)

[f]See note above for advice on how to understand, rate, and use trials or other studies with wide confidence intervals

[g]An *absolute SpPin* is a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis. An *absolute SnNout* is a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis

[h]Met when all patients died before the prescription became available, but some now survive on it; or when some patients died before the prescription became available, but none now die on it

[i]Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive

[j]Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into *derivation* and *validation* samples

[k]A poor-quality cohort study is one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor-quality case-control study, we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders

[l]A poor-quality prognostic cohort study is one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors

diagnostic studies for diagnosis; prospective cohort studies for differential diagnosis; inception cohort studies for prognosis; and high-quality economic studies for economic and decision analysis. In the case of diagnosis and prognosis, studies considered for meta-analysis should have ideally used clinical decision rules already validated on independent populations.

Table 11.2 Grades of recommendation according to the Oxford Centre for Evidence-Based Medicine

Grade of recommendation	Level of studies considered[a]
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies *or* extrapolations[b] from level 1 studies
C	Level 4 studies **or** extrapolations[b] from level 2 or 3 studies
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

[a]With reference to Table 11.1
[b]Where data are used in a situation that has potentially clinically important differences compared to the original study situation

This evidence ranking influences the *grade of recommendations* to be issued (Table 11.2). This high levels of evidence and best practices are strongly related to the synthesis of the evidence that SR&MAs offer to healthcare services, as a basis for CEA in HTA [5].

Tables 11.1 and 11.2 clearly explain the impact of SR&MAs on clinical practice. Of note, guidelines and recommendations issued by governmental bodies and medical associations—based on the logic chain from primary studies to SR&MA and CEAs—are increasingly used for defining crucial aspect of healthcare, including insurance reimbursement or coverage by public systems as well as for evaluating the *value* of medical actions or cases of medical misconduct.

11.3 A Brief History of Systematic Reviews

The historical pathway of SRs is not a long one. As underlined by Ian Chalmers, Larry V. Edges, and Harris M. Cooper [2], formal methods for this approach are relatively recent:

> Although the need to synthesize research evidence has been recognized for well over two centuries, explicit methods for this form of research were not developed until the twentieth century. The development of methods to reduce statistical imprecision using quantitative synthesis (meta-analysis) preceded the development of methods to reduce biases, the latter only beginning to receive proper attention during the last quarter of the twentieth century.

However, efforts to reduce the likelihood of being misled by biases and chance in research synthesis have quite a long history. In the eighteenth century, for example, James Lind, a Scottish naval surgeon, was confronted with a plethora of reports about the prevention and treatment of scurvy. The title of his famous article [7] declares that it contains *A treatise of the scurvy: in three parts, containing an inquiry into the nature, causes, and cure, of that disease, together with a critical and chronological view of what has been published on the subject*. L. Brunt [8] relates that, in 1768, Arthur Young, an English farmer who played a pioneering role in the development of sample surveys, noted that "*it is impossible from single experiments, or from a great number, in different lands, separately considered, to deduce a satisfactory proof of the superiority of any method*." This problem remained substantially unresolved up to the end of the last century.

In fact, prior to the 1990s, combining data from multiple studies was the task of *narrative reviews*. An expert (or a group of experts) in a given research field would read the studies that addressed a clinical question, summarizing the findings in a narrative (discussion-like) style, then proposing a conclusion. This approach clearly suffers from subjectivity and lack of transparency. For example, different reviewers (here meaning the authors of a review) might use different criteria for selecting primary studies to be considered, thus leading to potentially different conclusions. Another limitation of narrative reviews is that a conclusion may be drawn on the direction (i.e., a given treatment is effective, not effective, or even harmful) but no magnitude of the effect may be provided nor a statistical significance. In other words, narrative reviews provide qualitative, not quantitative results.

The approach used by formal SRs is quite different. The Cochrane Collaboration [9] defines a SR as *a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review*. In a SR, reviewers do not conduct a new original study on a given topic, enrolling patients to

provide *primary evidence*. Instead, they perform a *secondary analysis* including primary studies to provide, when possible, a *secondary evidence*. SRs have been increasingly adopted in the last 20 years as evidence synthesis informing medical and governmental bodies issuing recommendations and guidelines. There still is a degree of subjectivity in setting criteria for a SR as well as in drawing conclusions. However, because all criteria are clearly specified a priori, the whole procedure can be considered as transparent.

The term *systematic review* became more widely used than *research synthesis* probably because the former was used by Archibald L. Cochrane [10] in his foreword to a compilation of research syntheses relating to many aspects of care during pregnancy and childbirth published during the late 1980s. The term was subsequently promoted to distinguish the measures to control biases in searching the primary studies (the SR) from the statistical procedures to provide a precise estimation of a treatment effect size or a technique diagnostic accuracy, for which the term *meta-analysis* was suggested [11, 12]. This last step provides new results, based on a population of patients larger than that of each individual primary study. Unlike narrative reviews, where reviewers subjectively assign some importance to each primary study, in MA weights are assigned using mathematical criteria that are defined in advance.

11.4 Methods of Systematic Reviews

The amount of information to face when trying to answer a clinical question is huge and continuously increasing. As per December 30, 2018, over 29 million articles are cited in the *PubMed* database [13]. More than one paper per minute is added to the database. A recent review [14] has estimated the size of other databases as follows: *Scopus*, 69 million; *Web of Science Core Collection*, over 67.5 million; *Web of Science, ten databases included Core Collection*, over 105.5 million; *Google Scholar*, over 389 million. Based on estimates provided in 2014–2015 [15], about 28,100 peer-reviewed English-language journals were active in 2014, collectively publishing 2.5 million of articles/year. In 2015, the *CrossRef* database included over 71 million digital object identifiers (DOIs), of which 55 million refer to journal articles from a total of over 36,000 journals. Even though the estimate of articles quoted in Google Scholar has been considered as questionable [14], all these figures give an idea of the difficulties inherent to the search for clinical evidence in the published literature.

Of note, other than the quantity of information, its quality should be considered in drawing conclusions. From this viewpoint, *access to high-quality SRs represents a clear advantage for physicians and policy makers*. A single study, even if well conducted, may not be able to demonstrate the efficacy of a treatment or of a diagnostic tool, even if performed on a relatively large sample of patients.

Differently from primary studies, which are designed specifically for the study objectives, the quality of information provided by a SR is strongly related to the quality of the available evidence. Although this is an a priori limitation of SRs, it should be noted that, even if the source primary studies have quality limitations, a SR will still provide higher-level evidence than that of individual studies because it will present a more comprehensive view of the evidence and its limitations. As such, SRs must be based on a detailed and exhaustive *research protocol*, whose basic steps are listed below:

1. Definition of a clinical or health-related question
2. Systematic search of sources
3. Appraisal of the methodological quality of the analyzed studies
4. Quantitative synthesis of data, when appropriate

Specifying the methods in advance reduces the risk of introducing biases into the SR. Here we briefly highlight the basic principles of the above-mentioned steps. Thereafter, we will outline the specific role of IPD-MAs and the general advantages and limitations of MAs. Suggested

readings are the Cochrane Handbook for Systematic Reviews of Interventions [4] and the Cochrane Handbook for Diagnostic Test Accuracy [3].

Definition of the clinical question. As with any research, the first and most important step in preparing a SR is to determine its focus framing the question it seeks to answer. This is done specifying the types of population (participants), types of interventions and comparisons, and outcomes of interest, summarized by the acronym PICO (*participants*, *interventions*, *comparisons*, and *outcomes*). In the case of SRs about diagnostic test accuracy, intervention and comparison are substituted by the investigated index test and the reference standard; comparators other than the reference standard can be taken into consideration. First, the disease or condition of interest should be defined using explicit criteria for establishing their presence or not, determining the characteristics of participants. Second, the investigated intervention (or diagnostic tool) and the reference against which this will be compared (comparisons) have to be defined, taking into consideration intervention variations (e.g., technical issues and examination protocol of diagnostic tool). Third, specific outcomes, meaningful to decision makers, should be chosen. Outcomes may include clinical issues such as survival (or mortality[3]), key events (e.g., stroke or myocardial infarction), patient-reported outcomes (e.g., symptoms, quality of life), burdens (e.g., demands on caregivers, frequency of imaging tests, restrictions on lifestyle), and economic outcomes (e.g., cost and resource use). In the case of diagnostic test accuracy, outcomes can be measures of performance such as sensitivity, specificity, or area under the curve (AUC) at receiver operating characteristics (ROC) analysis.

[3]Note that *survival* and *mortality* are not supplementary quantities. This is due to the fact that survival is usually computed on a cohort of patients diagnosed with a disease while mortality is computed as rate for inhabitants of a given territory. In the case of relevant increase of overdiagnosis, temporal trends for the two quantities can be strongly contradictory: strong increase of survival versus stability of mortality.

Systematic search of sources and eligibility criteria. A systematic and reproducible search of several sources to identify as many relevant studies as possible is necessary. This is a major factor distinguishing SRs from narrative reviews. For biomedical SRs, a search of PubMed (MEDLINE) alone is generally not considered adequate. A number of other electronic databases can be used: EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), BioMed Central, Public Library of Science, Web of Science, Scopus, CINAHL, ScienceDirect, and Google Scholar. Hand-search may be a useful adjunct, especially for articles published before 1991, when there was no indexing term for randomized trial in PubMed. Factors to be considered when planning a systematic search commonly include year of publication and language (usually English and the reviewers' mother tongue). Standardized terms, such as MeSH for PubMed and EMTREE for EMBASE, together with Boolean operators (AND, OR, and NOT) may help the search.

The systematic search typically provides hundreds of citations that must be screened for eligibility. This screening should be performed possibly by two independent readers with discordances solved by arbitration from a third reader. The initial screening typically proceeds by reading only the title and the abstract of all articles retrieved by the systematic search. At a second step, those articles passing the initial screening for eligibility should be read in full for a final application of the eligibility criteria.

Appraisal of quality of the analyzed studies. The extent to which a SR can draw conclusions on the effects of an intervention or diagnostic technique depends on the quality of the analyzed studies. The validity of a study may be considered as having two dimensions. The first dimension is whether the study is focused on an appropriate research question that relates to a clear application or population. This is often referred to as *external validity* and is closely connected with its applicability and generalizability (that is, whether the study findings apply or transfer beyond the specific study setting). The second dimension is whether the study answers its clinical question correctly, i.e., free from biases,

described as *internal validity*, the only dimension appraised when conducting a SR [16]. Several tools have been proposed to assess the *risk of bias* (that is a more appropriate way to indicate the appraised quality), most of them in the form of checklists. The most used tool for assessing the risk of bias of studies dealing with diagnostic accuracy is the revised *QUality Assessment of Diagnostic Accuracy Studies* (QUADAS-2) [17]. Formal statistical methods to mathematically weight studies for their risk of bias are not well developed yet. The simplest and most used way to incorporate the risk of bias in results is just to analyze all studies and present a description of the risk of bias.

Quantitative synthesis of data. Once the systematic search of sources has been conducted and articles for analysis have been selected, data that are relevant to the SR are extracted from each of them. As for the systematic search, this step should be performed by two independent reviewers with arbitration. Extracted data include, of course, the main endpoints (e.g., the rate of survived patients, the sensitivity and specificity of a diagnostic technique) plus any study characteristics (covariates) such as year of publication, the number of patients, technical issues, and protocols that might impact the results, or might account for some of the clinical heterogeneity. These data are then entered in an electronic database to be meta-analyzed.

Here we briefly present the main characteristics to allow the reader to interpret the results reported in the next paragraphs of this and in the other chapters. For a deeper insight on this matter, we refer the reader to the already suggested readings [3, 4].

A MA provides a weighted mean of the endpoint extracted from all included studies. To do so, some conditions must be verified. In particular, we need to know whether or not the endpoint is consistent across studies. If it *is* consistent, then we want to estimate the mean endpoint as accurately as possible and to report that it is a robust estimation. On the other hand, if the endpoint varies substantially from study to study, we want to quantify the extent of this variance and consider the implications. A MA is able to address these issues, whereas a narrative review is not.

The most commonly used format to report the results of each study and that of the MA is the so-called *forest plot*. We use here an example of a forest plot taken from Chap. 21 of this book (Fig. 11.1).

In this case, the table inside the figure lists in chronologic order the eight articles that matched the inclusion criteria of a SR on the sensitivity of screening MRI in women with a personal history of breast cancer (BC). Articles are identified with the name of the first author and the year of publication in the first column on the left side.

Model	Study name	Statistics for each study						Event rate and 95% CI
		Event rate	Lower limit	Upper limit	*Z* Value	*p* Value	Total	
	Brennan 2010	0.972	0.678	0.998	2.479	0.013	17/17	
	Berg 2012	0.750	0.238	0.966	0.951	0.314	3/4	
	Gweon 2014	0.833	0.523	0.958	2.078	0.038	10/12	
	Weinstock 2015	0.846	0.549	0.961	2.218	0.027	11/13	
	Lehman 2016	0.800	0.572	0.923	2.480	0.013	16/20	
	Cho 2017	0.882	0.632	0.970	2.677	0.007	15/17	
	Kim 2017	0.818	0.493	0.954	1.924	0.054	9/11	
	Park 2018	0.750	0.238	0.966	0.951	0.341	3/4	
Fixed		0.835	0.742	0.899	5.612	0.000		

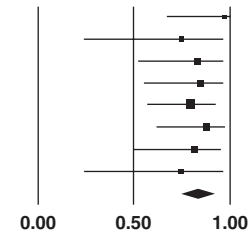

Fig. 11.1 Forest plot of the meta-analysis reported in Chap. 21 of this book, showing eight studies reporting sensitivity of breast MRI in women with personal history of breast cancer. Note that the event rate for the first study (Brennan 2010) for a sensitivity of 17/17 (per-woman analysis) is 0.972 instead of 1.000 due to a correction factor applied to extreme values, i.e. those close to 0.000 and 1.000. See text for other explanations

The following columns report *statistics* for each study, from left to right: the extracted endpoint (*event rate*, here sensitivity); the lower and upper limits of this event rate, calculated as 95% confidence interval (CI); the z value (i.e., for each event rate, the number of standard deviations from the mean value of the reference population of the study); the p value, which indicates, for each study, the probability that the reported sensitivity is different from 0.500, i.e., better than a 50% distribution of true negatives and false negatives; the *Total* column, showing the numerator (true positives) and the denominator (all women with a BC, sum of true positives and false negatives) of sensitivity. On the right side, a graph shows a visual representation of data reported in the columns. In particular, squared dots indicate the point estimate in the scale used for MA, whose size is proportional to the number of patients enrolled by each study. The horizontal line represents the 95% CI associated to each endpoint, whose width is also an indirect measure of the study sample size (the larger the interval, the smaller the study sample, and the larger the uncertainty around the estimate). In the last row, we see the *pooled endpoint* (or pooled estimate) reported as a weighted mean of all included studies (a sensitivity of 0.835) together with its 95% CI (0.742–0.899). The pooled endpoint is shown in the graph as a diamond-like symbol, whose width reflects its 95% CI (much narrower than that of each study), indicating the increased precision of the pooled sensitivity estimate (and less uncertainty around that pooled estimate). On bottom-left, the term *fixed* indicates which of the two main statistical methods is used to calculate the weights for each study when calculating the weighted mean of all endpoints. It refers to the so-called *fixed-effect model*, which only considers the study sample size to calculate study weights. The other meta-analytic technique uses the so-called *random-effect model*, which also considers the *heterogeneity* across studies [18].

Heterogeneity is worthy of further considerations. As said earlier, when working with a collection of different studies, we must verify whether or not the endpoint is consistent (homogeneous) across the studies. In the example of Fig. 11.1, the sensitivity ranges from 0.750 in both the studies by Berg 2012 and Park 2018 to 1.000 in the study by Brennan 2010 (the forest plot reports 0.972 due to a correction factor, as also explained in the figure legend), with some variation between these two boundaries. This variation is referred to as data heterogeneity and it reflects the combined effect of two sources: (1) sampling error and (2) actual differences among the experiments conducted by the different authors. The former is unavoidable but should be small in principle if all studies have been performed in exactly the same fixed conditions (hence the use of the *fixed-effect model*: all studies have measured *the same thing*). The latter, instead, is associated with real random differences in the experiment conditions, inclusive of clinical or setting variability. For example, some of the studies may evaluate patients that are younger or healthier than those evaluated in other studies, some may have used 1.5-T MRI units while others 3-T units, some may have used 0.1 mmol/kg of contrast material while others 0.2 mmol/kg, etc. Thus, a high heterogeneity is an indication of the fact that the analyzed studies do not really measure the same sensitivity but rather a random distribution of all possible sensitivities (hence the use of the *random-effect model*: the studies may have measured *different things*).

Heterogeneity is typically quantified using the I^2 coefficient, which is a measure of how much of the observed variability is due to real differences among the studies. For example, an I^2 of 70% would practically mean that the studies are likely different from one another, with their endpoints potentially reflecting different things. Calculating a pooled endpoint where such heterogeneity exists could be considered questionable. However, especially when studies of diagnostic tests are reviewed, this does not preclude meta-analysis as long as appropriate methods are used to allow for, and to possibly explore sources of, heterogeneity between studies, as well explained in the Chap. 10 of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [18]. Indeed, the above-mentioned random-effect model is a statistical technique that assigns weights to meta-analyzed studies considering

also heterogeneity other than the study sample size. However, before proceeding with the calculation of the pooled endpoint using the random-effect model, when I^2 is large (50% is a commonly used threshold, although empiric in nature) an effort to explain (understand the source of), heterogeneity should be made by means of subgroup analysis or meta-regression. These two latter statistical techniques are used to investigate the effect on the endpoint of categorical covariates (e.g., 1.5-T versus 3-T magnets, ductal versus lobular carcinoma) and continuous covariates (e.g., lesion size, patients age), respectively. Substantially, exploring heterogeneity among studies using such analytic methods allows identification of issues that clarify differences in results among studies. For example, a MA of MRI in the detection of multifocal disease found that the quality of the reference standard was significantly associated with differences in the reported accuracy of MRI across studies [19].

One final remark is specifically needed for SR&MA of diagnostic test accuracy, which requires even more complex statistical techniques compared to SR of interventions. This is essentially due to the paired nature of sensitivity and specificity as combined measures of diagnostic accuracy: in general, the higher the sensitivity for a given disease/condition, the lower the specificity, and vice versa. This means that they are related to each other (there is a trade-off between these measures) and not independent measures. As a consequence, we cannot simply perform a MA of sensitivity and, separately, a MA of specificity. Instead, a bivariate model such as that proposed by J.B. Reitsma and coworkers [20] must be used, which allows the reviewers to handle both sensitivity and specificity contemporarily. Suggested reading on this topic is again Chap. 10 of the Cochrane Handbook for Diagnostic Test Accuracy [18].

Individual patient (or participant) data MAs. Differently from standard study-level MAs we have considered above, in IPD-MAs line-by-line data of each patient are collected from each study, instead of just the usual aggregate data. Thus, we can consider standard MAs as *aggregate data MAs* (AD-MAs). The IPD approach allows the reviewers to define interventions, comparisons, and outcomes consistently across studies, and to adjust for the same confounders, reducing the heterogeneity [21]. Of course, to collect IPD is not an easy task, also because, in the majority of cases, IPD will be available only if the authors of each study accept the practice of *data sharing*, implying the need to use a common agreed format that will make this analysis possible [22]. Importantly, IPD-MAs also require specialized statistical skills such as those regarding the choice between the *one-stage approach* (analyzing IPD from all studies simultaneously) or the *two-stage approach* (deriving AD from each study separately and then performing a standard AD-MA) [23]. IPD-MAs are becoming more and more popular [23], but a recent review of the literature [24] showed that similar results and conclusions can be obtained using either the IPD-MA or the standard AD-MA approach. As a consequence, before initiating a resource-demanding IPD-MA, a standard AD-MA should initially be explored.

Advantages and limitations of SR&MAs. From what discussed in the previous paragraphs, the advantages of SR&MAs should have become clear to the reader: they summarize the available literature on a given topic, weighting studies according to their quality in a transparent way and offering a quantitative pooled estimate of one (or more) end-point that represents a more precise and higher level of evidence in comparison with that provided by each original study. The meta-analytic approach can also represent a reasonable alternative to the performance of a new large prospective study, with its costs and the long time needed for obtaining the results (especially in the case of survival data); it is also the only way for the case of rare diseases (where individual studies have great difficulties in reaching an acceptable statistical power).

However, limitations of SR&MAs should also be taken into account. One of them is given by the potential so-called *publication bias* (studies reporting statistical significances are more probably published than studies not reporting statistical significance) so that the sum of results may reinforce the bias. However, the risk of publica-

tion bias may be evaluated using specific statistical techniques, as one of the results of the SR&MA. Other limitations are inherent to the nature of any SRs, even when they are performed according to appropriate methodology, and should be considered. First, the reliability of a SR&MA is dependent on the *quality of the included studied*, in particular on the quality of the largest ones [25]. This can de facto lead to a number of inconclusive SR&MAs, as noted in a specific field such as pediatric cardiology [26]. Second, a SR&MA, considering the time needed for selection of studies, data extraction/collection, data analysis, manuscript drafting, etc., up to publication introduces a relatively long time interval (usually more than 1 year) before the last study is included and the publication of the SR&MA. However, when considering the date of all included studies, a SR&MA may represent the summary of a relatively old evidence, not that of the state-of-the art of medical tools recently developed or refined. In other words, SR&MAs are a *conservative approach* in terms of EBM. This affirmation implies that they cannot take into account the most recent developments. The good side of this limitation is the following: when a medical innovation is positively evaluated by a SR&MA on the basis of a relatively large application by multiple primary studies, we have a robust factor in favor of its practical application [6].

11.5 MRI for Screening High-Risk Women: Secondary Evidence on Diagnostic Performance

A list of eight articles that summarized the evidence on diagnostic performance of breast MRI as a screening tool in high-risk women, including six formal MAs, is presented in Table 11.3.

A first attempt to summarize studies on MRI for screening high-risk women was published online on 29 September 2006 (and printed in April 2007) by Francesco Sardanelli and Franca Podo [27]. Even though it was not a formal SR&MA, this review showed, on the basis of five studies and 3,571 screened women, that the sensitivity of MRI was more than double (82%) in comparison to that of mammography (40%) and that the rate of interval cancers observed in those multimodal screening studies was reduced to approximately 5%; the positive predictive value (PPV) of mammography (47%) and MRI (53%) was comparable, while that of clinical breast examination (CBE) and ultrasound (US) was lower (33% and 18%, respectively).

In 2007, the American Cancer Society updated the guidelines for BC screening in relation to risk levels. Saslow and coworkers [28] reported data from six studies, including data only from the first report of the Italian study (published in 2002) and retrospective data published by the International Breast MRI Consortium (mainly by the United States). These data, although still limited, were considered enough for recommending in favor of annual MRI as an adjunct to mammography in women with an approximately 20–25% or greater lifetime risk (LTR) of BC, *including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease* (who underwent thoracic radiation therapy, see Chap. 14). The basis for this recommendation by the expert panel was the combination of the large gap in sensitivity between MRI (77–100%) and either mammography or US (16–40%) joined to an acceptable MRI specificity (81–99%).

Later in 2007, Sarah J. Lord and coworkers [29] published the first systematic AD-MA including data from five prospective studies totaling 2,059 high-risk women and about 4,500 screening events. They found that the addition of MRI provided a higher sensitivity (93–100%) compared to mammography alone (25–59%) or mammography combined with US or also CBE (49–67%). The incremental sensitivity of MRI was 58% when compared to mammography alone, 44% when compared to mammography plus US. The authors observed a three- to fivefold higher risk of patient recall for false positives when MRI is added to mammography-alone results. The included studies did not provide strong evidence that MRI allowed an earlier disease diagnosis. Thus, the authors concluded that the effectiveness of MRI therefore depends on

assumptions about the benefits of early detection from trials of mammographic screening in older average risk populations.[4]

In 2008, Ellen Warner and coworkers [30] published a second AD-MA considering 11 studies totaling 4,983 women and approximately 10,000 screening events. The particular contribution of this work was the evaluation of the differences in performance between mammography and MRI when considering different thresholds for test positivity. As expected, when BI-RADS ≥ 3 was considered as positive for both mammography and MRI, sensitivities were slightly higher and specificities lower than when only BI-RADS ≥ 4 was considered as positive; however, the gap in sensitivity in favor of MRI remained over 30% (see Table 11.3). These authors also calculated the summary positive likelihood ratio (PLR) and negative likelihood ratio (NLR) for both mammography and MRI, again considering the two above-mentioned thresholds (Table 11.4). Of note, MRI had a two- to threefold higher capability of reducing the post-test probability of cancer, in the case of a negative result of the test, when compared to mammography; combining MRI and mammography, the NLR was further approximately halved. On the other hand, the MRI-mammography combination did not increase the PLR in comparison to MRI alone.

Also, in 2008, Elon J. Granader and coworkers [31] meta-analyzed eight studies totaling 4,331 women and 9,000 screening events. Again, a very large overall difference in estimates of sensitivity between mammography (38%) and MRI (97%) was observed (Table 11.3). Focusing on only the three studies judged to have level 2b evidence, they could distinguish very high-risk women (*BRCA1/2* mutation carriers and their first-degree relatives) from women at increased risk without known *BRCA1/2* mutations. For the very high-risk subset, they reported a pooled sensitivity of 33% for mammography, 84% for MRI, and 93% for their combination as well as a pooled specificity of 95%, 90%, and 86%, respectively. For the increased-risk subset, the same data were 41%, 81%, 95% and again 95%, 90%, 86%, respectively. In other words, the risk level did not substantially influence the diagnostic performance of the two tests, even though the difference in sensitivity seemed to be larger for very high-risk women.

Insightful contributions came from three MAs integrating IPD from six prospective studies published from 2005 to 2015, all of which were performed by the same international research group, as described below.

In 2015, Xuan-Anh Phi and coworkers [32] explored potential differences in diagnostic performance in relation to high-risk women age. The relevant question was the following: is the difference in sensitivity between MRI and mammography still relevant after menopause? Due to the known higher sensitivity of mammography in the presence of fatty breasts rather than in dense breasts, a reduced gap between the two tests could be hypothesized, suggesting to stop MRI screening after 50. However, two other factors argue against this hypothesis: the general higher breast density in high-risk women and the propensity of BCs in this subset of women, especially in *BRCA1* mutation carriers, to exhibit false benign characteristics, i.e., regular round border, absence of spiculations or microcalcifications. Thus, only a subgroup analysis by age stratification, as can be easily enabled by the IPD approach, could investigate this issue. The results, based on 1,514 *BRCA1/2* mutation carriers with 140 BCs in the subgroup of women below 50 years of age and 437 *BRCA1/2* mutation carriers with 43 BCs in the subgroup aged 50 and older, were very clear: the sensitivity of mammography was 40% and 38%, that of MRI 93% and 96%, respectively, with specificities ranging from 79% to 86% (see Table 11.3). Of note, in women aged 50 or older, combining MRI and mammography significantly increased screening sensitivity compared with mammography alone (94% versus 38%) but the two tests combined were not significantly more sensitive than MRI alone (94% versus 84%).

This IPD-MA provided new important evidence, suggesting not to stop MRI screening in

[4]The reader can find an extended discussion on the impact of breast MRI high-risk screening on patient outcome in Chap. 13.

Table 11.3 Summary of reviews on breast MRI and comparative tools for screening high-risk women

First author, year [reference]	Study design	Number of studies (year interval)	Screened women (events/ woman)	Screen-detected cancers	Interval cancers	Detected cancers/ rounds	Tumor size ≤1 cm	Invasive cancers	N+	Sensitivity				Specificity				Positive predictive value			
										CBE	Mam	US	MRI	CBE	Mam	US	MRI	CBE	Mam	US	MRI
Sardanelli, 2007 [27]	Only prospective studies	5 (2004–2007)	3,571 (2.7)	155	8	1.60%	49%	82%	19%[a]	16%	40%	43%	82%	nr	nr	nr	nr	33%	47%	18%	53%
Saslow, 2007 [28]	Prospective and retrospective studies	6 (2002–2005)	3,818 (nr)	162		nr	nr	nr	nr	nr	16–40%	16–40%	77–100%	nr	93–99%	91–96%	81–99%	nr	nr	nr	nr
Lord, 2007 [29]	Prospective studies	5 (2004–2007)	2,059 (2.2)	133		2.90%	nr	nr	nr		25–59%	nr	93–100%	nr	nr	nr	nr	nr	nr	nr	nr
Warner, 2008 [30]	Prospective studies, AD-MA	11 (2004–2007)	4,983 (2)	203	15	2.00%	29–86%	73–92%[b]	0–26%	nr	32%, 39%[c]	nr	75%, 77%[c]	nr	95%, 99%[c]	nr	86%, 96%[c]	nr	15%, 34%[c]	nr	8%, 25%[c]
Granader, 2008 [31]	Prospective and retrospective studies; AD-MA	8 (2001–2005)	4,331 (2.1)	nr	nr	1.90%	nr	nr	nr	nr	38%	nr	97%	nr	96%	nr	90%	nr	nr	nr	nr
Phi, 2015 [32]	Only *BRCA1/2*; IPD-MA	6 (2005–2015)	<50-yo: 1,514 (nr)	< 50-yo: 140	nr	nr	nr	nr	nr	40%	nr	86%	nr	93%		79%	nr	nr	nr	nr	
			≥50-yo: 437 (nr)	≥ 50-yo 43						38%		84%		96%		85%					

(continued)

Table 11.3 (continued)

First author, year [reference]	Study design	Number of studies (year interval)	Screened women (events/ woman)	Screen-detected cancers	Interval cancers	Detected cancers/ rounds	Tumor size ≤1 cm	Invasive cancers	N+	Sensitivity				Specificity				Positive predictive value			
										CBE	Mam	US	MRI	CBE	Mam	US	MRI	CBE	Mam	US	MRI
Phi, 2016 [33]	Only *BRCA1/2*; IPD-MA	6	≤40-yo *BRCA1*: 605 (nr)	38	8	nr	22%	80%	nr	nr	39%	nr	78%	nr	95%		84%	nr	nr	nr	nr
		(2005–2015)	≤0-yo *BRCA2*: 301 (nr)	15	3		13%	83%			56%		53%		92%		80%				
			41 to 50-yo *BRCA1*: 482 (nr)	35	3		29%	92%			34%		93%		92%		83%				
			41 to 50-yo *BRCA2*: 308 (nr)	33	4		46%	65%			38%		86%		92%		86%				
			>50-yo *BRCA1*: 310 (nr)	25	3		32%	89%			29%		89%		97%		90%				
			>50-yo *BRCA2*: 228 (nr)	16	1		36%	65%			46%		85%		97%		91%				
Phi, 2017 [34]	Strong family history, non-carriers of known gene mutations; IPD-MA	6	≤40-yo: 987	13	1	nr	8%	93%	nr	nr	51%	nr	92%	nr	95%	nr	83%	nr	5%	nr	4%
		(2005–2015)	41 to 50-yo: 1,044	35	1		39%	70%			57%		92%		91%		80%		9%		7%
			>50-yo: 527	36	1		39%	76%			67%		86%		94%		90%		24%		20%

MRI magnetic resonance imaging, *Mam* mammography, *N+* node positive cases, *nr* not reported (or not judged to be informative in this table); *BRCA1/2 BRCA1/2* mutation carriers, *AD-MA* aggregate data meta-analysis, *IPD-MA* individual patient data meta-analysis

[a]Calculated as percentage of only invasive cancer cases

[b]Excluding two studies, one with 6/6 invasive cancers and one with 1/1 in situ cancer

[c]The two percentages are obtained changing the thresholds for positivity (BI-RADS ≥3 or ≥4)

Table 11.4 Summary positive and negative likelihood ratios of mammography, MRI, and their combinations, as reported by Warner et al. [30]

	Number of studies	Screening events	Number of cancers	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Mammography (LT)	4	6,678	108	8.7 (4.4–17.5)	0.64 (0.55–0.75)
Mammography (HT)	7	8,818	178	24.8 (11.6–53.0)	0.70 (0.59–0.82)
MRI (LT)	5	6,719	109	4.2 (3.0–5.9)	0.29 (0.21–0.41)
MRI (HT)	8	8,857	178	16.6 (11.1–25.0)	0.22 (0.12–0.43)
Mammography and MRI (LT)	3	2,509	63	4.1 (3.6–4.7)	0.09 (0.04–0.23)
Mammography and MRI (HT)	5	4,272	115	16.4 (11.1–24.1)	0.14 (0.05–0.42)

Data from Warner et al. [30]

CI confidence interval, *LT* low threshold (the test was considered positive for cases assigned BI-RADS ≥3); *HT* high threshold (the test was considered positive for cases assigned BI-RAD ≥4). Note that, with the only exception for the negative likelihood ratios for both tests with LT, all the likelihood ratios were associated with considerable significant statistical heterogeneity

BRCA mutation carriers after 50 years of age. The authors concluded that the *addition of MRI to mammography for screening BRCA1/2 mutation carriers aged ≥ 50 years improves screening sensitivity by a magnitude similar to that observed in younger women* and that *limiting screening MRI in BRCA1/2 carriers at age 50 years should be reconsidered*.

Another relevant issue was to better explore the possible differences in diagnostic performance of diagnostic breast imaging modalities between *BRCA1* and *BRCA2* mutation carriers, with the specific aim to define the contribution of mammography when both tests are used, taking age into consideration. The underlying idea was to evaluate *whether, considering the very high MRI sensitivity, the adjunct of mammography to MRI was needed or not*. In 2016, Xuan-Anh Phi and coworkers [33] faced this new question using IPD from the same six studies already meta-analyzed in 2015 [32]. The subgroup analysis allowed by the IPD approach (see Table 11.3) showed that, considering *BRCA1/2* mutation carriers of all ages, adding mammography to MRI did not significantly increase sensitivity. However, the marginal increase in sensitivity by mammography was only 4% in *BRCA1* and 13% in *BRCA2* women, and in women with *BRCA2* mutation aged 40 or younger, one-third of BCs were detected by mammography only. This was due to the MRI sensitivity in high-risk women aged ≤40, reduced from 78% in *BRCA1* mutation carriers to 53% in *BRCA2* mutation carriers, while mammography showed an inverted trend of sensitivity (39% and 53%, respectively). Data on age over 40 were more stable: mammography sensitivity from 34% to 46%; MRI sensitivity from 85% to 93%.

The observed differences were made clear using the number of screens needed (NSN) approach. In fact, NSN for mammography to detect one BC not detected by MRI was much higher for *BRCA1* compared with *BRCA2* mutation carriers at first and repeat screening events. In particular, under the age of 40, NSN for mammography to detect one BC not detected by MRI was 278 for *BRCA1* versus 55 for *BRCA2* at the first screening event, 775 versus 141 at repeat screening event (Table 11.5).

The authors concluded that *the additional detection from mammography in BRCA1 mutation carriers who receive MRI screening is minimal and might not outweigh potential disadvantages (potential cancer induction by radiation, false-positive results)* and that *it may be reasonable* to *consider potential omission of mammography screening in BRCA1 mutation carriers or to open discussion on its potential omission given its limited contribution.* Conversely, *in BRCA2 mutation carriers, the contribution of mammography above MRI is more evident*, so *different screening recommen-*

Table 11.5 Number of screens needed (NSN) for one MRI-missed and mammography-detected cancer in *BRCA1* or *BRCA2* mutation carriers who undergo both tests annually, stratified by age and first or repeat screening events

Mutational status, age range	NSN (first screening event)	NSN (repeat screening events)
BRCA1, ≤40 years	278	775
BRCA1, 41–50 years	Na	797
BRCA1, >50 years	Na	578
BRCA1 all ages	527	717
BRCA2, ≤40 years	55	141
BRCA2, 41–50 years	204	222
BRCA2, >50 years	139	430
BRCA2, all ages	94	231

Data from Phi et al. [33]
Na not available, as no cancers was detected at first event in these subgroups

dations for these two groups of women defined by BRCA mutation status should be considered.[5]

In 2017, the same group, using the same database, published a third IPD-MA [34] assessing the diagnostic performance of MRI screening women at familial risk of BC *without* a known gene mutation. In fact, this subset of high-risk women had remained not sufficiently investigated due to the heterogeneity of population samples of the individual studies, frequently mixing *BRCA* mutation carriers with cases of BC family history without proven deleterious mutation, also with a relatively low LTR. Using again the database of the six studies already obtained for the previous two IPD-MAs [32, 33], also for this category of high-risk women the gap between the sensitivity of mammography (from 51% to 67%, across different age ranges) and that of MRI (from 86% to 92%, across different age ranges) was confirmed, even though it was very large (plus 41%) for age up to 40 (additional sensitivity from MRI above that from mammography), intermediate for age 41–50 (plus 35%), and limited to "only" 19% over 50. Considering all ages, sensitivity was 55% for mammography and 89% for MRI, while specificity was 94% and 83%, respectively; adding MRI to mammography significantly increased sensitivity to 98% but significantly lowered specificity to 79% in comparison to mammography alone. The authors concluded that *in women with strong familial BC risk but without a known gene mutation adding MRI to mammography substantially increased screening sensitivity with a tradeoff in terms of specificity*. They also said that MRI screening alone may be appropriate for these women but that comparative accuracy studies need to be complemented by health-economic cost-effective analyses.

[5]The reader can find further material on the possibility to use breast MRI only for screening high-risk women and on the risk of radio-induced BCs in this particular population in Chaps. 9 and 10 and in Chap. 12, respectively.

11.6 MRI for Screening High-Risk Women: Cost-Effective Analyses

A number of CEAs of breast MRI for screening in high-risk women were published in the last 12 years [35–41]. Their results are summarized in Table 11.6.

Without entering into the details, we can generally say that cost-effectiveness of breast MRI screening in terms of cost related to gained quality-adjusted life years (QALYs) depends on disease prevalence and age ranges. The higher the LTR of BC and younger the age of the woman (starting from 25), the better the cost-effective ratio. This means that:

- The cost-effectiveness of breast MRI is higher for screening *BRCA1/2* mutation carriers than for women with BC family history with lower LTR levels (or, of course, with average BC risk) [35, 36, 38].
- Breast MRI is more cost-effective for screening *BRCA1* than *BRCA2* mutation carriers [35].
- A high-risk screening strategy that differentiates the use of MRI and mammography according to age ranges may be more cost-effective than a yearly MRI plus mammography generalized strategy from age 25 [39].

However, several studies highlighted the key role of the cost of the MRI in determining cost-effectiveness [36, 37, 40, 41]. According to Susan G. Moore and coworkers [37], *MRI screening becomes lower than USD 50,000/QALY when the MRI cost was lower than 315 USD*, a cost very close to the reimbursement practiced by European public healthcare systems. Reka Pataky and coworkers [40] calculated that *as the cost is increased from USD 200 to USD 700 per scan, the incremental cost-effectiveness ratio ranges from USD 37,100/QALY to USD 133,000/QALY*.

Thus, considering that the cost or, better to say, the amount of money paid for a breast MRI is quite different in different countries, cost-effectiveness of breast MRI screening is variable.

Table 11.6 Summary of studies on cost-effectiveness of breast MRI for screening high-risk women

First author, year, country [reference]	Methods	Results	Conclusions
Plevritis, 2006, USA [35]	Model of life histories of *BRCA1/2* MCs, incorporating effects of MAM/MRI screening based on published data. Survival without screening based on prescreening SEER database, adjusted for adjuvant therapy. Utilization/costs based on literature and Medicare in 2005	Screening with annual MRI and MAM implies a cost per QALY gained ranging 45,000–700,000 USD, depending on age and *BRCA* mutation. The cost per QALY gained by adding MRI to MAM alone for age 35–54 is 55,420 USD for *BRCA1* MCs, 130,695 USD for *BRCA2* MCs, and 98,454 US for *BRCA2* MCs with dense breasts	Breast MRI is more cost-effective for *BRCA1* than *BRCA2* MCs. The cost-effectiveness of adding MRI to MAM varies greatly by age
Griebsch, 2006, UK [36]	Based on data from the MARIBS study: 649 high-risk women aged 35–49 screened with MRI and MAM, totaling 1,881 screens	For all women, the incremental cost per cancer detected with MRI plus MAM was £ 28,284 compared to MAM alone. For only *BRCA1/2* MCs, the cost was £ 11,731 (MRI versus MAM) and £ 15,302 (MRI plus MAM versus MAM). Results were most sensitive to cost estimate for an MRI test.	Contrast-enhanced MRI might be a cost-effective screening modality for women at high risk, particularly for *BRCA1* and *BRCA2* subgroups
Moore, 2009, USA [37]	The Markov model to compare annual screening over 25 with either breast MRI or MAM, based on published studies and costs according Medicare and U.S. Federal Supply Scale. Costs and benefits discounted at 5%/year	Breast MRI provided 14.1 QALYs at 2006 USD 18,167 while MAM provided 14.0 QALYs at a cost of USD 4760 over 25 years of screening. In univariate analysis, MRI screening became lower than USD 50,000/QALY when the MRI cost was lower than USD 315	Breast MRI may provide health benefits when compared to MAM, but it does not appear to be cost-effective even at willingness-to-pay thresholds above $120,000/QALY
Taneja, 2009, USA [38]	Model to depict the effect of MRI and/or MAM screening for cohorts of 10,000 *BRCA1/2* MCs and other high-risk women	Among the 400 of 10,000 *BRCA1/2* MCs diagnosed with BC, 361 cases would be detected with MRI and MAM, 290 with MRI alone, and 160 with MAM alone. False positives would total 1,526, 1,190, and 528, respectively. Cost per QALY gained with MRI + MAM compared with MAM alone was USD 25,277 for *BRCA1/2* MCs. For other high-risk women, this cost per QALY gained varied depending on cancer prevalence from USD 45,566 to $310,616. The cost-effectiveness of MRI alone compared with MAM alone was similar	In *BRCA1/2* MCs, MRI screening, alone or combined with MAM, is cost-effective by current standards compared with MAM alone. In other high-risk women, MRI screening may also be cost-effective, depending on the expected prevalence of undiagnosed BC at the time of screening

(continued)

Table 11.6 (continued)

First author, year, country [reference]	Methods	Results	Conclusions
de Bock, 2013, The Netherlands [39]	Simulation model for *BRCA1* and *BRCA2* MCs, with outcomes/costs from published and registry data. Simulation situated in the Netherlands and in the UK, comparing Dutch strategy (age 25–30, MRI every year; 30–60, MRI + MAM every year; 60–75, MAM every 2 years), UK strategy (age 30–50, MRI+ MAM every year; 50–70, MAM every 3 years), and USA strategy (all ages, MRI + MAM every year), with the population screening as a reference. Discount rate 3%	The most cost-effective was the USA strategy, followed by the Dutch and the UK, with small differences. Applying the USA strategy in the Netherlands, the costs were €43,800 and 68,800 for an additional life-year gained for *BRCA1* and *BRCA2*, respectively. At a threshold of €20,000 per life-year gained, implementing the US strategy in the Netherlands has a very low probability of being cost-effective. Stepping back to the less-effective UK strategy would save relatively little in costs and results in life-years lost. When implementing the strategies in the UK, Dutch and USA strategies have a high probability of being cost-effective	From a cost-effectiveness perspective, the Dutch screening strategy is preferred for screening high-risk women in the Netherlands as well as in the United Kingdom
Pataky, 2013, Canada [40]	The Markov model of annual MRI and MAM screening for *BRCA1/2* MCs, using local data and published values	The ICER of annual MAM plus MRI screening, compared to annual MAM alone, was USD 50,900/QALY. MRI screening is expected to be cost-effective, 86% of the time at a willingness-to-pay of USD 100,000/QALY, and 53% of the time at a willingness-to-pay of USD 50,000/QALY. The model is highly sensitive to the cost of MRI; as the cost is increased from USD 200 to USD 700 per scan, the incremental cost-effectiveness ratio (ICER) ranges from USD 37,100/QALY to USD 133,000/QALY	The sensitivity of the results to the cost of the MRI warrants consideration: With high MRI costs, screening may not be cost-effective, but improving the MRI screening efficiency will also improve cost-effectiveness
Ahern, 2014, USA [41]	Microsimulation model to generate life histories for different risk profiles. Twelve screening strategies combining annual or biennial MRI with MAM and CBE in intervals of 0.5, 1, or 2 years versus without, and reported ICERs. Discount rate 3%	Based on an ICER threshold of USD 100,000/QALY, the most cost-effective strategy for women at 25% LTR was to stagger MRI and MAM plus CBE every year from age 30 to 74, yielding ICER USD 58,400 (compared to biennial MRI alone). At 50% LTR and with 70% reduction in MRI cost, the recommended strategy was to stagger MRI and MAM plus CBE every 6 months (ICER USD 84,400). At 75% LTR, the recommended strategy is biennial MRI combined with MAM plus CBE every 6 months (ICER USD 62,800)	The high costs of MRI and its lower specificity are limiting factors for annual screening schedule of MRI, except for women at sufficiently high risk

MAM mammography, *MRI* magnetic resonance imaging, *SEER* surveillance, epidemiology and end result, *QALY* quality-adjusted life-year, *USD* United States dollars, *MC* mutation carrier, *CBE* clinical breast examination, *LTR* life-time risk, *ICER* incremental cost-effectiveness ratio

Paradoxically, we observe the highest cost of breast MRI in the USA, where its use as screening tool is not only recommended for high-risk women (with the 20% LTR threshold, without any age limitation [39]) but also recently open to the large category of the so-called women with a higher-than-average BC risk [42].[6] One way to solve this problem is the adoption of abbreviated protocols for contrast-enhanced breast MRI, as discussed in Chap. 4. However, as done for mammography in organized population-based screening programs, the cost of any test, including breast MRI, could be redefined, considering that the probability of a true negative test is dramatically higher than that in a diagnostic test in symptomatic women, implying a much shorter reporting time.

11.7 Conclusions

To summarize, secondary studies analyzing the published evidence (in particular, AD-MAs [29–31]) showed a high pooled sensitivity of breast MRI for screening high-risk women and a significantly large gap in comparison to the lower pooled sensitivity of mammography (and also of CBE, and US, variably combined with mammography, for the few studies that reported their sensitivity). MRI pooled specificity, as expected for any high-sensitivity tool, was shown to be lower than its sensitivity but allowed, when considering a relatively high cancer prevalence (depending on the risk level), for acceptable PPVs. Thus, from the viewpoint of the diagnostic performance, breast MRI has been accepted and therefore recommended also in multidisciplinary and governmental guidelines as a screening tool in high-risk women.

A peculiar contribution came from IPD-MAs. These studies provided evidence in favor of breast MRI screening of high-risk women over 50 [32] and showed the limited value of mammography as an adjunct to MRI at least for *BRCA1* mutation carriers [33] as well as the value of breast MRI screening for women at familial risk of BC without a known gene mutation [34].

Cost-effectiveness analyses [35–41] pointed out that the higher the risk and earlier the expected onset of the cancer, the higher the incremental cost-effective ratio of MRI added to mammography, with the cost of the breast MRI as a key factor influencing the economic efficiency of MRI-including screening programs for high-risk women.

Notably, no secondary analysis was available regarding the patient outcome, due to the absence of randomized control trials. However, while in 2007 [29] the effectiveness of breast MRI screening in high-risk women could be considered as only depending on *assumptions about the benefits of early detection from trials of mammographic screening in older average risk populations*, one decade after we have some more data showing a positive impact of this high-sensitivity screening on high-risk patients' outcome, as extensively discussed in Chap. 13.

[6]The reader can find an extended discussion on breast MRI screening for the intermediate risk in Chap. 22.

References

1. Cooper HM (2010) Research synthesis and meta-analysis: a step-by-step approach, 4th edn. SAGE, Los Angeles
2. Chalmers I, Hedges LV, Cooper H (2002) A brief history of research synthesis. Eval Health Prof 25:12–37
3. Deeks JJ, Bossuyt PM, Gatsonis C (eds) Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0. The Cochrane Collaboration. http://srdta.cochrane.org/. Accessed 30 Jun 2020
4. Higgins JPT, Green S (eds) (2011) Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane Collaboration. http://handbook.cochrane.org. Accessed 30 Jun 2020
5. Sanders GD, Neumann PJ, Basu A et al (2016) Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 316:1093–1103
6. Oxford Centre for Evidence-based Medicine (2009) Levels of Evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 30 Jun 2020
7. Lind J (1753) A treatise of the scurvy: in three parts, containing an inquiry into the nature, causes, and cure, of that disease, together with a critical and chronological view of what has been published on the

subject. http://www.who.int/iris/handle/10665/72991. Accessed 30 Jun 2020
8. Brunt L (2001) The advent of the sample survey in the social sciences. Statistician 50:179–189. https://doi.org/10.1111/1467-9884.00270. Accessed 30 Jun 2020
9. National Health System Centre for Reviews and Dissemination (2001) Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4, 2nd edn, University of York. http://ph.cochrane.org/sites/ph.cochrane.org/files/public/uploads/Unit_One.pdf. Accessed 30 Jun 2020
10. Cochrane AL (1989) Foreword. In: Chalmers I, Enkin M, Keirse MJNC (eds) Effective care in pregnancy and childbirth. Oxford University Press, Oxford
11. Chalmers I, Altman DG (eds) (1995) Systematic reviews. BMJ Books, London
12. Egger M, Davey Smith G, Altman D (eds) (2001) Systematic reviews in health care: meta-analysis in context, 2nd edn. BMJ Books, London
13. National Library of Medicine. https://www.ncbi.nlm.nih.gov/pubmed. Accessed 30 Jun 2020
14. Gusenbauer M (2018) Google Scholar to overshadow them all? Comparing the sizes of 12 academic search engines and bibliographic databases. Scientometrics. https://doi.org/10.1007/s11192-018-2958-5. Accessed 30 Jun 2020
15. Ware M, Mabe M (2015) The STM report: an overview of scientific and scholarly journal publishing. University of Nebraska, Lincoln. http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1008&context=scholcom. Accessed 30 Jun 2020
16. Sardanelli F, Di Leo G (2009) Biostatistics for radiologists. Springer, Milan, pp 166–178
17. Whiting PF, Rutjes AW, Westwood ME et al; QUADAS-2 Group (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536
18. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y (2010) Chapter 10: Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C (eds), Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0. The cochrane collaboration. http://srdta.cochrane.org/. Accessed 30 Jun 2020
19. Houssami N, Ciatto S, Macaskill P et al (2008) Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 26:3248–3258
20. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 58:982–990
21. Riley RD, Lambert PC, Abo-Zaid G (2010) Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 340:c221
22. Sardanelli F, Alì M, Hunink MG, Houssami N, Sconfienza LM, Di Leo G (2018) To share or not to share? Expected pros and cons of data sharing in radiological research. Eur Radiol 28:2328–2335
23. Burke DL, Ensor J, Riley RD (2017) Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med 36:855–875
24. Tudur Smith C, Marcucci M, Nolan SJ et al (2016) Individual participant data meta-analyses compared with meta-analyses based on aggregate data. Cochrane Database Syst Rev 9:MR000007
25. Ioannidis JP, Lau J (1999) Pooling research results: benefits and limitations of meta-analysis. Jt Comm J Qual Improv 25:462–469
26. Poryo M, Khosrawikatoli S, Abdul-Khaliq H, Meyer S (2017) Potential and limitations of Cochrane reviews in pediatric cardiology: a systematic analysis. Pediatr Cardiol 38:719–733
27. Sardanelli F, Podo F (2007) Breast MR imaging in women at high-risk of breast cancer. Is something changing in early breast cancer detection? Eur Radiol 17:873–887
28. Saslow D, Boetes C, Burke W et al; American Cancer Society Breast Cancer Advisory Group (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
29. Lord SJ, Lei W, Craft P et al (2007) A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer 43:1905–1917
30. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 148:671–679
31. Granader EJ, Dwamena B, Carlos RC (2008) MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach. Acad Radiol 15:1590–1595
32. Phi XA, Houssami N, Obdeijn IM et al (2015) Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol 33:349–356
33. Phi XA, Saadatmand S, De Bock GH et al (2016) Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 114:631–617
34. Phi XA, Houssami N, Hooning MJ et al (2017) Accuracy of screening women at familial risk of breast cancer without a known gene mutation: individual patient data meta-analysis. Eur J Cancer 85:31–38
35. Plevritis SK, Kurian AW, Sigal BM et al (2006) Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA 295:2374–2384
36. Griebsch I, Brown J, Boggis C et al; UK Magnetic Resonance Imaging in Breast Screening (MARIBS) Study Group (2006) Cost-effectiveness of screening

with contrast enhanced magnetic resonance imaging vs x-ray mammography of women at a high familial risk of breast cancer. Br J Cancer 95:801–810
37. Moore SG, Shenoy PJ, Fanucchi L, Tumeh JW, Flowers CR (2009) Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. BMC Health Serv Res 9:9
38. Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J (2009) Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol 6:171–179
39. de Bock GH, Vermeulen KM, Jansen L et al (2013) Which screening strategy should be offered to women with BRCA1 or BRCA2 mutations? A simulation of comparative cost-effectiveness. Br J Cancer 108:1579–1586
40. Pataky R, Armstrong L, Chia S (2013) Cost-effectiveness of MRI for breast cancer screening in BRCA1/2 mutation carriers. BMC Cancer 13:339
41. Ahern CH, Shih YC, Dong W, Parmigiani G, Shen Y (2014) Cost-effectiveness of alternative strategies for integrating MRI into breast cancer screening for women at high risk. Br J Cancer 111:1542–1551
42. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA (2018) Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol 15: 408–414

12 Radioprotection Issues for Women with Hereditary Predisposition for Breast Cancer

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Abbreviations

AT	Ataxia-telangiectasia
ATM	Ataxia-telangiectasia mutated
BC	Breast cancer
CI	Confidence interval
CXR	Chest X-ray
DNA	Deoxyribonucleic acid
DSB	Double-strand break
HR	Hazard ratio
HRS	Hyper-radiosensitivity
ICRP	International Commission on Radiological Protection
IR	Ionizing radiation
LORD	Low and repeated dose effect
MN	Micronucleus
OR	Odds ratio
RR	Relative risk

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12.1 Introduction

One may consider two types of breast cancer (BC) susceptibility: (1) genetic susceptibility that corresponds to a spontaneous risk of BC observed in the subpopulation affected (or not) by a BC familial history [1]; (2) radio-susceptibility that reflects the radio-induced risk of BC due to the exposure to ionizing radiation (IR), one of the most carcinogenic physicochemical agents [2]. Hence, in the context of familial history of BC, an important challenge of BC screening is to evaluate the relative contribution of each of these types of risk defined above and to determine the best strategy for the surveillance of these women.

12.2 Genetic Susceptibility to BC

While about 5% of BCs are generally attributed to familial risk, only the mutations of *BRCA1* and *BRCA2* genes are screened routinely in high-risk families. Besides, only 15% of screened high-risk women were found to be carriers of a *BRCA1* or *BRCA2* mutation, strongly suggesting the existence of other BC susceptibility genes. Mutations in about ten different genes are supposed to be associated with inherited BC. All the products of these genes are involved in pathways critical for genomic integrity [3]. *BRCA1*, *BRCA2*, *CHEK2*, *PTEN*, *TP53* as well as ataxia-telangiectasia mutated

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(*ATM*) genes are well known to be involved in BC predisposition. Interestingly, all the products of these genes act directly or indirectly on the response to deoxyribonucleic acid (DNA) double-strand breaks (DSBs).

The relative risk (RR)[1] of BC may range from 14 to 33 in *BRCA1* mutation carriers and from 10 to 20 in *BRCA2* mutation carriers compared to the general population risk [1]. A mutation in *CHEK2* confers a two- to threefold risk of BC [4, 5]. *PTEN* mutations lead to significant higher BC risk associated with rare cancer syndromes [6]. A germline *TP53* mutation confers a very high risk of early-onset cancers [7]. In adults, the tumor distribution was characterized by the predominance of BCs observed in about 80% of the females. The *TP53* mutation detection rate in females with BC before age 31 years was 6% [7].

Several epidemiological surveys of cancer incidence in relatives of ataxia-telangiectasia (AT) cases were conducted, and they confirmed the increased risk of BC. The bi-allelic inactivation of the *ATM* gene causes AT, a complex neurological disease associated with a high risk of leukemia and lymphoma. The risk of these types of cancer for AT patients is about 100 times higher than in unaffected age-matched subjects [8]. However, a potentially higher risk of BC in AT homozygotes is difficult to assess due to their relatively low life span. Women heterozygous for *ATM* were estimated to be 5.1 more likely to have BC than non-carriers [8]. Nevertheless, the causality of such risk remains not well known: Is the BC predisposition directly linked to the heterozygous *ATM* mutation? Or is BC linked to previous breast radiation exposures in a familial history of BC? In 1991, Swift and coworkers argued that women heterozygous for *ATM*, i.e., at least 1 over 100 women in the population, "should avoid mammography because of their enhanced radiogenic risk" [8].

More recently a small but significant contribution of *PALB2* gene (partner and localizer of *BRCA2*) mutations to the BC susceptibility was shown [9]. Interestingly heterozygous mutations of *PALB2* was linked to the DSB repair pathways [10]. *RAD51* paralog mutation also confers breast and ovarian cancer predisposition [11].

12.3 Radio-Induced Breast Cancer in the General Population

The second well-identified risk factor of BC in the general population is exposure to IR [2]. Considering radio-induced BC, there is a large consensus about several points [2, 12, 13]. The risk heavily depends on age at exposure, is very important before age 20, and is proven up to age 40. The excess risk appears from about age 30. The minimum latent period is 10–15 years after initial exams. The excess risk remains up to 50 years after exposure. Recent data highlight the age at menarche as a strong modifier of breast radiation effect which increases with decreasing age at menarche [14].

Because of the limits of epidemiology in assessing very low-dose effect, European Union researchers currently combine epidemiology and radiobiology to assess cancer risk with cumulated equivalent doses on the order of 100 mSv or below [15]. Actually, to evaluate low-dose effects from cohort data in the general population, two fundamental limits were pointed out. Firstly, the direct estimation is not possible because too large cohorts would be required, namely, hundreds of thousands of women to compare exposed and

[1]The relative risk (RR) is a metrics for comparing one risk to another used in prospective studies, being based on measures of the risk of future events (it is a real comparison between risks). The risk for the "exposed" subjects (A) is calculated as the rate of the number of "cases," here the number of women diagnosed with a BC, among the total number of "exposed" subjects, here the total number of women being BRCA mutation carriers. The risk for the "non-exposed" subjects (B) is calculated as the rate of "cases," here the number of women diagnosed with a BC, among the total number of "non-exposed" subjects, here the total number of women of the general population, assumed not to be BRCA mutation carriers. The RR is calculated as A/B, which is practically *a simple ratio between two prospective incidences*. Note that the term "exposed" and "not exposed" should be interpreted as the association or not association with any variable, here the presence or the absence of a deleterious BRCA mutation. A RR for BC of 14 in BRCA mutation carriers means that this risk in these woman is 14 times higher than that in the general female population. The RR is a real metrics of the future risk of an event. See the next footnotes for the definition of *odds ratio* and *hazard ratio*.

non-exposed cohorts [16]. Secondly, the exact low-dose response curve remains unknown [17].

Based on several large cohorts, repeated radiological exams were demonstrated to be associated with an increase of BC for doses higher than 100 mGy or about 100 mGy for exposures at a young age. The first type of cohorts concerned women exposed to fluoroscopy in the United States and Canada [18]. Estimated cumulative doses of 900 mGy were necessary to reveal an association with radio-induced BCs after breast exposure in adult women. However, "non-exposed" control population was defined as receiving cumulative doses less or equal to 100 mGy. Hence, only the comparison of women between 100 mGy (or less) and women with doses higher than 100 mGy was explored. Consequently, the effect of low-dose radiation less than 100 mGy could not be analyzed in these studies. The second type of cohorts concerned women exposed to multiple radiographic examinations for scoliosis during childhood and adolescence [19, 20]. A level of cumulative estimated dose to the breast of about 100 mGy was associated with an increased BC rate at adult age.

12.4 Radio-Induced BCs: Data Regarding Women with BC Hereditary Predisposition

Data are available only for the *BRCA1* or *BRCA2* mutation carriers. Because the BRCA1 and BRCA2 proteins are directly or indirectly implicated in the cellular response to IR, there is evidence that some germline mutations may also make the carrier more susceptible to radio-induced BC and subsequent carcinogenesis. Due to the role of tumor suppressor genes in radio-induced DNA damage signaling and repair, *BRCA1* and *BRCA2* mutation carriers are considered to be more susceptible to radio-induced BC than non-carriers, as suggested by a meta-analysis in 2010 [21]. The radio-induced risk of BC after exposure to X-ray at low-doses was investigated in some cohorts of mutated women [22–28], as well as in modeled risk studies in relation to the effects of mammographic screening. These issues are considered below.

12.4.1 Modeled Risk

The impact of familial history on the radio-induced BC risk from screening mammography was evaluated by Amy Berrington de Gonzales and Gillian Reeves [29]. The underlying BC rate was about two to three times higher in women with one or two affected first-degree relatives than in the general population. Consequently, these women were estimated to have a cumulative excess risk of radiation-induced BC mortality approximately two and three times higher than the general population.

Amy Berrington de Gonzales and colleagues [30] published the estimation of the lifetime risk of radio-induced BC in *BRCA1/2* mutation carriers by modeling consequences on mortality of five successive annual mammographic screening in three age ranges: 25–29, 30–34, and 35–39. The results suggested that there would be no net mortality benefit from five annual mammographic screening of *BRCA* mutation carriers at age 25–29 years; the net benefit would be zero or small at age 30–34 years, but there should be some benefit at age 35 or older. This study was not designed to simulate the effects of 10–20 or more annual mammograms, when starting at age 25, 30, or 35, as recommended in most current international guidelines [31, 32]. The cumulative effect of long-term annual mammography (more than five exams) was not assessed. Consequently, the risk of radio-induced BC is likely to be higher than the risk evaluated in cohorts of mutated women who were exposed to a relatively lower number of mammograms [33–35].

12.4.2 Data from Cohorts of *BRCA1* or *BRCA2* Mutation Carriers Exposed to X-Ray

Focusing on the effects of low-dose X-ray on BC risk in *BRCA1* or *BRCA2* mutation carriers [36],

Table 12.1 Studies conducted to identify a link between diagnostic X-ray exposure and breast cancer risk among adult *BRCA1/2* carriers

First author, year [reference number]	X-ray procedures	BC link with cumulative breast low dose	Compared cohorts
Goldfrank, 2006 [24]	Only mammography	OR = 1.08 (p = 0.03)	BRCA1/2 E/NE
Narod, 2006 [35]	Only mammography	Not found	BRCA1/2 E/NE
Andrieu, 2006 [22]	Only chest X-ray	Before age 20, RR = 4.6 (95% CI 2.2–10.9) Before age 40, RR = 2 (95% CI 1.2–2.9)	BRCA1/2 E/NE
Gronwald, 2008 [25]	Only chest X-ray	OR = 1.8 (95% CI = 1.2–2.9)	BRCA1 versus non-mutated women
Lecarpentier, 2011 [26]	Only chest X-ray	HR = 4.29 (95% CI = 2.09–8.81)	BRCA1/2 E/NE
Pijpe, 2012 [27]	Any exposure involving chest or shoulders	Before age 20, cumulative dose 6.6 mGy, HR = 3.16 (95% CI 1.19–8.36) Before age 30, cumulative dose 17 mGy: HR = 3.84 (95% CI 1.67–8.79)	BRCA1/2 E/NE
John, 2013 [34]	Only chest X-ray	Not found	BRCA1/2 E/NE
Giannakeas, 2014 [33]	Only mammography	Not found	BRCA1/2 E/NE

OR odds ratio, *HR* hazard ratio, *RR* relative risk, *E/NE* exposed cohorts vs non-exposed cohorts, *NR* not reported. Data from Colin et al. [36]

we note that seven of eight studies assessed the effects of only one diagnostic modality, mammography (n = 3) [24, 33, 35] or chest X-ray (CXR) (n = 4) [22, 25, 26, 34]. Only one study took into account any kind of radiological breast exposure involving chest or shoulders, dosimetry variations with time period, and countries [27].

Considering the seven studies evaluating exposure to only one radiological modality, no association with BC risk was found in three of them [33, 34, 37]. Overall, five of eight studies demonstrated a radio-induced risk of BC for low doses [22, 24–27] (Table 12.1). One study showed a modest but significant link for *BRCA1* mutation carriers exposed to mammograms (adjusted odds ratio [OR][2] 1.08) [24]. Three of the four studies investigating the effects of only CXR supported an association between early X-ray exposure and BC risk [22, 25, 26]. Only one CXR study was associated with an increased BC risk, with a RR of 2.0 (95% confidence interval [CI] 1.2–2.9) before age 40, and a RR of 4.6 (95% CI 2.2–10.9) before age 20 [22]. By comparing the histories of CXR exposures by age-matching with non-mutated women before age 30, the OR for having had a CXR was 1.8 (95% CI 1.2–2.9) [25]. In the third study, any exposure to CXR was associated with a signifi-

[2]The odds ratio (OR) is a metrics for comparing two probabilities of a given event in retrospective studies, being based on measures of past events. The first probability (A) is the odds for exposition among the cases, here the number of BRCA mutation carriers exposed to mammography being diagnosed with BC over the number of BRCA mutation carriers exposed to mammography not diagnosed with BC. The second probability (B) is the odds for exposition among the controls, here the number of BRCA mutation carriers not exposed to mammography being diagnosed with BC over the number of BRCA mutation carriers not exposed to mammography nor diagnosed with BC. The odds ratio is calculated as A/B. In this case, an OR of 1.08 means that the rate of BRCA mutation carriers exposed to mammogram among the women diagnosed with BC (the "cases") was 8% superior to that of the rate of BRCA mutation carriers not exposed to mammogram among the women not diagnosed with BC (the "controls"). Note that when the number of cases is very low, the OR is very close to the RR applied in prospective studies (see note 1).

cantly increased risk of BC, with a hazard ratio (HR)[3] of 4.29 (95% CI 2.09–8.81) [26].

Considering all these studies involving only one radiological modality, designs are heterogeneous and results conflicting, even if most of them demonstrated radio-induced BC effects of low doses. Delivered doses were estimated with a standard attribution per radiological exam in only two of them [22, 27]. Estimated doses to the breast from radiological exams varied depending on time period and countries. These variations were taken into account in only two studies [22, 27]. In addition, survival biases [22, 24, 25, 35] or small numbers of women [24–26, 34] were reported. Regarding the study by Vasily Giannakeas and colleagues [33], we have to consider the following issues: results were not expressed in terms of dose/effect relationship; the cutoff was no mammogram versus one or more mammograms at baseline in order to compare two populations; the cumulative breast dose per woman remains unknown with no gradient of exposure in mGy explored. Of note, stratifying the cumulative doses is an important condition to explore a potential association between exposures and BC.

Finally, a large European retrospective cohort study [27] of *BRCA1* and *BRCA2* mutation carriers took into account any kind of radiological breast exposure involving chest or shoulders, dosimetry variations with time period, and countries. Anouk Pijpe and colleagues [27] considered an entire cohort of 1,993 *BRCA1* or *BRCA2* mutation carriers, 48% of them (n = 919) reported to have had a radiogram somehow involving breast, 33% (n = 649) reported at least a mammogram, and 16% (n = 280) a fluoroscopy. Only a small number of *BRCA1* or *BRCA2* carriers (<5%) were exposed to computed tomography (1.5%, n = 29) and/or other types of medical radiation exposure such as thyroid scintigraphy (2.7%, n = 53). The estimated risk attributable to mammograms only before age 30 was not significant. The overall results including all radiological exposures revealed an increased risk of BC for low doses. A threefold risk of BC was observed for cumulative doses as low as 6.6 mGy per breast (HR 3.16, 95% CI 1.19–8.36) before age 20. Almost a fourfold BC risk for an estimated cumulative breast dose equal to or greater than 17 mGy (HR 3.84, 95% CI 1.67–8.79) was observed before age 30 at exposure, with a dose-response pattern. No association with BC risk was apparent for exposures at age up to 30, but the follow-up of this study was not long enough to detect a potential association for women exposed at ages 30–40. This study highlighted a fourfold BC risk for an estimated cumulative breast dose about 17 mGy for *BRCA1/2* mutation carriers. *Basically, considering the levels of cumulative doses inducing BC, epidemiological cohort data pointed to a threshold (17 mGy) 45 times lower than the threshold found for the adult general population (i.e., about 900 mGy with repeated fluoroscopies).*

More generally, it must be noted that all epidemiological studies include biases in recalling, self-reported procedures and lack of cumulative individual breast dose estimates. While the radiological dose level per exam was estimated and standardized, no study reported an individual prospective dosimetry, which should require a huge implication of physicists for any individual radiological exposure.

12.5 Radiobiological Features

Differences in individual response to IR are now well-established with cumulative evidence for a higher radiosusceptible population even if all inherent molecular and cellular mechanisms are not fully elucidated [38–41]. However, some specific radiobiological assays help quantify undeniable differences according to the dose and the genetic status. Focusing on the consequences of screening mammography, there are concerns for

[3]The hazard ratio (HR) is the probability of an event, i.e., the hazard (the instantaneous event rate), occurring in a group exposed to a variable divided by the hazard (the instantaneous event rate) of the same event occurring in a not exposed control group. It is typically used in the context of time-to-event or survival analysis. Note that while the HR is based on instantaneous risks, the RR is based on cumulative risks. Here, a HR of 4.29 means that the hazard of BC of mutated women exposed to CXR was more than four times higher than that of non-mutated women.

women with hereditary predisposition to BC. The analysis of radiobiologists deals with the following issues.

1. Mammography may concern radiosusceptible subpopulations. However, the recommendations issued by the International Commission on Radiological Protection (ICRP) do not take into account the fact that some individuals may be more susceptible to radio-induced BC [42].
2. The phenomenon of hyper-radiosensitivity (HRS) to low-dose exposure suggests that a low-dose may produce, under certain conditions, biological effects similar to those encountered after 10 times higher doses [43]. This low-dose HRS has never been considered in calculating the radio-induced risk.
3. Standard two-view mammography results in two doses per breast separated by a few minutes. However, the biological effect of a repeated dose is not necessarily equivalent to that observed after the sum of the delivered doses [44]. No repeated dose effect was considered in any calculations of the radio-induced risk.

Notably, these three features of individual response are combined and interplay in a mammogram exam.

12.5.1 Hyper-radiosensitivity to Low-Dose Exposure

To date, immunofluorescence techniques allow for detecting individual DNA damage inside each cell nucleus, particularly when low-dose exposure is used. Several studies revealed the existence of radio-induced DSBs and a lack of DNA repair at low dose [45–48]. This lack of DSB repair was notably shown at doses as low as 1 mGy in non-tumoral and untransformed human cells [44, 49, 50].

The ATM protein kinase is a central component of a signal transduction process that responds to DSB. The contribution of ATM to survival after IR exposure and to cancer avoidance was pointed out [51]. More recently a molecular explanation for the low-dose HRS phenomenon has been proposed [52]. The ATM protein kinase is mainly localized in the cytoplasm as a dimeric and inactive form. The cytoplasmic ATM becomes monomeric and phosphorylated after radiation exposure and quickly migrates to the nucleus where it participates to the DSB recognition and repair. Any delay in ATM nucleo-shuttling is responsible for a lack of DSB recognition, with significant biological and clinical consequences. In the case of low-dose IR, the amount of monomeric ATM forms may be too low to recognize radio-induced DSBs. For some gene mutations and some individual status, this specific HRS phenomenon may be particularly exacerbated: low-dose may induce unrepaired DSBs (then participating to cell lethality) or misrepaired DSBs (then participating to carcinogenesis) [52].

12.5.2 Repetition of Low Doses: a Supra-additive Effect

According to the current ICRP recommendations, the biological effects of two repeated doses are considered to be equivalent to the sum of the effects due to each dose taken separately [42]. However, by simulating a two-view mammogram exposure of ex vivo human mammary epithelium, the exposures "2 + 2 mGy" at 3-min interval provided more deleterious DNA damage than a 2 mGy-exposure but, notably, also more than a single 4 mGy-exposure, whatever the risk status [53]. This effect of low-dose repetition was called *low and repeated dose* (LORD) effect. The LORD effect was shown to be strongly dependent on the time interval separating the two doses but concerns any individual whatever her/his radiosensitivity. If this time is not long enough to allow a complete DSB repair, the second dose may increase the severity of induced DNA damage [44, 54]. In addition to effects on mammary epithelial cells involved in carcinogenesis, some authors described radio-induced effects on the breast stroma. They suggested that repeated low doses disrupt the breast tissue microenvironment with fibroblast modifications, inducing dysregulated cell-cycle and death pathways of epithelial cells, and increased cytokines and growth factors [55] (Fig. 12.1).

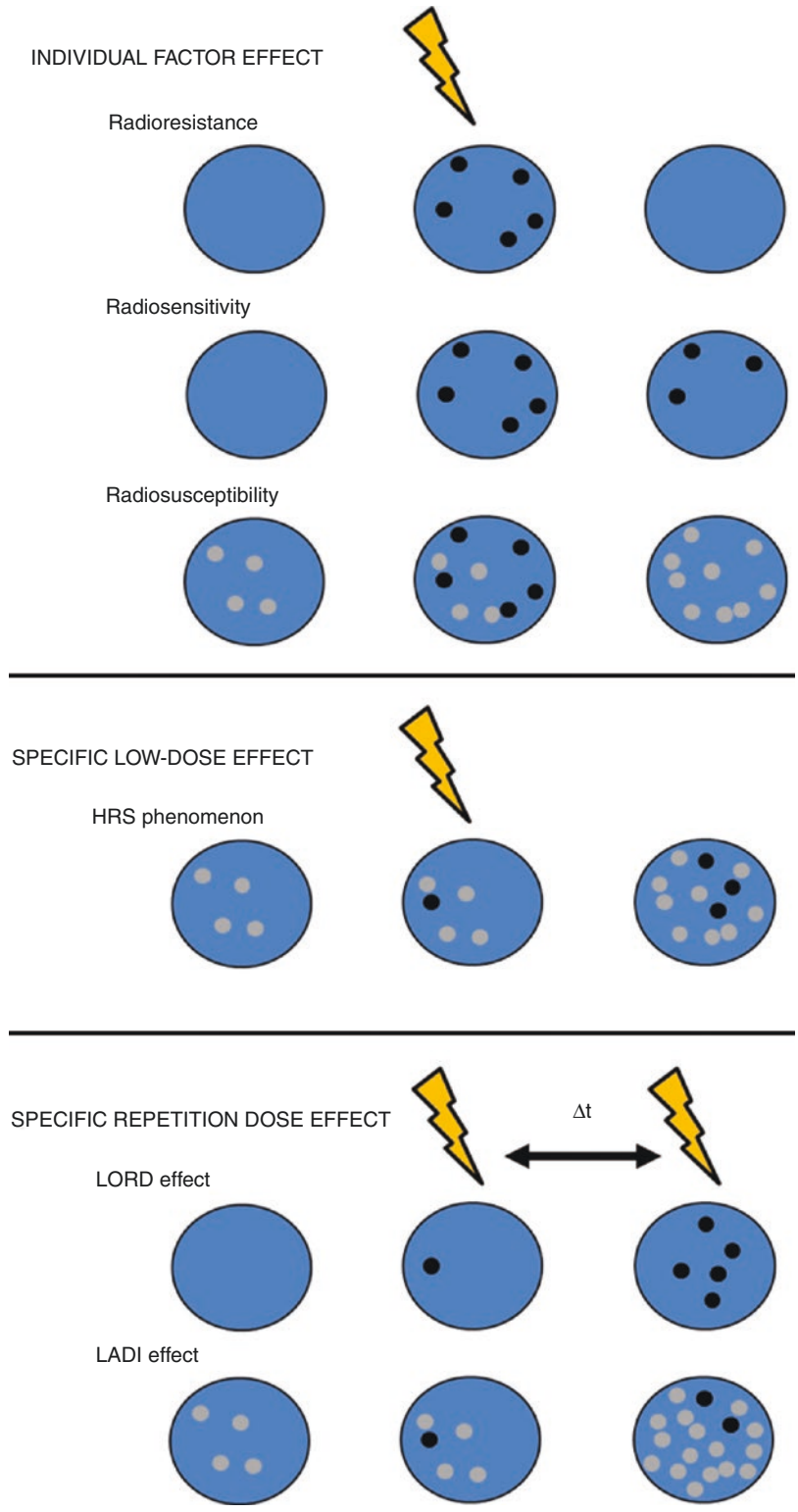

Fig. 12.1 Risk after exposure to low-dose ionizing radiation: graphical representation of factors that modify effects. The cell nuclei are represented as blue disks (the black spots indicate unrepaired DSBs, and the gray spots misrepaired DSBs). The lightning symbol indicates ionizing irradiation. *Radioresistant* individuals repair DSBs and recover to the initial status. *Radiosensitive* individuals are not able to repair all the DSBs, so that a certain amount of DSBs remain unrepaired after irradiation. *Radiosusceptible* individuals have misrepaired DSBs also before a new irradiation; when irradiated, they misrepair the DSBs so that the overall number of DSBs increases. High radiosensitivity (HRS) results in an amplification of the unrepaired and misrepaired DSBs at low-dose exposure, more likely for radiosusceptible patients. Repeated dose effect: with repeated low doses in a few minutes (with a period = Δt), the effect may be not additive but supra-additive (LORD effect). It can concern also radioresistant subjects with low risk of cancer. If patients are radiosusceptible, IR exposures can amplify the hyper-recombination process, which increases the number of misrepaired DSBs (LADI effect)

12.5.3 DNA Repair and Hyper-Recombination

Dominika Slonina and colleagues [56, 57] revealed for the first time that a low-dose HRS may be an individual characteristic. They highlighted, at low-dose, more X-ray-induced DNA damage in human cells (fibroblasts and keratinocytes) from predisposed patients with cancer. Individual susceptibility to low radiation dose has also been confirmed using two mediators of DNA repair, MRE11 and H2AX, as biomarkers for DNA damage [58].

There are at least two major DSB repair pathways in humans. The first one is called *non-homologous end-joining* (NHEJ) and consists in ligating the two broken ends. The recognition of DSB managed by NHEJ is insured by the ATM-dependent phosphorylation of the H2AX histone variant (γH2AX). The second DSB repair pathway is named recombination and consists in cutting some DNA sequences and inserting them in the radio-induced gap like a patch system. A lack of control in recombination called hyper-recombination is a well-identified cause of mis-repaired DSBs, genomic instability and cellular transformation [59].

Numerous tumor suppressor proteins interact with ATM in cytoplasm, notably BRCA1, BRCA2, and p53, all involved in the response to IR. Besides, there is previous evidence that BRCA1 and BRCA2 are required for genome surveillance and repair of several DNA damage types, notably DSB [60, 61]. The HRS phenomenon may therefore be particularly observed in cells from high family risk women, mutated or not [44].

Main indicators of hyper-recombination are a higher spontaneous DNA damage and the so-called *low-dose additional and induced* (LADI) DSB effect.

A significantly higher spontaneous rate of DSBs per nucleus was highlighted in ex vivo breast epithelial cells from high-risk patients [44]. These cells were called highly damaged cells (HDC). This phenomenon may result from a lack of genome maintenance and a high rate of hyper-recombination [44].

After exposures of breast epithelial cells ex vivo in the conditions of mammography, the γH2AX foci rate per cell (which represents the DSB rate in 1:1 manner) systematically increased from 10 min to 24 h. These data suggest a lack of control in the genome maintenance associated with hyper-recombination and the LADI DSB effect [44]. The latter effect was exacerbated in high-risk women.

12.6 Assays to Quantify Radio-Susceptibility

Individual radio-susceptibility can be explored with functional assays in cells (fibroblasts or peripheral blood lymphocytes) exposed to IR [62] with the following rationale: since cancer-prone persons exhibit an abnormal DNA damage response pattern after irradiation [63, 64], persons exhibiting abnormal DNA damage response pattern after irradiation of cells (fibroblasts or peripheral blood lymphocytes) can be considered cancer-prone, especially after exposure to IR.

G_2 assay. The G_2 chromosomal radiosensitivity assay tests the quality of the G_2/M checkpoint of cell cycle arrest after exposure to IR with the rationale that cancer proneness may result from a dysregulation of cell cycle. Ram Parshad and colleagues [65] developed the G_2 assay and concluded that chromatid damage after G_2 phase irradiation of cells from cancer-prone individuals implicates deficiency in DNA repair. Then the G_2 assay was applied in BC patients who exhibited an abnormal response in the rate range of 42–46% in comparison with 6–13% of healthy controls [65–70]. Thus, an abnormal G_2 assay in women can be interpreted as a predisposition to BC. Abnormal G_2 assay results were similar in many other cancer patients [62].

Micronucleus (MN) assay. The MN assay measures residual chromosome fragments after IR exposure with a good correlation with the dose. Thus, an excess of MN which results from an abnormal DNA DSB repair may be linked to radiosusceptibility [64]. MN yields were reported as abnormally high in 31% of BC patients compared with 5% of healthy controls [70].

DNA misrepair assays. Since cancer proneness is associated with misrepaired DNA breaks [71], their detection has been a major challenge over decades. Pulse field gel electrophoresis and southern blotting can be successfully combined, but this technique requires too long a time for routine application [72]. In cell-free plasmid assays [73, 74], the DNA hyper-recombination rate of a circular plasmid incubated in extracts of cells is observed in cancer-prone patients [75]. So far, there is no clear consensus about immunofluorescence biomarkers that may reflect cancer proneness. However in cells derived from cancer-prone diseases the number of MRE11 foci may reflect DSB misrepair [75]. Regarding γH2AX foci observed after exposure to IR, it is clearly established that they sign the presence of unrepaired DNA DSBs and, therefore, the presence of all the other DNA insults associated with IR, which are more frequent than DSBs. Since an excess of γH2AX foci has been observed in cells exposed to IR from high-risk BC women [44] in certain cases, γH2AX foci assays may be useful to predict genomic instability and cancer proneness.

12.7 Conclusions

While radio-induced BC risk obviously depends on age at exposure, it appears that the genetic status of women may also constitute another main parameter. Convergent epidemiological and biological data lead to be highly cautious when considering X-ray effects on the breast tissues of *BRCA1/2* mutation carriers. Radiobiological effects at low X-ray doses using relevant cellular ex vivo models were demonstrated in agreement with epidemiological data. Strong indicators of a hyper-recombination phenomenon were pointed out in cells from high family risk patients, a phenomenon which is linked to genomic instability and cancer proneness. The main results were more spontaneous DNA damage with high damage cells before any experimental irradiation, unrepaired DNA damage in agreement with previous radiobiological data at low doses, higher supra-additive low-dose effect, and additional DNA damage several hours after irradiation.

If the initial responses to IR damage appear to increase linearly with the dose, the processing and repair of the DNA damage from repeated exposures in a short time may be non-linear and possibly supra-additive also depending on individual/genetic status. Consequently, models used for the extrapolation of risk to the low-dose region need to be critically re-examined, notably when evaluating the risk-benefit ratio of mammography and MRI for breast screening.

Epidemiological data about radio-induced BC from low-doses are available only for *BRCA1/2* mutation carriers. Study designs were very heterogeneous. As a consequence, some of them revealed biases. To be admissible, we insist on the absolute necessity of study data stratified by age, age at exposure, and cumulative dose range. In 2012, a strong alert about breast low-dose exposure consequences before age 30 came from a cohort study for *BRCA1/2* mutation carriers [27]. Following the discovery of *BRCA1/2* gene mutations in 1994–1995, cohort data studies to investigate the potential consequences of cumulative and repeated IR after age 30 with longer follow-up are necessary. *While awaiting further advances, indications of any kind of IR exposure involving breast, chest, or shoulders should be systematically justified in BRCA1/2 mutation carriers. In particular, computed tomography including thorax should be avoided as much as possible*. We also suggest carefully justifying any radiological examination including the thorax for the children of a mutation carrier (woman or man) while waiting for the possibility of mutation test at adult age.

With regard to screening, in order to decrease breast exposures in women with elevated genetic-familial risk of BC and taking into account MRI performances, when MRI is performed and mammography is thought to provide additional sensitivity, only one mediolateral oblique projection may be taken, thus halving the exposure [53, 76].

References

1. Antoniou A, Pharoah PD, Narod S et al (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130
2. Ronckers CM, Erdmann CA, Land CE (2005) Radiation and breast cancer: a review of current evidence. Breast Cancer Res 7:21–32
3. Walsh T, King MC (2007) Ten genes for inherited breast cancer. Cancer Cell 11:103–105
4. Cybulski C, Wokołorczyk D, Jakubowska A et al (2011) Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol 29:3747–3752
5. Narod SA (2010) Testing for CHEK2 in the cancer genetics clinic: ready for prime time? Clin Genet 78:1–7
6. Heaney RM, Farrell M, Stokes M, Gorey T, Murray D (2017) Cowden syndrome: serendipitous diagnosis in patients with significant breast disease. case series and literature review. Breast J 23:90–94
7. Bougeard G, Renaux-Petel M, Flaman JM et al (2015) Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 33:2345–2352
8. Swift M, Morrell D, Massey RB, Chase CL (1991) Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med 325:1831–1836
9. Damiola F, Schultz I, Barjhoux L et al (2015) Mutation analysis of PALB2 gene in French breast cancer families. Breast Cancer Res Treat 154:463–471
10. Obermeier K, Sachsenweger J, Friedl TW, Pospiech H, Winqvist R, Wiesmüller L (2016) Heterozygous PALB2 c.1592delT mutation channels DNA double-strand break repair into error-prone pathways in breast cancer patients. Oncogene 35:3796–3806
11. Golmard L, Caux-Moncoutier V, Davy G et al (2013) Germline mutation in the RAD51B gene confers predisposition to breast cancer. BMC Cancer 13:484
12. Mole RH (1978) The sensitivity of the human breast to cancer induction by ionizing radiation. Br J Radiol 51:401–405
13. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr (2002) Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 158:220–235
14. Brenner AV, Preston DL, Sakata R et al (2018) Incidence of breast cancer in the life span study of atomic bomb survivors: 1958–2009. Radiat Res 190:433–444
15. EpiRadBio. Combining epidemiology and radiobiology to assess cancer risks in the breast, lung, thyroid and digestive tract after exposures to ionizing radiation with total doses in the order of 100 mSv or below. European Commission supported project. Coordinator: Jacob P. http://www.epiradbio.eu. Accessed 30 Jun 2020
16. Brenner DJ, Doll R, Goodhead DT et al (2003) Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A 100:13761–13766
17. Land CE (1980) Estimating cancer risks from low doses of ionizing radiation. Science 209:1197–1203
18. Howe GR, McLaughlin J (1996) Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. Radiat Res 145:694–707
19. Doody MM, Lonstein JE, Stovall M, Hacker DG, Luckyanov N, Land CE (2000) Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. Spine (Phila Pa 1976) 25:2052–2063
20. Hoffman DA, Lonstein JE, Morin MM, Visscher W, Harris BS 3rd, Boice JD Jr (1989) Breast cancer in women with scoliosis exposed to multiple diagnostic x rays. J Natl Cancer Inst 81:1307–1312
21. Jansen-van der Weide MC, Greuter MJ, Jansen L, Oosterwijk JC, Pijnappel RM, de Bock GH (2010) Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis. Eur Radiol 20:2547–2556
22. Andrieu N, Easton DF, Chang-Claude J et al (2006) Effect of chest x-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol 24:3361–3366
23. Bernstein JL, Haile RW, Stovall M et al (2010) Radiation exposure, the ATM Gene, and contralateral breast cancer in the women's environmental cancer and radiation epidemiology study. J Natl Cancer Inst 102:475–483
24. Goldfrank D, Chuai S, Bernstein JL et al (2006) Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiol Biomark Prev 15:2311–2313
25. Gronwald J, Pijpe A, Byrski T et al (2008) Early radiation exposures and BRCA1-associated breast cancer in young women from Poland. Breast Cancer Res Treat 112:581–584
26. Lecarpentier J, Noguès C, Mouret-Fourme E et al (2011) Variation in breast cancer risk with mutation position, smoking, alcohol, and chest xray history, in the French National BRCA1/2 carrier cohort (GENEPSO). Breast Cancer Res Treat 130:927–938
27. Pijpe A, Andrieu N, Easton DF et al (2012) Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ 345:e5660
28. Bernstein JL, Teraoka SN, John EM et al (2006) The CHEK2∗1100delC allelic variant and risk of breast cancer: screening results from the Breast Cancer Family Registry. Cancer Epidemiol Biomark Prev 15:348–352

29. Berrington de Gonzalez A, Reeves G (2005) Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. Br J Cancer 93:590–596
30. Berrington de Gonzalez A, Berg CD, Visvanathan K, Robson M (2009) Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. J Natl Cancer Inst 101:205–209
31. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
32. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
33. Giannakeas V, Lubinski J, Gronwald J et al (2014) Mammography screening and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a prospective study. Breast Cancer Res Treat 147:113–118
34. John EM, McGuire V, Thomas D et al (2013) Diagnostic chest X-rays and breast cancer risk before age 50 years for BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomark Prev 22:1547–1556
35. Narod SA, Lubinski J, Ghadirian P et al (2006) Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 7:402–406
36. Colin C, Foray N, Di Leo G, Sardanelli F (2017) Radiation induced breast cancer risk in BRCA mutation carriers from low-dose radiological exposures: a systematic review. Radioprotection 52:231–240
37. Narod SA (2011) Screening of women at high risk for breast cancer. Prev Med 53:127–130
38. Bourguignon M, Foray N, Colin C, Pauwels E (2012) Radiosensibilité individuelle et risque aux faibles doses médicales [Individual radiosensitivity and health risks from exposure to low levels of medical ionizing radiation]. Médecine Nucléaire 36:424–428
39. Foray N, Bourguignon M, Hamada N (2016) Individual response to ionizing radiation. Mutat Res 770:369–386
40. Foray N, Colin C, Bourguignon M (2012) 100 years of individual radiosensitivity: how we have forgotten the evidence. Radiology 264:627–631
41. Pauwels EK, Foray N, Bourguignon MH (2016) Breast cancer induced by X-ray mammography screening? A review based on recent understanding of low-dose radiobiology. Med Princ Pract 25:101–109
42. No authors listed (2007) The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP 37:1–332
43. Joiner MC, Marples B, Lambin P, Short SC, Turesson I (2001) Low-dose hypersensitivity: current status and possible mechanisms. Int J Radiat Oncol Biol Phys 49:379–389
44. Colin C, Devic C, Noël A et al (2011) DNA double-strand breaks induced by mammographic screening procedures in human mammary epithelial cells. Int J Radiat Biol 87:1103–1112
45. Geisel D, Heverhagen JT, Kalinowski M, Wagner HJ (2008) DNA double-strand breaks after percutaneous transluminal angioplasty. Radiology 248:852–829
46. Kuefner MA, Grudzenski S, Hamann J et al (2010) Effect of CT scan protocols on x-ray-induced DNA double-strand breaks in blood lymphocytes of patients undergoing coronary CT angiography. Eur Radiol 20:2917–2924
47. Kuefner MA, Grudzenski S, Schwab SA et al (2009) DNA double-strand breaks and their repair in blood lymphocytes of patients undergoing angiographic procedures. Investig Radiol 44:440–446
48. Lobrich M, Rief N, Kühne M et al (2005) In vivo formation and repair of DNA double-strand breaks after computed tomography examinations. Proc Natl Acad Sci U S A 102:8984–8989
49. Grudzenski S, Raths A, Conrad S, Rübe CE, Löbrich M (2010) Inducible response required for repair of low-dose radiation damage in human fibroblasts. Proc Natl Acad Sci U S A 107:14205–14210
50. Rothkamm K, Lobrich M (2003) Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. Proc Natl Acad Sci U S A 100:5057–5062
51. Lobrich M, Jeggo PA (2005) The two edges of the ATM sword: co-operation between repair and checkpoint functions. Radiother Oncol 76:112–118
52. Bodgi L, Foray N (2016) The nucleo-shuttling of the ATM protein as a basis for a novel theory of radiation response: resolution of the linear-quadratic model. Int J Radiat Biol 92:117–1131
53. Colin C, Foray N (2012) DNA damage induced by mammography in high family risk patients: only one single view in screening. Breast 21:409–410
54. Viau M, Perez AF, Bodgi L et al (2016) Repeated radiation dose effect and DNA repair: Importance of the individual factor and the time interval between the doses. Cancer Radiother 20:217–225
55. Tsai KK, Chuang EY, Little JB, Yuan ZM et al (2005) Cellular mechanisms for low-dose ionizing radiation-induced perturbation of the breast tissue microenvironment. Cancer Res 65:6734–6744
56. Słonina D, Biesaga B, Urbanski K, Kojs Z, Waligórski M (2006) Evidence of low-dose hyper-radiosensitivity in normal cells of cervix cancer patients? Radiat Prot Dosim 122:282–284
57. Slonina D, Biesaga B, Urbański K, Kojs Z (2007) Low-dose radiation response of primary keratinocytes and fibroblasts from patients with cervix cancer. Radiat Res 167:251–259
58. Colin C, Granzotto A, Devic C et al (2011) MRE11 and H2AX biomarkers in the response to low-dose exposure: balance between individual susceptibility to radiosensitivity and to genomic instability. Int J Low Radiat 8:96–106

59. Gaillard H, Garcia-Muse T, Aguilera A (2015) Replication stress and cancer. Nat Rev Cancer 15:276–289
60. Powell SN, Kachnic LA (2003) Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. Oncogene 22:5784–5791
61. Venkitaraman AR (2002) Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 108:171–182
62. Health Protection Agency, United Kingdom. Advisory Group on Ionising Radiation (2013) Human Radiosensitivity (RCE-21). Accessed 30 Jun 2020. http://webarchive.nationalarchives.gov.uk/20150318203945/. http://legacytools.hpa.org.uk/Publications/Radiation/DocumentsOfTheHPA/RCE21HumanRadiosensitivity/. Accessed 30 Jun 2020
63. Rothfuss A, Schütz P, Bochum S et al (2000) Induced micronucleus frequencies in peripheral lymphocytes as a screening test for carriers of a BRCA1 mutation in breast cancer families. Cancer Res 60:390–394
64. Shahidi M, Mozdarani H, Bryant PE (2007) Radiation sensitivity of leukocytes from healthy individuals and breast cancer patients as measured by the alkaline and neutral comet assay. Cancer Lett 257:263–273
65. Parshad R, Sanford KK, Jones GM (1983) Chromatid damage after G2 phase X-irradiation of cells from cancer-prone individuals implicates deficiency in DNA repair. Proc Natl Acad Sci U S A 80:5612–5616
66. Baeyens A, Van Den Broecke R, Makar A, Thierens H, De Ridder L, Vral A (2005) Chromosomal radiosensitivity in breast cancer patients: influence of age of onset of the disease. Oncol Rep 13:347–353
67. Riches AC, Bryant PE, Steel CM et al (2001) Chromosomal radiosensitivity in G2-phase lymphocytes identifies breast cancer patients with distinctive tumour characteristics. Br J Cancer 85:1157–1161
68. Sanford KK, Parshad R, Gantt R, Tarone RE, Jones GM, Price FM (1989) Factors affecting and significance of G2 chromatin radiosensitivity in predisposition to cancer. Int J Radiat Biol 55:963–981
69. Scott D (2004) Chromosomal radiosensitivity and low penetrance predisposition to cancer. Cytogenet Genome Res 104:365–370
70. Scott D, Barber JB, Levine EL, Burrill W, Roberts SA (1998) Radiation-induced micronucleus induction in lymphocytes identifies a high frequency of radiosensitive cases among breast cancer patients: a test for predisposition? Br J Cancer 77:614–620
71. Jeggo PA, Lobrich M (2007) DNA double-strand breaks: their cellular and clinical impact? Oncogene 26:7717–7719
72. Lobrich M, Rydberg B, Cooper PK (1995) Repair of x-ray-induced DNA double-strand breaks in specific Not I restriction fragments in human fibroblasts: joining of correct and incorrect ends. Proc Natl Acad Sci U S A 92:12050–12054
73. Meyn MS (1993) High spontaneous intrachromosomal recombination rates in ataxia-telangiectasia. Science 260:1327–1330
74. Thacker J (1989) The use of integrating DNA vectors to analyse the molecular defects in ionising radiation-sensitive mutants of mammalian cells including ataxia telangiectasia. Mutat Res 220:187–204
75. Joubert A, Zimmerman KM, Bencokova Z et al (2008) DNA double-strand break repair defects in syndromes associated with acute radiation response: at least two different assays to predict intrinsic radiosensitivity? Int J Radiat Biol 84:107–125
76. Colin C, de Vathaire F, Noël A et al (2012) Updated relevance of mammographic screening modalities in women previously treated with chest irradiation for Hodgkin disease. Radiology 265:669–676

13 Impact of MRI Screening on High-Risk Patient Outcome

Franca Podo, Ellen Warner, Filippo Santoro, and Francesco Sardanelli

Abbreviations

BCS-OS	Breast cancer–specific overall survival
BCT	Breast conserving therapy
CPM	Contralateral preventive mastectomy
DCIS	Ductal carcinoma in situ
DDFS	Distant disease–free survival
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HIBCRIT-1	High Breast Cancer Risk Italian 1 (study)
HR	Hazard ratio
IDC	Invasive ductal cancer
LCIS	Lobular carcinoma *in situ*
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
PR	Progesterone receptor
RCT	Randomized controlled trial
SFH	Strong family history of breast or ovarian cancer
TNBCs	Triple negative breast cancers

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13.1 Introduction

This chapter is dedicated to the crucial point concerning the impact of contrast-enhanced magnetic resonance imaging (MRI) screening on the clinical outcome of women at high risk of breast cancer. We would like to answer *yes* unequivocally to the question: using breast MRI for screening, are we able to save lives of *BRCA* mutation carriers and other women at high risk? As we will see, the answer is not so straightforward. Important methodological issues underlie this discussion, including the level of evidence

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needed for recommending annual breast MRI for screening these women.

We start with an apparently trivial discussion of the use of the terms *screening* or *surveillance* in this context, then defining why the evidence-based recommendations are different for *screening* tests as compared to so-called *diagnostic* tests. After explaining the absence of randomized controlled trials (RCTs) evaluating breast MRI screening of high-risk women, we summarize the results of non-randomized studies that have reported on patient outcome. Critical issues in the evaluation of high-risk patient outcome are discussed. Finally, we illustrate the survival analysis of triple-negative versus non-triple negative breast cancers in the HIBCRIT-1 study. We conclude highlighting unresolved issues for further research.

13.2 *Screening* or *Surveillance*?

Words are important, in science as well as in day-to-day life. The Emperor Justinian said that *Nomina sunt consequentia rerum*, i.e., *names are a consequence of things* [1]. The use of breast MRI in asymptomatic high-risk women with the aim of earlier cancer detection than that attainable with mammography and ultrasonography has been described in the literature either with the term *screening* or the term *surveillance*. Is there any difference between them?

Indeed, asking PubMed [2] for the number of published papers for "MRI + BRCA + screening," "MRI + BRCA + surveillance," "MRI + BRCA + screening OR MRI + BRCA + surveillance," and "MRI + BRCA + screening AND MRI + BRCA + surveillance," you find 127, 61, 134, and 54 papers, respectively. These figures indicate a preference for the term screening but an overlap does exist. Notably, the two terms do not have exactly the same meaning. According to the *Oxford Dictionary* [3], the definition of *screening* (in the healthcare context) is *to check, test, examine, investigate, scan*, and that of *surveillance* is *observation, scrutiny, watch, view, inspection, monitoring*. According to the MedlinePlus Medical Dictionary [4], *to screen* means *to test or examine for the presence of something (as a disease)*, while *surveillance* indicates *close and continuous observation or testing*. Notably, both terms refer to asymptomatic populations. In the case of symptomatic subjects, we should choose the term *diagnostic test* instead of *screening or surveillance test*.

Bearing in mind the classical model of periodic screening mammography for secondary prevention of breast cancer in the general population of women, we can perceive a difference between the two terms. We would not refer to periodic mammography in an average-risk female population as a *surveillance* program. However, the term *surveillance* could be used when a more intensive program than "simple" screening is planned. This distinction is related to a high pretest disease probability, i.e., to a higher disease prevalence in the tested population. In the case of women with a previous breast cancer history, the term *surveillance* is generally used by convention. However, in the case of unaffected women at much higher than average risk of developing breast cancer such as *BRCA* mutation carriers, the distinction between these terms is a matter for debate. On the one hand, a higher disease prevalence justifies a more intensive program (which we could name *surveillance*). On the other hand, differences in the intensity of testing do not change the intent of the program, which is aimed at obtaining earlier diagnosis of a disease in asymptomatic subjects. In this chapter, we will arbitrarily use the term *screening* to refer to both previously affected and unaffected women at much greater than average risk.

13.3 Diagnostic Tests, Screening Tests, Overdiagnosis, and Screening Biases

Relevant differences do exist in the application of tests in the clinical (diagnostic) context versus the screening context [5]. These differences are listed in Table 13.1. The majority of them can be arrived at intuitively. It is easy to understand that differences in disease prevalence result in different predictive values: all other things being equal, if the proportion of subjects affected with the disease is higher (clinical context), the prob-

Table 13.1 Differences in the application of tests in the clinical or screening context

Characteristic	Clinical (diagnostic) context (symptomatic population)	Screening context (asymptomatic population)
Disease prevalence	Higher	Lower
Positive predictive value (PPV)[a]	Higher	Lower
Negative predictive value (NPV)[b]	Lower	Higher
Disease stage	Often more advanced	Often initial
Sensitivity[c]	Higher	Lower
Specificity[d]	Lower	Higher
Overdiagnosis	Highly improbable	Unavoidable
Overtreatment	Possible	Mainly due to overdiagnosis

[a]PPV = true positives / (true positives + false positives)
[b]NPV = true negatives / (true negatives + false negatives)
[c]Sensitivity = true positives / (true positives + false negatives)
[d]Specificity = true negatives / (true negatives + false positives)

ability of positives is higher, and that of negatives is lower. The reverse would be expected, if the proportion of subjects affected with the disease is lower (screening context). The impact of disease stage on sensitivity is also simple: it is easier to detect larger than smaller cancers. In addition, the relatively higher specificity in the screening context is due to a strong effect of the numerator on the ratio which generates this index. Due to the low disease prevalence (notably, also in a high-risk population), the large majority of the screened subjects are negative, so the largest fraction of subjects will be true negative. As a consequence, the specificity will be high, even in the presence of a relatively high absolute number of false positives. This is the reason for which, in the screening context, the weight of false positives is better evaluated using the positive predictive value (PPV) than using the specificity.

The bottom lines of Table 13.1 introduce two crucial issues: overdiagnosis and overtreatment. *Overdiagnosis* occurs when *a diagnosis is correctly performed according to current professional standards but the disease diagnosed would not have been detected during the patient's lifetime in the absence of screening*. It is caused by a variable combination of the two following phenomena [6]:

1. Sensitive tests that identify abnormalities that are indolent, non-progressive, or regressive
2. Expanded definitions of disease

The first of these two occurrences is what we could define more technically *overdetection* and typically, for imaging tests, results from the radiological work. The basic underlying issue is the variable biological nature of (breast) cancers, implying highly different levels of aggressiveness in the presence of similar characteristics at histopathology. The second occurrence calls into question the interpretation by the pathologist of the tissue needle sample performed under image-guidance by the radiologist. This distinction between detection and diagnosis implies a distinction between *overdetection* and *overdiagnosis* [7], the latter to be considered in the light of the suboptimal reproducibility of pathological reporting of breast needle biopsies, especially in the case of lesions with atypia, such as *atypical ductal hyperplasia* and *ductal carcinoma in situ* [7–9].

For diagnostic tests, the probability of overdiagnosis is negligible. A palpable breast lesion (or a lesion-inducing nipple retraction or bloody discharge), if diagnosed to be malignant, has a low probability of being clinically irrelevant, having already induced symptoms. There is a very low residual probability that an incidental finding unrelated to the symptomatic (benign or malignant) lesion may be diagnosed by the clinical test performed, leading to overdiagnosis and overtreatment.

This justifies the evidence-based approach for decision making about performing diagnostic tests. In the clinical context (*diagnosis*), a test should be preferred on the basis of sensitivity and specificity studies conducted in consecutive patients with a reliable and systematically applied reference standard, using well-defined

clinical decisions rules [10]. Homogeneous meta-analyses of high-quality studies and multicenter studies generate the highest level of evidence. The intra-individual comparative study design is a powerful tool for choosing between an old and a new test. No RCTs are required.

This is not the case for screening tests. The risk of *overdiagnosis* is one of the reasons that make the introduction of new screening tests more evidence-demanding than that of new diagnostic tests. Suppose one has a new test providing a large increase in the detection rate of a disease as compared to an old test. Evidence-based medicine tells us that the new test cannot be adopted as a generalized screening tool before the demonstration of a clinically relevant and statistically significant impact on patient outcome, by means of RCTs and their homogeneous meta-analyses [10]. *An advantage in terms of sensitivity and specificity only is not enough*. According to the European Council Recommendation on cancer screening [11], evidence from RCTs is needed before introducing new screening tools.

In the last years, we faced this situation when considering digital breast tomosynthesis for breast cancer screening of average-risk women. Indeed, tomosynthesis was demonstrated to provide, when compared to two-dimensional digital mammography, not only an increase in cancer detection rate ranging from 0.5 to 2.7 per thousand screened women but also a reduction in the false-positive recall rate ranging from 0.8 to 3.6 per 100 screened women [12]. However, this is not enough for routine usage of tomosynthesis for breast cancer screening. In fact, we do not know what proportion of the additional cancers detected are *indolent or non-progressive*, determining the rate of overdiagnosis and overtreatment. Position papers by the European Society of Breast Imaging [13] and Italian breast imaging and screening bodies [14] adopted a cautious approach affirming the necessity to wait for more evidence before the generalized adoption of tomosynthesis for breast cancer screening. Taking into account the relatively long time and the complexity of studies needed to provide an accurate estimate of the rate of overdiagnosis of a new test [15], one solution is to adopt a proxy of this estimate, i.e., the interval cancer rate or the rate of screen-detected T2-stage tumors. If tomosynthesis will be shown to consistently reduce these indices, the probability that the increased detection rate is mainly determined by overdiagnosis will be predicted to be low. Thus, we have to wait at least for this demonstration before adopting tomosynthesis for breast cancer screening [13, 14].

We should place this issue in the context of the general epidemiological theory of screening. Overdiagnosis is an extreme case of *length bias* (Fig. 13.1). This bias has to be taken into account when analyzing the results of a screening program. For instance, the effect on survival should take into account both screen-detected

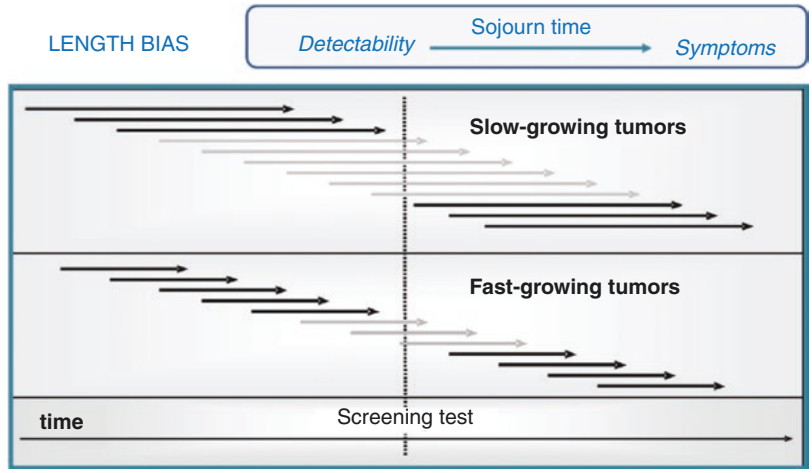

Fig. 13.1 Scheme showing that a screening test has higher probability to detect slow-growing tumors (with a longer sojourn time) than fast-growing tumors (with a shorter sojourn time). When the sojourn time exceeds the woman's life span (the woman will die for concurrent death causes), the detected cancer is overdiagnosed. In other words, *overdiagnosis is an extreme case of length bias*

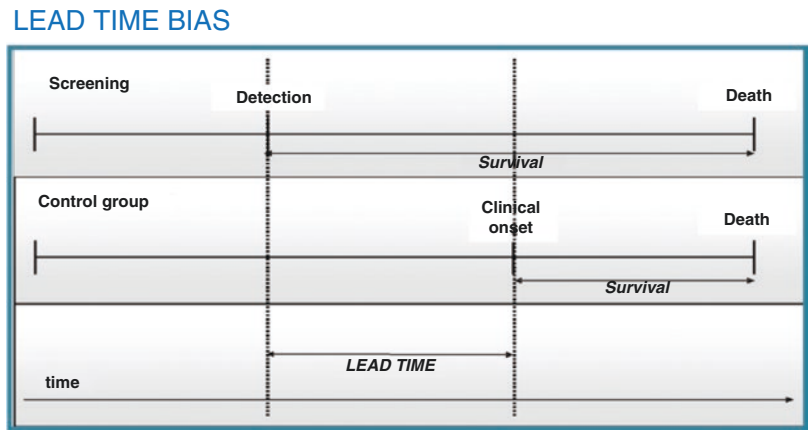

Fig. 13.2 Scheme showing the effect of the *lead time bias* in terms of false prolonged survival of women having screen-detected cancers. If the screening has the only effect of anticipating the diagnosis but no real effect on survival, this anticipation, i.e. the lead time, is the difference between the apparent survival from detection to death of the woman who had a screen-detected cancer and the survival of an equivalent case in the non-screening control group

and interval cancers, because the screen-detected cancers could show a more favorable outcome due to their intrinsically longer sojourn time. However, when a screening program has to be evaluated in terms of its effect on survival rates, another bias should be considered, the *lead time bias* (Fig. 13.2). RCTs are the best way to address all these problems.

13.4 The Lack of RCTs Evaluating Breast MRI for High-Risk Screening

As illustrated in the previous paragraphs, the main pathways to acquiring the best evidence for the effectiveness of a screening test are the classical RCTs. The Working Group of the International Agency for Cancer Research summarized the results of RCTs that still inform the use of screening mammography: those studies showed in average that women from 50 to 69 years of age *who attend* biennial screening have a 40% reduction in breast cancer mortality, while considering all women who are invited (attending and non-attending the screening) the reduction in mortality is 23% [16]. With RCTs we could analyze overdiagnosis by evaluating what happens after stopping the screening in the two arms. If a screening regimen works well, the anticipated diagnosis should result in a corresponding drop in incidence, at least temporarily, when compared to the non-screened arm. If there has also been some overdiagnosis, the drop will be smaller, not corresponding to the incidence peak due to the screen detection [15]. Of note, overdiagnosis by screening mammography is still a hotly debated matter, its estimated frequency depending on: the definition of overdiagnosis used for calculations, methodological approaches, analytical adjustments, epidemiological assumptions such as underlying incidence trends, type of studies considered, and true difference in overdiagnosis due to different populations and screening sensitivity [15]. Overdiagnosis can be estimated using different approaches. The type of methodology has a dramatic effect on overdiagnosis estimation: from 10% to 22% for RCTs, 1% to 19% for cohort studies, 1% to 76% for ecological studies, and 0.3% to 32% for modeling studies [17].

As a matter of fact, we do not have any RCTs evaluating breast MRI for high-risk screening. Why not? Here we face a real-life phenomenon not so rare in the recent history of medicine, known as the Buxton's law: "It is always too early [for rigorous evaluation] until suddenly it's too late" [18, 19]. Here we can substitute "RCT" for "rigorous evaluation": *it is always too early for a RCT, until suddenly it's too late*.

We do not live in a perfect world where all is planned and the speeds of social processes (including advancement of science and medical research) are synchronized. Like in biological evolution, the real life is much more chaotic and partially unpredictable. Thus, while in 1986 we had the first preliminary demonstration of the high potential sensitivity of contrast-enhanced breast MRI [20], more than 10 years were necessary for an adequate development of the technique (dedicated coils, sequences, protocols, etc.) to a stage that could allow for its usage for a screening study. As we explain in Chap. 2 of this book, enthusiasm for MRI screening was also initially blunted by fear of the so-called "low specificity" of breast MRI. Of note, the interpretation of dynamic curves was standardized in the late 1990s [21] while MRI descriptors and diagnostic categories in the Breast Imaging Reporting and Data System were firstly introduced in 2003 [22]. Important for a breast MRI screening application, systems for MR-guided breast biopsy were firstly available in 1994 [23] and validated by a multicenter trial only in 2002 [24].

The first study investigating the value of MRI in women at increased risk of breast cancer was published by Christiane Kuhl et al. in 2000 [25]. Among the 105 women for whom at least a 1-year follow-up was available, the difference in sensitivity between MRI (100%) and mammography combined with ultrasonography (44%) was over 56%. As illustrated in Chap. 11 of this book, during the early 2000s and thereafter, many prospective studies on high-risk women confirmed this large gap in sensitivity. Twelve years after the Kuhl's seminal paper, Wendy Berg et al. [26] got exactly the same difference in a large subgroup of women at increased risk who had supplemental MRI after mammography and ultrasonography ($n = 612$); the MRI sensitivity was 100% (16/16), that of mammography plus ultrasonography only 44% (7/16), the same 56% difference in sensitivity obtained by Kuhl et al. in 2000. Berg and coworkers summarized the results of their study using the interesting metrics of the number of screens needed to detect one cancer: 127 for mammography, 234 for supplemental ultrasonography, and only 68 for MRI after negative mammography and ultrasonography [26]. Considering the body of evidence accumulated in the last 15 years, we can refer to the results of the individual-patient data meta-analysis [27], including a total of 1,951 *BRCA* mutation carriers and 184 cancers: the absolute difference in sensitivity between mammography (36%) and MRI (89%) was 53%.

All these results made planning an RCT enrolling high-risk women such as *BRCA* mutation carriers impossible, if the plan had to be a control arm randomized to only conventional imaging (mammography/ultrasonography) and an interventional arm randomized to MRI (alone or as an adjunct to conventional imaging).

In addition, we have to consider the high speed of cancer growth in high-risk women. In *BRCA* mutation carriers, the mean doubling time has been estimated to be 28 days in women under 40 years of age, 68 days between age 41 and 50, and 81 days for women over age 50, compared to 83, 121, and 173 days, respectively, in non-mutated high-risk women [28]. For comparison, the mean doubling time has been recently estimated to be 191 days in women between 50 and 74 years based on the screening program in Nijmegen, the Netherlands [29], without significant variations for age subgroups.

This means that a missed cancer in a *BRCA* mutation carrier under age 40 would double its volume with a six times higher growth velocity as compared to a missed cancer over 50 in the general female population. The theoretical consequence is that in *BRCA* mutation carriers overdiagnosis, if any, is highly improbable. Also in non-mutated high-risk women, at least up to 50 years of age, the growth velocity is substantially faster than that in the general population.

In this context, a loss in sensitivity of about 50% in women randomized to not receive screening MRI but only conventional imaging is not acceptable. No researchers proposed such a RCT. No Ethical Committee would have approved a similar protocol. If ever approved, informed consent to be randomized would have been very difficult to acquire. Thus, we do not have such RCTs. We will not have them in future. Other means had to be used to get outcome evidence for MRI screening in high-risk women.

13.5 Studies on High-Risk Patient Outcome, Focusing on *BRCA1* Mutation Carriers

Screening that includes MRI has been proven to detect earlier stage breast cancers in asymptomatic high-risk women when compared to screening strategies lacking MRI. This conclusion can be indirectly drawn looking at the small size of cancers detected only by MRI in many prospective studies [30–40]. In the absence of RCTs, other investigations are needed to clarify the impact of MRI on clinical outcome of patients belonging to different risk categories [36, 41–43]. The breast cancer–specific overall survival (BCS-OS) and distant disease–free survival (DDFS) rates may in fact critically depend on a variety of factors such as genomic signatures, specific prognostic factors, and treatment options. Indeed, treatment is a variable dramatically affecting outcome, which has also changed over time and varied across different countries. We should consider differences in the rates of unilateral mastectomy versus breast conserving therapy (BCT) with or without radiation therapy, versus bilateral mastectomy (including contralateral preventive mastectomy (CPM) after unilateral cancer) and the timing and uptake of prophylactic oophorectomy, as well as the continuously evolving hormonal and chemotherapy protocols.

A retrospective analysis of data regarding unscreened patients diagnosed with primary invasive breast cancer between 1980 and 2001 within families with an identified deleterious *BRCA1* mutation ascertained at the Erasmus–Daniel den Hood Cancer Center (Rotterdam) reported a mean tumor size of 24 mm, a 5-year BCS-OS rate as low as 73% and a 5-year DDFS rate of 68% [44].

Several multivariate analyses [45–49] found breast cancers in *BRCA1* mutation carriers to more commonly be histologic grade 3 and negative for estrogen receptor (ER) and progesterone receptor (PR) expression compared to sporadic cancers (Table 13.2). Tumor size was a strong prognostic factor not only for *BRCA1*-associated but also for age-matched sporadic breast cancers. However, unlike sporadic cases, the prognostic impact of positive nodal status in *BRCA1*-associated breast cancers was significant only for four or more positive nodes [44]. Furthermore, the incidence of contralateral breast cancer was significantly higher for patients with *BRCA1*-associated cancers than for age-matched patients with sporadic cancers (univariate hazard ratio [HR] 4.98).

The non-randomized prospective MRI-including Dutch MRISC screening study [36], carried out from 1999 to 2006 on a combined cohort of women with higher than 15% cumulative lifetime risk, showed that the sensitivity of MRI (71%) markedly exceeded that of mammography (41%) and clinical breast examination (21%). Notably, 43% of breast cancers in this cohort were detected by MRI only. The median tumor size of the detected invasive cancers was largest for the interval cancers (16.5 mm) and smallest (9.0 mm) for cancers detected by MRI only. Regarding patient outcome, the 6-year BCS-OS rate estimated for the combined subgroup of invasive *BRCA1*- and *BRCA2*-associated cancers was 93%, a value substantially higher than that reported for BRCA1 patients in the retrospective Rotterdam study of unscreened women (5-year BCS-OS of 73%) [44]. An update of the MRISC study (last date of enrollment, August 2007; last date of follow-up, August 2013) with a 9-year median follow-up of 93 breast cancer patients (including 33 *BRCA1* and 18 *BRCA2* mutation carriers) reported that 9% of patients (8/93, including 4 *BRCA1* and 1 *BRCA2*) had developed distant metastasis and 8% (7/93, including 3 *BRCA1* and 1 *BRCA2*) had died of breast cancer [50]. Compared with these MRI-screened patients, a control group of 93 patients who received no screening if younger than 50 years of age and bi-annual mammography if 50 years or older had tumors of significantly larger size (48% versus 13% with pT > T2) and a significantly higher rate of positive nodal status (56% versus 31%). Regarding treatment, the control group of unscreened patients had significantly higher rates of breast conserving surgery (47% versus 29%) and adjuvant chemotherapy (77% versus 39%). Compared to unscreened controls, the MRI-screened patients showed lower

Table 13.2 Clinical features and survival of invasive BRCA-associated breast cancers detected in nonrandomized prospective MRI-including screening studies on asymptomatic high-risk women, compared with a retrospective study on unscreened patients with BRCA1 mutation

STUDY TYPE		**RETROSPECTIVE STUDY**			**MRI-INCLUDING SCREENING STUDIES**							
TARGET POPULATION		BRCA1 mutation carriers diagnosed with primary invasive breast cancer, compared with age-matched sporadic controls			Asymptomatic women with proven BRCA mutation found affected with invasive breast cancer							
ORGANIZER/STUDY NAME		***Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands***			***Dutch MRI Screening Study MRISC***			***University of Toronto, Ontario, Canada***			***Norway Surveillance Program***	***HIBCRIT-1 Study***
STUDY TIME FRAME		1980–2001 [44]			1999–2006 [36] and 1999–2007 [50]			1997–2009 [41]			2001–2010 [42]	2000–2008 [35, 38, 43]
PATIENTS	**Subgroups**	**Sporadic**	**BRCA1**	***p***	**BRCA1**	**BRCA2**	***p***	**BRCA1**	**BRCA2**	***p***	**BRCA1**	**BRCA1**
	Number	*N* = 446	*N* = 170		*N* = 28	*N* = 13		*N* = 23	*N* = 14		*N* = 63	*N* = 20
PROGNOSTIC FACTORS												
Mean age at diagnosis (range)		41 years (23–82)	42 years (23–82)		NR	NR		NR	NR		49 years (25–74)	49 years (36–64)
Mean tumor size (range)		25.2 mm (4–98)	23.9 mm (1–98)	0.14	NR	NR		11.0 mm (3–30)	8.9 mm (4–20)	0.29	14.3 mm (2–45)[a]	13.2 mm (5–22)
T-status < T2		43% (194/446)	48% (81/170)	0.41	64% (18/28)	92% (12/13)	0.005	NR	NR		44% (30/68)[a]	90% (18/20)
Pathologic subtype	Ductal	88% (394/446)	86% (146/170)		86% (24/28)	77% (10/13)	0.52	NR	NR		NR	90% (18/20)[b]
	Lobular	9% (40/446)	3% (6/170)		*N* = 0	8% (1/13)		NR	NR		NR	5% (1/20)[c]
	Medullary	2% (9/446)	7% (12/170)		11% (3/28)	15% (2/13)		NR	NR		NR	5% (1/20)
	Others/unknown	1% (3/446)	4% (6/170)		4% (1/28)	*N* = 0		NR	NR		NR	*N* = 0
Histologic grade	G1	5% (21/446)	1% (1/170)	0.002	4% (1/27)	18% (2/11)	0.52	4% (1/23)	14% (2/14)	0.12	5% (3/60)	*N* = 0
	G2	17% (76/446)	7% (12/170)		18% (5/27)	27% (3/11)		43% (10/23)	64% (9/14)		27% (16/60)	25% (5/20)
	G3	45% (200/446)	55% (93/170)		78% (21/27)	55% (6/11)		52% (12/23)	21% (3/14)		68% (41/60)	75% (15/20)
	Unknown	33% (149/446)	37% (63/170)		*N* = 1	*N* = 2		*N* = 0	*N* = 0		*N* = 3	*N* = 0

Receptor expression	***ER*** negative	24% (108/446)	45% (77/170)	<0.001	82% (23/28)	36% (4/11)	0.02	65% (15/23)	14% (2/14)	0.006	76% (45/59)	80% (16/20)
	ER positive	48% (216/446)	17% (29/170)		18% (5/28)	64% (7/11)		35% (8/23)	86% (12/14)		24% (14/59)	20% (4/20)
	ER unknown	27% (122/446)	38% (64/170)		*N* = 0	*N* = 2		*N* = 0	*N* = 0		*N* = 4	*N* = 0
	PR negative	19% (86/446)	38% (64/170)	<0.001	82% (23/28)	42% (5/12)	0.02	78% (18/23)	29% (4/14)	0.005	NR	85% (17/20)
	PR positive	35% (158/446)	18% (31/170)		18% (5/28)	58% (7/12)		22% (5/23)	71% (10/14)		NR	15% (3/20)
	PR unknown	45% (202/446)	44% (75/170)		*N* = 0	*N* = 1		*N* = 0	*N* = 0		NR	*N* = 0
	HER2 negative	NR	NR		NR	NR		96% (22/23)	93% (13/14)	1	90% (45/50)	70% (14/20)
	HER2 positive	NR	NR		NR	NR		4% (1/23)	7% (1/14)		10% (5/50)	30% (6/20)
	HER2 unknown	NR	NR		NR	NR		*N* = 0	*N* = 0		*N* = 13	*N* = 0
Nodal status	Negative	45% (201/446)	61% (104/170)	<0.001	64% (18/28)	67% (8/12)		87% (20/23)	93% (13/14)		80% (48/60)	90% (18/20)
	Positive	50% (223/446)	36% (61/170)		36% (10/28)	33% (4/12)		13% (3/23)	7% (1/14)		20% (12/60)	10% (2/20)
	Unknown	5% (22/446)	3% (5/170)		*N* = 0	*N* = 1		*N* = 0	*N* = 0		*N* = 3	*N* = 0
TREATMENT												
Primary surgery	None/biopsy only	4% (15/446)	3% (5/170)	0.15	NR	NR		NR	NR		NR	*N* = 0
	BCT	54% (241/446)	46% (76/170)		NR	NR		NR	NR		NR	35% (7/20)
	Mastectomy	42% (189/446)	51% (85/170)		NR	NR		NR	NR		NR	65% (13/20)
Prophylactic surgery	CPM	1.5% (7/446)	22% (37/170)	<0.001	NR	NR		NR	NR		NR	40% (8/20)
Adjuvant chemotherapy	Yes	48% (208/446)	51% (84/170)	0.55	NR	NR		61% (14/23)	21% (3/14)	0.04	65% (41/63)	85% (17/20)
	No	NR	NR		NR	NR		39% (9/23)	79% (11/14)		NR	10% (2/20)
	Unknown	NR	NR		NR	NR		*N* = 0	*N* = 0		NR	*N* = 1

(continued)

Table 13.2 (continued)

STUDY TYPE		RETROSPECTIVE STUDY			MRI-INCLUDING SCREENING STUDIES							
ORGANIZER/STUDY NAME		*Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*			*Dutch MRI Screening Study MRISC*			*University of Toronto, Ontario, Canada*			*Norway Surveillance Program*	*HIBCRIT-1 Study*
PATIENTS	Subgroups	Sporadic	BRCA1	*p*	BRCA1	BRCA2	*p*	BRCA1	BRCA2	*p*	BRCA1	BRCA1
	Number	*N* = 446	*N* = 170		*N* = 28	*N* = 13		*N* = 23	*N* = 14		*N* = 63	*N* = 20
OUTCOME												
Follow-up duration (range)		5.1 years[d] (0.1–21.9)	4.3 years[d] (0.5–21.9)	0.09	9 years[d] (0–14)			8.4 years[d]			4.2 years[e] (1–12)[a]	8.2 years[d] (0.5–13.1)
Patients who died of invasive breast cancer		NR	NR		*N* = 3 (10%)	*N* = 1 (6%)		*N* = 1 (4%)	*N* = 0		*N* = 9 (14%)	*N* = 2 (10%)
Breast cancer specific overall survival	5-year rate	77%	73%	0.94	93% at 6 years[f]			96% at 8 years	100% at 8 years		75%[g]	89% ± 7%
	10-year rate	56%	62%								69%[h]	-
Distant disease-free survival	5-year rate	60%	68%	0.03	84% at 6 years[i]			96% at 8 years	100% at 8 years		NR	73% ± 10%
	10-year rate	49%	60%								NR	-

[a] determined in 68 BRCA1 patients, including 63 affected with invasive breast cancers and 5 with ductal carcinoma in situ (DCIS)
[b] including mixed invasive ductal carcinoma (IDC) *plus* DCIS
[c] mixed lobular carcinoma in situ (LCIS) *plus* DCIS
[d] median value
[e] mean value
[f] 93% (95% confidence interval 79%–98%)
[g] 75% (95% confidence interval 56%–86%)
[h] 69% (95% confidence interval 48%–83%)
[i] 84% (95% confidence interval 64%–93%)
Abbreviations: BCT breast-conserving therapy, *BRCA1 BRCA1* mutation carriers, *BRCA2 BRCA2* mutation carriers, *CPM* contralateral preventive mastectomy, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *NR* not recorded, *PR* progesterone receptor

rates of distant metastasis (9% versus 23%) and breast cancer–related mortality (8% versus 21%). This study, however, does not have a comparison group of patients screened with mammography with or without ultrasound, nor does it correct for screening lead time.

A prospective study reported in 2011 by Ellen Warner and colleagues on 1,271 *BRCA1* and *BRCA2* mutation carriers under surveillance with or without MRI for a mean of 3.2 years [51] showed a significant reduction in the cumulative incidence of advanced stage breast cancers (larger than 2 cm or node-positive) in the MRI-screened group (HR 0.30). These data reinforced the expectation that, due to its superior sensitivity, an intensive MRI screening could contribute to reduce the breast cancer–specific mortality in MRI-screened *BRCA* mutation carriers. This study also showed that the protective effect of MRI screening on advanced breast cancer was greater for *BRCA2* (HR 0.15) than for *BRCA1* mutation carriers (HR 0.40). Furthermore, a recent study by Dafydd Gareth Evans and colleagues showed that an intensive breast screening with annual MRI and mammography improved survival from breast cancer in female *BRCA2* mutation carriers, compared to a control group who had their first breast cancer diagnosed without intensive screening [52].

Differences in the outcome of *BRCA1*- and *BRCA2*-associated breast cancers may, in principle, derive from the different patterns of tumor progression of these tumors, in relation to the different hormone receptor expression levels, other prognostic factor profiles, and imaging findings, as reported in retrospective analyses of *BRCA* mutation carriers. Julia Krammer and coworkers [53] performed a retrospective analysis of 496 *BRCA* mutation carriers diagnosed with breast cancer from 1999 to 2013. *BRCA1*-associated cancers exhibited significantly higher nuclear and histological grade compared to *BRCA2*-associated cancers. A basal-like tumor receptor status was significantly more frequent in *BRCA1* mutation carriers, while hormone receptor-positive tumors were more frequent in *BRCA2* mutation carriers. *BRCA2* mutation carriers had a more frequent diagnosis of ductal carcinoma in situ (DCIS) not in combination with other malignancies as well as presenting calcifications. The sensitivity of mammography was significantly lower in *BRCA1* mutation carriers (81%) than in *BRCA2* mutation carriers (89%) while that of MRI was 99% in each group, without significant difference for age (over or below 40 years). Mammography detected only two cancers that were false-negative at MRI (1 invasive, 1 DCIS). Similar trends were observed using the approach of the individual-patient data meta-analysis (see Chap. 11).

Analyses of data collected from prospective MRI-screened high-risk women (examples in Table 13.2) showed significantly higher rates of ER and PR negativity in *BRCA1*- compared with *BRCA2*-associated breast cancers (ER negativity, 65–82% versus 14–36%; PR negativity, 78–85% versus 29–42%), along with a higher percentage of grade 3 cancers (52–78% versus 21–55%) [36, 41–43].

Focusing on *BRCA1*-associated breast cancers, the mean tumor size of lesions reported in different prospective MRI-including screening studies typically ranged from 9 to 14 mm [39, 41–43] compared with a mean tumor size of about 24 mm reported for the hospital-based cohort of the retrospective Rotterdam study [44]. In most screening studies [36, 41, 43], the smaller MRI-detected tumors were associated with higher 5-year BCS-OS rates (up to about 90% versus 70–75% estimated for unscreened *BRCA1* patients [39]). An exception to this trend was reported by Paul Møller and colleagues [42] from the MRI-based surveillance offered in Norway to *BRCA1* mutation carriers between 2001 and 2010. The rather small mean tumor size of 14 mm reported in this study for patients diagnosed with invasive breast cancer was in fact associated with 5-year and 10-year BCS-OS rates as low as 75% and 69%, respectively (Table 13.2), i.e., lower than expected. Yet, using a multivariate model, it was confirmed that the tumor size at diagnosis was a critical issue for patient outcome. In fact, the 10-year survival rate was 93% for women with a cancer size ≤10 mm, 58% for women with a cancer size 11–20 mm, and only 23% for women with a cancer size >20 mm.

This body of evidence suggests that, beyond the encouraging results regarding breast cancer stage, a firm assessment of the impact of MRI on high-risk patient outcome still requires extensive investigation with regard to the interplay among benefits of earlier detection, tumor prognostic factors, and treatment. A key concern in this context appears to be the high incidence among patients with *BRCA1* mutations of triple negative breast cancers (TNBCs), a highly aggressive, heterogeneous clinical subset characterized by ER and PR negativity in the absence of epidermal growth factor receptor 2 (HER2) overexpression [54–57]. This immunohistochemically defined subset partially overlaps the molecular-defined basal-like breast cancer subtype [58]. Frequent phenotype features of TNBCs in the general female population are high tumor grade (G3), large tumor size (pT2–pT3), weak relationship between tumor size and nodal status, high risk of hematogenous in addition to lymphatic spread, and poor clinical outcome [57, 59–62].

The high percentage of TNBCs in *BRCA1*-mutated patients might, therefore, in principle strongly reduce the advantages of an intensive MRI-including surveillance program for this population. The earlier tumor detection by MRI might in fact result in a mere anticipation of diagnosis (i.e., lead time) for a high proportion of ultimately fatal TNBC cases. In this context, it is worth noting that the poor correlation between node negativity and tumor aggressiveness often led in the past to therapeutic options which, unfortunately, excluded the application of adjuvant chemotherapy to TNBCs, whereas accruing clinical evidence has more recently shown that among TNBCs, *BRCA1*-related cancers are more chemosensitive than sporadic tumors [63].

Limited attention has so far been focused on comparing phenotype features and survival rates of TNBCs versus non-TNBCs detected in high-risk women entered in the MRI-including screening programs performed in the last decades. The main results of the recently reported prospective Italian multi-center multimodality screening study focusing on this crucial issue [43] are summarized in the next section.

13.6 Outcome of Triple Negative versus Non-triple Negative Cancers in the HIBCRIT-1 Study

Most population-based breast cancer studies have reported a 10–20% prevalence of TNBCs, although higher rates have been found in some ethnic groups [57, 59, 60, 64, 65]. TNBCs are more common in premenopausal women and over-represented among the interval cancers in population-based mammography screening programs [66]. A significantly shorter 10-year overall survival rate (75%) was reported by the International Breast Cancer Group Trials VIII and IX for patients with TNBCs compared with hormone receptor-positive patients with either low or high proliferative activity (survival rates of 89% and 83%, respectively) in a cohort of 1,951 early-stage node-negative breast cancer patients diagnosed between 1988 and 1999 [62].

Clinical data retrospectively analyzed by Rebecca Dent and coworkers [61] in a hospital-based cohort of 1,601 women diagnosed with primary breast cancer in Toronto (1987–1997) showed that, compared to other cancer phenotypes, TNBC patients (11%) had a significantly lower age at diagnosis (53 versus 58 years), a larger mean tumor size (30 mm versus 21 mm), a higher rate of G3 tumors (66% versus 28%), and a lower rate of negative nodal status (45% versus 54%) (Table 13.3). Recurrence and survival analyses showed that TNBCs typically had an earlier risk of recurrence, with a peak at 1–3 years from diagnosis, distant recurrence rarely preceded by local recurrence, and rapid progression from distant recurrence to death [61]. Compared with other women with breast cancer, those affected with TNBC had an increased likelihood of distant recurrence (HR 2.6, $p < 0.0001$) and death (HR 3.2, $p < 0.001$) within 5 years of diagnosis but not thereafter. The Kaplan-Meier survival analyses for BCS-OS and DDFS in TNBC and non-TNBC patients are reported in Fig. 13.3 (panels **a**, **b**). It is worth noting that the studies by Dent and coworkers [61] and Metzger-Filho and colleagues [62] reported on patients diagnosed before the routine use of chemotherapy in node-negative patients and before the use of anthracycline plus taxane chemotherapy.

The first comparative analysis of phenotype characteristics and survival rates of TNBCs versus non-TNBCs diagnosed in high-risk women during a prospective MRI-including screening study has been recently reported [43] using data from eighteen Italian centers [35, 38]. The study, conducted on a cohort of 501 asymptomatic high-risk women and based on the results of 1,592 annual screening sessions including mammography, ultrasonography, and MRI, was performed in the context of the High Breast Cancer Risk Italian 1 (HIBCRIT-1) project funded by the Italian Ministry of Health

Table 13.3 Clinical features, treatment and survival of TNBC and non-TNBC patients in a MRI-including screening study on high-risk women compared with a retrospective study on hospital-based unscreened cohort

STUDY TYPE		**RETROSPECTIVE STUDY**			**MRI-INCLUDING SCREENING STUDY**			
TARGET POPULATION		Hospital-based unscreened cohort of patients with primary breast cancer			Asymptomatic high-risk women found affected with invasive breast cancer			
ORGANIZER/ STUDY NAME		***Women's College Hospital, Toronto***			***High Breast Cancer Risk Italian Study (HIBCRIT-1)***[a]			
STUDY TIME FRAME		1987–1997 [61]			2000–2008 [35, 38, 43]			
TOTAL PATIENTS		***N* = 1,601**			***N* = 44**			
PATIENTS	**Subgroups**	**TNBC**	**Non-TNBC**	***p***	**TNBC**	**Non-TNBC**	***p***	**BRCA1**
	Number	*N* = 180	*N* = 1,421		*N* = 14	*N* = 30		*N* = 20 (11 TNBC, 9 Non-TNBC)
	Percentage	11% (10%–13%)[b]	89% (87%–90%)[b]		32% (18%–46%)[b]	68% (54%–82%)[b]		-
Mean age at diagnosis (range)		53.0 years	57.7 years	<0.0001	49.0 years (36–63)	52.0 years (35–72)	0.325	49.1 years (36–64)
Risk categories	BRCA1	NP	NP		79% (11/14)	30% (9/30)	0.004	100% (20/20)
	BRCA2	NP	NP		14% (2/14)	23% (7/30)	0.695	-
	SFH	NP	NP		7% (1/14)	47% (14/30)	0.015	-
PROGNOSTIC FACTORS								
Mean tumor size (range)		30.0 mm	21.0 mm	<0.0001	16.4 mm (8–25)	11.9 mm (6–35)	<0.007	13.2 mm (5–22)
T-status < T2		37%	63%	<0.0001	78%	97%	0.078	90%
Pathologic subtype	IDC	NR	NR		86% (12/14)	43% (13/30)	0.010	70% (14/20)
	IDC *plus* DCIS	NR	NR		7% (1/14)	33% (10/30)	0.076 0.030	20% (4/20)
	Other	NR	NR		7% (1/14)	23% (7/30)	0.402	10% (2/20)
Receptor expression	***ER*** negative	100%	13% (12%–15%)		100%[c]	37% (20%–54%)[b]	<0.001	80% (63%–98%)[b]
	PR negative	100%	25% (22%–27%)		100%[c]	40% (23%–58%)[b]	<0.001	85% (62%–97%)[b]
	HER2 positive	0%	16% (14%–19%)		0%[c]	47% (29%–65%)[b]	0.002	30% (12%–54%)[b]
Histologic grade 3		66% (59%–73%)	28% (25%–31%)	<0.0001	86% (57%–98%)	53% (34%–72%)	0.049	75% (51%–91%)
Nodal status negative		45% (37%–52%)	54% (51%–57%)	0.02	92% (64%–100%)	65% (44%–83%)	0.120	89% (67%–99%)

(continued)

Table 13.3 (continued)

STUDY TYPE		RETROSPECTIVE STUDY			MRI-INCLUDING SCREENING STUDY			
ORGANIZER/ STUDY NAME		*Women's College Hospital, Toronto*			*High Breast Cancer Risk Italian Study (HIBCRIT-1)*[a]			
TOTAL PATIENTS		*N* = 1,601			*N* = 44			
PATIENTS	Subgroups	TNBC	Non-TNBC	*p*	TNBC	Non-TNBC	*p*	BRCA1
	Number	*N* = 180	*N* = 1,421		*N* = 14	*N* = 30		*N* = 20 (11 TNBC, 9 Non-TNBC)
	Percentage	11% (10%–13%)[b]	89% (87%–90%)[b]		32% (18%–46%)[b]	68% (54%–82%)[b]		-
TREATMENT								
Primary surgery	Breast conserving therapy[d]	NR	NR		21% (3/14)	57% (17/30)	0.050	35% (7/20)
	Uni- or bilateral mastectomy[d]	NR	NR		79% (11/14)	43% (13/30)		65% (13/20)
Prophylactic surgery	CPM	NR	NR		43% (6/14)	10% (3/30)	0.019	40% (8/20)
Adjuvant chemotherapy	Yes	49%	25%	<0.0001	100%	44%	<0.001	89%
	No	51%	74%		0%	56%		11%
	Unknown	*N* = 3	*N* = 20		*N* = 1	*N* = 3		*N* = 1
OUTCOME								
Follow-up time from diagnosis		7.9 years[e]	8.9 years[e]	<0.004	9.0 years[f]	9.8 years[f]	0.668	8.2 years[f]
Breast cancer-related deaths		42%	28%	<0.0001	14% (2/14)	13% (4/30)	1.000	10% (2/20)
Mean time from diagnosis to death		4.2 years	6.0 years	<0.0001	3.7 years	4.9 years	NC[g]	4.7 years
5-year overall survival		*See Fig. 13.3 panel a*			86% ± 9%	93% ± 5%	0.946[i]	89% ± 7%
Risk of death within 5 years		HR 3.2 (2.3–4.5)[h] *TNBC versus non-TNBC*		<0.001	-	-		-
5-year disease-free survival		*See Fig. 13.3 panel b*			77% ± 12%	76% ± 8%	0.216[i]	73% ± 10%
Risk of local recurrence within 5 years		HR 1.5 (1.0–2.5)[h] *TNBC versus non-TNBC*		0.08	-	-		-
Risk of distant recurrence within 5 years		HR 2.6 (2.0–3.5)[h] *TNBC versus non-TNBC*		<0.0001	-	-		-

[a] non-randomized prospective screening study including annual mammography, ultrasonography, and MRI examinations; 501 enrolled asymptomatic high risk women, 1,592 screening sessions; 44 patients found affected with invasive breast cancer; follow-up lasted until 2015 (median follow-up time 9.7 years)
[b] 95% confidence interval
[c] receptor expression in the TNBC subset: ER expression, <1% in 13 of 14 and 1% to 10% in 1 of 14 patients; PR expression, <1% in 12 of 14 and 1% to 10% in 2 of 14 patients; HER2 expression, score 0 in 12 of 14 and score 1 in 2 of 14 patients
[d] surgery at the screening breast cancer event
[e] mean value
[f] median value
[g] sample size too small for statistical comparison
[h] Cox model
[i] log-rank test

Abbreviations: BRCA1 BRCA1 mutation carriers, *BRCA2 BRCA2* mutation carriers, *CPM* contralateral preventive mastectomy, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HR* hazard ratio, *IDC* invasive ductal carcinoma, *NC* not calculated, *NP* not performed, *NR* not reported, *PR* progesterone receptor, *SFH* strong family history for breast and/or ovarian cancer

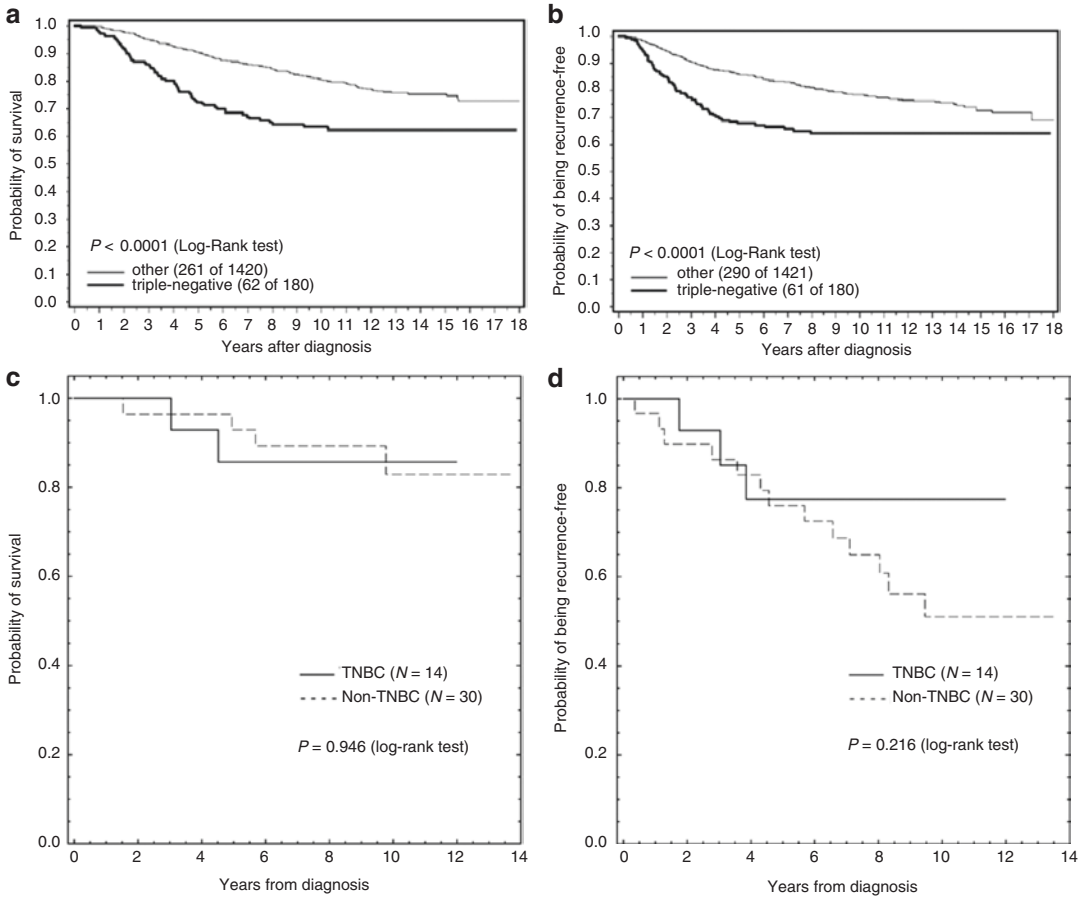

Fig. 13.3 Kaplan-Meier survival analyses carried out to compare breast cancer–specific survival and recurrence-free survival of TNBCs versus non-TNBCs in either a hospital-based cohort of unscreened patients diagnosed with primary invasive breast cancer (top panels; ref. 61) or in high-risk women found affected with invasive breast cancer during the MRI-including screening HIBCRIT-1 study (bottom panels; ref. 43). Top panels: rates of breast cancer–specific survival (panel **a**) and distant recurrence (panel **b**) [*reproduced with permission from R. Dent et al (2007) Clin Cancer Res;13:4429–4434*]. Bottom panels: rates of breast cancer–specific survival (panel **c**) and rates of either local or distant disease–free survival (panel **d**) [*reproduced with permission by the Authors F. Podo et al (2016) Clin Cancer Res;22:895–904*]

and coordinated by the Istituto Superiore di Sanità, Rome, from June 2000 to March 2008. Survival data were collected with a median follow-up of 9.7 years until June 2015 [43]. The cohort included either proven *BRCA1* (n = 184) or *BRCA2* mutation carriers (n = 146), first-degree relatives of *BRCA1* or *BRCA2* mutation carriers (n = 12), or women with a strong family history of breast or ovarian cancer (SFH) in the absence of an identified deleterious gene mutation (n = 159). Overall, cancers were detected in 52 women, 44 of them (85%) invasive cancers and 8 (15%) DCIS. The 44 cases of invasive cancer were detected in 20 women with *BRCA1* mutations (45%), in 9 with *BRCA2* mutations (21%), and in 15 women with SFH (34%). With respect to sensitivity, MRI significantly outperformed mammography (90% versus 43%), ultrasonography (61%), and the combination of mammography and ultrasonography (66%), without significant differences between the TNBC and non-TNBC subsets. The proportion of cancers detected by MRI only was 25% among TNBCs and 31% among non-TNBCs.

The 44 invasive cancers (41 screen-detected and 3 interval) included 14 TNBCs (32%) and 30 non-TNBCs (68%). The two subsets did not

show significant differences for age at diagnosis, menopausal status, prophylactic oophorectomy, induced menopause, or previous breast cancer (which had occurred in about 50% of both subgroups). Of note, all three interval cancers were *BRCA1*-associated TNBCs.

The distribution of patients in different breast cancer risk categories differed with high statistical significance, between the TNBC and non-TNBC subsets. In particular, 79% (11/14) of TNBCs were associated with a deleterious *BRCA1* mutation (Fig. 13.4, panel **a**), while non-TNBCs were significantly less likely to be *BRCA1*-related (30%, 9/30). Notably, about 50% (11/20) of BRCA1-associated breast cancers were TNBCs (Fig. 13.4, panel **b**). The breast cancer patients who had been enrolled for SFH ($n = 15$) were mostly diagnosed with non-TNBCs (93%). Furthermore, SFH patients represented a significantly higher proportion of the non-TNBC subgroup (47%, 14/30) than the TNBC subgroup (7%, 1/14). The nine patients with a BRCA2 mutation were more likely to develop non-TNBCs (78%), but, due to the small subgroup size, this trend did not reach statistical significance.

Regarding prognostic factors, TNBCs detected in HIBCRIT-1 had a significantly larger mean tumor size (16 ± 5 mm) than non-TNBCs (12 ± 6 mm), a higher percentage of invasive disease in the tumor mass (invasive ductal cancer [IDC], 86% versus 43%), and a higher proportion of grade 3 IDCs (71% versus 23%). Despite the significantly larger mean tumor size and other phenotype characteristics indicative of greater cancer aggressiveness, the TNBC subgroup showed a non-significant tendency toward lymph node negativity (92% versus 65%, $p = 0.120$). This feature was in general agreement with the reported disruption of the positive correlation between breast tumor size and nodal status in BRCA1-related breast cancers [67].

Data reported in Table 13.3 show that, despite the unavoidably different size of the patient cohorts, some significant differences could be appreciated in the prognostic factors of both the TNBC or non-TNBC subsets reported in the prospective HIBCRIT-1 screening study (2000–2008) [43] versus the corresponding subsets of unscreened patients diagnosed at the Women's College Hospital, Toronto (1987–1997), reported

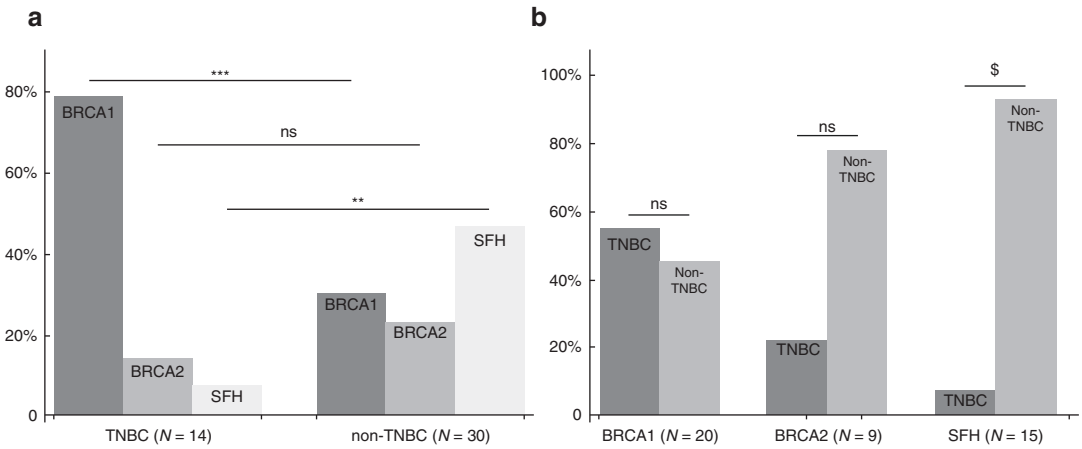

Fig. 13.4 Distribution of the HIBCRIT-1 high-risk patients between the TNBC and non-TNBC subsets (panel **a**) and percentages of TNBCs (and non-TNBCs) in different breast cancer risk categories (panel **b**) (from data in ref. 43). *Abbreviations*: *BRCA1*, asymptomatic women enrolled in HIBCRIT-1 for proven deleterious *BRCA1* mutation and found affected with invasive breast cancer; *BRCA2*, asymptomatic women enrolled for proven deleterious *BRCA2* mutation and found affected with invasive breast cancer; *SFH*, asymptomatic women enrolled for strong family history of breast or ovarian cancer in the absence of tested or identified deleterious gene mutations and found affected with invasive breast cancer. *Statistical significance of differences*: panel **a**, *** $p = 0.004$, ** $p = 0.015$, ns, non-significant difference (evaluated by Fisher exact test); panel **b**, $ significant difference; ns, non-significant difference (evaluated from the lack of overlap of 95% CIs)

in the retrospective hospital-based study by Rebecca Dent and colleagues [61]:

1. A threefold higher percentage of TNBCs in HIBCRIT-1 (32% versus 11%), as expected for a cohort enriched in *BRCA1* mutation carriers
2. Higher levels of tumor aggressiveness in HIBCRIT-1 non-TNBCs, as detected by higher percentages of ER negativity (37% versus 13%), and grade G3 tumors (53% versus 28%), and even, surprisingly, a substantially higher rate of HER2 positivity (47% versus 16%)
3. A trend toward a higher percentage of histologic grade 3 tumors in HIBCRIT-1 TNBCs (86% versus 66%)
4. A substantially smaller mean tumor size in both the TNBC and non-TNBC subsets in the HIBCRIT-1 screening study (16.5 mm versus 30.0 mm and 11.9 mm versus 21.0 mm, respectively)

Overall, the data reported in Table 13.3 favors the hypothesis that an intensive MRI-including screening may allow an earlier detection of both TNBCs and non-TNBCs in high-risk women, despite the more aggressive tumor phenotypes generally exhibited by both subsets in high-risk women, compared with the corresponding subsets in the general population.

Regarding treatment, TNBCs had a higher rate of therapeutic mastectomy (79%) versus 43% in non-TNBCs, ($p = 0.050$), and significantly higher rates of CPM (43% versus 10%, $p = 0.019$) and adjuvant chemotherapy (100% versus 44%, $p < 0.001$). No patients received neoadjuvant chemotherapy. No similar full sets of data are presently available comparing treatment for TNBC and non-TNBC subsets in hospital-based cohorts of unscreened women in the general patient population, within similar observation time intervals.

Patient outcomes were evaluated in the HIBCRIT-1 study with an overall median follow-up time of 9.7 years (with a median 9.0-year follow-up for TNBCs and a median 9.8 year-follow-up for non-TNBCs, without significant differences between the two subsets). No patients were known to have died of non-breast cancer–related causes at the time of reporting.

Metastatic spread and death occurred for 14% (6/44) of all patients, 14% (2/14) of TNBCs (1 BRCA1, 1 BRCA2 with times from diagnosis to death of 4.5 and 3.0 years, respectively) and 13% (4/30) of non-TNBCs, including 1 BRCA1 (who died at 4.9 years after diagnosis), 1 BRCA2 (who died at 5.7 years), and 2 SFH (who died at 1.5 and 9.8 years, respectively). These results showed for the first time that screening MRI (combined with proper treatment) could decrease the percentage of TNBC-related deaths to a value comparable to that of non-TNBC-related deaths. Since 4 of these 6 deaths were in patients with a previous history of breast cancer (2 TNBCs and 2 non-TNBCs), recurrences from the original breast cancer might, in principle, lead to underestimating the benefit of screening MRI on survival and even act as a confounding factor in estimating the relative survival of TNBCs versus non-TNBCs. A detailed analysis of data from patients who died from metastatic breast cancer in the TNBC and non-TNBC subgroups, reported in the original paper (Table 3 in ref. 43), shows, however, that the original breast cancer was unlikely to have been the cause of recurrence for at least two of these patients: one *BRCA1* mutation carrier, who had a left medullary carcinoma (with mastectomy) at 39 years of age, a right IDC (TNBC with mastectomy) at 56 years during the HIBCRIT screening and died 4.5 years later; and one *BRCA2* mutation carrier who had a right ILC with mastectomy at 39 years, followed by a left IDC + DCIS (a non-TNBC with mastectomy) at 55 years during the HIBCRIT study and died 5.7 years later. Recurrence from the original cancer could not a priori be excluded for the other two patients, one *BRCA2* mutation carrier with previous IDC (with mastectomy) at 36 years, contralateral IDC (TNBC, with mastectomy) at 39 years, who died 3 years later; and one woman with SFH who had an IDC (with conserving surgery) at 37 years, followed by bilateral IDCs (both non-TNBC) at 39 years, who died 1.5 years later. An accurate evaluation of the impact of the previous history of breast cancer on the benefit of screening MRI on the survival of TNBCs and non-TNBCs would, of course, require larger cohort sizes and knowledge of the TNBC or non-TNBC classification of the previous cancer.

The 12 TNBC survivors were alive with no evidence of disease at their respective latest follow-up date (ranging from 7.5 to 12.0 years from diagnosis). Twenty-five non-TNBC survivors were alive with no evidence of disease at their latest follow-up date (ranging between 6.1 and 13.7 years from diagnosis); only one non-TNBC patient was lost to follow-up at 6 months from diagnosis, following bilateral mastectomy. The three patients with TNBCs detected as interval cancers during the study were all alive with no evidence of disease at their latest follow-up date (ranging between 8.0 and 12.0 years from diagnosis).

The Kaplan-Meier curves for BCS-OS of TNBC and non-TNBC patients diagnosed in the HIBCRIT-1 study are compared in Fig. 13.3, panel **c**. The 5-year BCS-OS survival rate was 86% ± 9% (mean ± standard error) for TNBCs and 93% ± 5% for non-TNBCs, with no significant difference between the two subsets. It was 91% ± 4% for the overall cohort of 44 patients, 89% ± 7% for the 20 patients with a proven BRCA1 mutation, and 93% ± 6% for the 15 SFH patients, without a significant difference between the two subgroups. For the 9 patients with a proven BRCA2 mutation, the 5-year overall survival rate was 89% ± 11%.

In addition to the distant recurrences mentioned above, there were two loco-regional relapses for two TNBC patients (one ipsilateral at 3.9 years from diagnosis and one axillary metastasis at 1.8 years followed by distant metastasis at 4.5 years) and eleven relapses for eight non-TNBC patients (three ipsilateral at 0.4, 8.0, and 9.5 years; one axillary metastasis at 2.8 years and seven contralateral cancers at 1.1, 3.6, 4.6, 6.6, 7.1, 8.0, and 8.3 years). The Kaplan-Meier curves for the overall progression-free survival are shown in Fig. 13.3, panel **d**. The 5-year disease-free survival rate was 77% ± 12% for TNBC and 76% ± 8% for non-TNBC patients, without significant difference between the two subsets, while that of patients with proven BRCA1 mutation was 73% ± 10%. The Kaplan-Meier curves (and survival rates) for DDFS of TNBC and non-TNBC patients in the HIBCRIT-1 study were practically overlapping with those obtained for BCS-OS (Fig. 13.3, panel **c**), due to the rapid progression (within 3-to-8 months) from the date of the first report of distant recurrence detection to that of patient death in both subgroups.

Despite the limitations due to restricted subset sizes, this study provided the first evidence that an intensive MRI-including screening program for high risk women, combined with appropriate therapy, could abolish the current disparity in outcome between TNBC and non-TNBC high-risk women, in spite of the more aggressive tumor characteristics of the former subset. The improved survival rates of TNBCs up to levels commonly reported for non-TNBCs could derive from multiple different factors such as:

1. The beneficial effect of an earlier tumor detection by MRI
2. The higher sensitivity of BRCA1-associated tumors to chemotherapy, due to impaired mechanisms of DNA repair [57, 59, 60, 68]
3. The frequent use for TNBCs of more aggressive treatment protocols, including adjuvant chemotherapy, as well as therapeutic mastectomy and CPM, even in the case of negative nodal status

To distinguish among these factors in the absence of RCTs is highly challenging. While the second factor is biologically fixed, the other two factors are dependent upon screening and therapeutic options. However, we confirm not only for the MRI screening but also for the therapy options the ethical and practical impossibility of performing RCTs that would include a "control" arm deprived of MRI and/or modern therapies.

13.7 Which Further Research?

Given the fact that RCT data will never be available, there is an emergent need for cooperative efforts devoted to the accrual of larger data sets and integrated individual patient meta-analyses of long-term follow-up data collected from cohorts of high-risk women. Important issues to be considered in this effort include:

1. Relevant differences in MRI sensitivity across the different studies from about 70% to over 90–95%, with a trend over time for higher sensitivities

2. Heterogeneous rates of hormonal treatment and chemotherapy, especially in the case of negative nodal status
3. Heterogeneous rates of mastectomy versus breast conserving surgery for detected cancers
4. Heterogeneous rates of prophylactic contralateral mastectomy
5. Heterogeneous rates of prophylactic bilateral mastectomy
6. Heterogeneous rates of oophorectomy

Differences in systemic and surgical treatment compound differences among the potential control groups who may be receiving only conventional imaging screening (mammography with/without supplemental ultrasound) or no screening at all. Moreover, results may not be generalizable to current practice due to treatment changes over time. How to manage these challenges is a matter for open discussion. The general future condition is to establish a strong international network of institutions that can dedicate specialized personnel to cooperative research projects.

A rich source of data on the outcomes of MRI-screened women in the era of modern systemic therapy will be the population-based high-risk screening program started in the province of Ontario (OBCP), Canada, in 2011 for women with an estimated lifetime breast cancer risk of 25% or higher based on genetic status, family history, or therapeutic chest radiation before age 30. These high-risk women receive annual MRI plus mammography starting at age 30 until age 69 [69]. To the best of our knowledge, this is the only program of this type in the world and, with 26 participating imaging sites of widely varying types (new or experienced, rural or urban, academic or community) as well as a wide variation in the sites to which patients with cancer are referred for treatment. The results should be rigorous (with patients rarely lost to follow-up) and highly generalizable to the "real world" setting. Interesting data were very recently reported by OBSP on performance measures of MRI plus mammography in a cohort of 8,782 women (280 screen-detected cancers from July 2011 to June 2015) [70]. This study allowed first evaluations of the different levels of effectiveness in using mammography as an adjunct to MRI for screening high-risk women in different age intervals. Further progress in this program is expected to impact on secondary prevention, cancer management and survival of high-risk women, especially mutation carriers.

References

1. Emperor Justinian. Institutiones. http://www.treccani.it/vocabolario/nomina-sunt-consequentia-rerum/. Accessed 30 Jun 2020
2. U.S. National Library of Medicine. https://www.ncbi.nlm.nih.gov/pubmed/?term=. Accessed 30 Jun 2020
3. Oxford Dictionary. https://medlineplus.gov/mplusdictionary.html. Accessed 30 Jun 2020
4. U.S. National Library of Medicine. https://medlineplus.gov/mplusdictionary.html. Accessed 30 Jun 2020
5. Sardanelli F, Di Leo G (2009) Biostatistics for radiologists. Springer-Verlag, Milan, pp 21–32
6. McCaffery KJ, Jansen J, Scherer LD et al (2016) Walking the tightrope: communicating overdiagnosis in modern healthcare. BMJ 352:i348
7. Colin C, Devouassoux-Shisheboran M, Sardanelli F (2014) Is breast cancer overdiagnosis also nested in pathologic misclassification? Radiology 273:652–655
8. Elmore JG, Longton GM, Carney PA et al (2015) Diagnostic concordance among pathologists interpreting breast biopsy specimens. JAMA 313:1122–1132
9. Davidson NE, Rimm DL (2015) Expertise vs evidence in assessment of breast biopsies: an atypical science. JAMA 313:1109–1110
10. Oxford Centre for Evidence-based Medicine (2009) Levels of Evidence. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 30 Jun 2020
11. European Council Recommendation on cancer screening, December 2, 2003 (2003/878/EC). https://ec.europa.eu/jrc/sites/jrcsh/files/2_December_2003_cancer_screening.pdf. Accessed 30 Jun 2020
12. Houssami N (2015) Digital breast tomosynthesis (3D-mammography) screening: data and implications for population screening. Expert Rev Med Devices 12:377–379
13. Sardanelli F, Aase HS, Álvarez M et al (2017) Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. Eur Radiol 27:2737–2743

14. Bernardi D, Belli P, Benelli E et al (2017) Digital breast tomosynthesis (DBT): recommendations from the Italian College of Breast Radiologists (ICBR) by the Italian Society of Medical Radiology (SIRM) and the Italian Group for Mammography Screening (GISMa). Radiol Med 122:723–730
15. Biesheuvel C, Barratt A, Howard K, Houssami N, Irwig L (2007) Effects of study methods and biases on estimates of invasive breast cancer overdetection with mammography screening: a systematic review. Lancet Oncol 8:1129–1138
16. Lauby-Secretan B, Scoccianti C, Loomis D et al; International Agency for Research on Cancer Handbook Working Group (2015) Breast cancer screening—viewpoint of the IARC working group. N Engl J Med 372:2353–2358
17. Carter JL, Coletti RJ, Harris RP (2015) Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. BMJ 350:g7773
18. Cook JA (2009) The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials 10:9
19. Ramsay CR, Grant AM, Wallace SA et al (2001) Statistical assessment of the learning curves of health technologies. Health Technol Assess 5:1–79
20. Heywang SH, Fenzl G, Hahn D et al (1986) MR imaging of the breast: comparison with mammography and ultrasound. J Comput Assist Tomogr 10:615–620
21. Kuhl CK, Mielcareck P, Klaschik S et al (1999) Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 211:101–110
22. American College of Radiology (2003) Breast imaging reporting and data system (BI-RADS), 4th edn. American College of Radiology, Reston, VA
23. Fischer U, Vosshenrich R, Keating D et al (1994) MR-guided biopsy of suspect breast lesions with a simple stereotaxic add-on-device for surface coils. Radiology 192:272–273
24. Perlet C, Heinig A, Prat X et al (2002) Multicenter study for the evaluation of a dedicated biopsy device for MR-guided vacuum biopsy of the breast. Eur Radiol 12:1463–1470
25. Kuhl CK, Schmutzler RK, Leutner CC et al (2000) Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 215:267–279
26. Berg WA, Zhang Z, Lehrer D et al; ACRIN 6666 Investigators (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
27. Phi XA, Saadatmand S, De Bock GH et al (2016) Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 114:631–637
28. Tilanus-Linthorst MM, Obdeijn IM, Hop WC et al (2007) BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imaging screening trials. Clin Cancer Res 13:7357–7362
29. Otten JD, van Schoor G, Peer PG et al (2018) Growth rate of invasive ductal carcinomas from a screened 50–74-year-old population. J Med Screen 25:40–46
30. Warner E, Plewes DB, Hill KA et al (2004) Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317–1325
31. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
32. Leach MO, Boggis CR, Dixon AK et al (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
33. Riedl CC, Ponhold L, Flőry D et al (2007) Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. Clin Cancer Res 13:6144–6152
34. Hagen AI, Kvistad KA, Maehle L et al (2007) Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast 16:367–374
35. Sardanelli F, Podo F, D'Agnolo G et al (2007) Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT Study): Interim results. Radiology 242:698–715
36. Rijnsburger AJ, Obdeijin I-M, Kaas R et al (2010) BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol 28:5265–5273
37. Kuhl CK, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
38. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the High Breast Cancer Risk Italian 1 Study). Final results. Investig Radiol 46:94–105
39. Evans DG, Kesavan N, Lim Y et al; MARIBS Group (2014) MRI breast screening in high-risk women: cancer detection and survival analysis. Breast Cancer Res Treat 145:663–672
40. Santoro F, Podo F, Sardanelli F et al (2014) MRI screening of women with hereditary predisposition to breast cancer: diagnostic performance and survival analysis. Breast Cancer Res Treat 147:685–687

41. Passaperuma K, Warner E, Causer PA et al (2012) Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 107:24–30
42. Møller P, Stormorken A, Jonsrud C et al (2013) (2013) Survival of patients with BRCA1-associated breast cancer diagnosed in an MRI-based surveillance program. Breast Cancer Res Treat 139:155–161
43. Podo F, Santoro F, Di Leo G et al (2016) Triple-negative versus non-triple negative breast cancers in high-risk women: phenotype features and survival from the HIBCRIT-1 MRI-including screening study. Clin Cancer Res 22:895–904
44. Brekelmans CTM, Seynaeve C, Pluymeers MM et al (2006) Survival and prognostic factors in BRCA1-associated breast cancer. Ann Oncol 17:391–400
45. Lakhani SR, Jacquemier J, Sloane JP et al (1998) Multifactorial analysis of differences between sporadic breast cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90:1138–1145
46. Philips K-A (2000) Immunophenotypic and pathologic differences between BRCA1 and BRCA2 hereditary breast cancers. J Clin Oncol 18:107s–112s
47. Verhoog LC, Brekelmans CTM, Seynaeve C et al (1998) Survival and tumour characteristics of breast cancer patients with germline mutations of BRCA1. Lancet 351:316–321
48. Ford D, Easton DF, Bishop T et al (1994) Risks of cancer in BRCA1-mutation carriers. Lancet 343:692–695
49. Alpert TE, Haffty BG (2004) Conservative management of breast cancer in BRCA1/2 mutation carriers. Clin Breast Cancer 5:37–42
50. Saadatmand S, Obdeijn IM, Rutgens E et al (2015) Survival benefit in women with BRCA1 mutation or familial risk in the MRI screening study (MRISC). Int J Cancer 137:1729–1738
51. Warner E, Hill K, Causer P et al (2011) Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol 29:1664–1669
52. Evans DG, Harkness EF, Howell A et al (2016) Intensive breast screening in *BRCA2* mutation carriers is associated with reduced breast cancer specific and all cause mortality. Hereditary Cancer Clin Pract 14:8
53. Krammer J, Pinker-Domenig K, Mark E, Robson ME et al (2017) Breast cancer detection and tumor characteristics in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 163:565–571
54. Lakhani SR, Van de Vijver MJ, Jacquemier J et al (2002) The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2 and p53 in patients with BRCA1 and BRCA2. J Clin Oncol 20:2310–2318
55. Foulkes WD, Brunet JS, Stefansson IM et al (2004) The prognostic implication of the basal-like (cycle E high/p27low/p53+/glomeruloid-microvascular proliferation+) phenotype of BRCA1-related breast cancer. Cancer Res 64:830–835
56. Reis-Filho JS, Tutt AN (2008) Triple negative tumors: a critical review. Histopathology 52:108–118
57. Foulkes WD, Smith IE, Reis-Filho IS (2010) Triple-negative breast cancer. N Engl J Med 363:1938–1948
58. Perou CM, Sørlie T, Eisen MB et al (2000) Molecular portraits of human breast tumors. Nature 406:747–752
59. Podo F, Buydens LM, Degani H et al (2010) Triple-negative breast cancer: present challenges and new perspectives. Mol Oncol 4:209–229
60. Bosch A, Eroles P, Zaragoza R, Viña JR, Lluch A (2010) Triple-negative breast cancer molecular features, pathogenesis, treatment and current line sod research. Cancer Treat Rev 36:206–215
61. Dent R, Trudeau M, Pritchard KI et al (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13:4429–4434
62. Metzger-Filho O, Sun Z, Viale G et al (2013) Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from International Breast Cancer Study Group Trials VIII and IX. J Clin Oncol 31:3083–3090
63. Paluch-Shimon S, Friedman E, Berger R et al (2016) Neo-adjuvant doxorubicin and cyclophosphamide followed by paclitaxel in triple-negative breast cancer among BRCA1 mutation carriers and non-carriers. Breast Cancer Res Treat 157:157–165
64. Hammond ME, Hayes DF, Dowsett M et al (2010) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784–2795
65. Jiao Q, Wu A, Shao G, Peng H et al (2014) The latest progress in research on triple negative breast cancer (TNBC): risk factors, possible therapeutic targets and progressive markers. J Thorac Dis 6:1329–1335
66. Domingo L, Salas D, Zubizarreta R et al, INCA Study Group (2014) Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. Breast Cancer Res 16:R3
67. Foulkes WD, Metcalfe K, Hanna W et al (2003) Disruption of the expected positive correlation between breast tumor size and lymph node status in BRCA1-related breast carcinoma. Cancer 98:1569–1577
68. Tan X, Peng J, Fu Y, An S et al (2014) miR-638 mediated regulation of BRCA1 affects DNA repair and sensitivity to UV and cisplatin in triple-negative breast cancer. Breast Cancer Res 16:435
69. Chiarelli AM, Prummel MV, Muradali D et al (2014) Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario high risk breast screening program. J Clin Oncol 32:2224–2230
70. Chiarelli AM, Blackmore KM, Muradali D et al (2020) Performance measures of magnetic resonance imaging plus mammography in the high risk Ontario breast screening program. J Natl Cancer Inst 112:136–144

14 The Special Case of Previous Chest Radiation Therapy

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Abbreviations

ACS	American Cancer Society
BC	Breast cancer
BI-RADS	Breast Imaging Reporting and Data System
COG	Children's Oncology Group
CRT	Chest radiation therapy
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
EUSOMA	European Society of Breast Cancer Specialists
HER2	Human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
RR	Relative risk
SIRM	Italian Society of Medical Radiology

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14.1 Introduction

Chest radiation therapy (CRT) is largely used to treat malignancies, in particular Hodgkin lymphoma (HL), in childhood, adolescence, and young adulthood that is in subjects aged up to 39 years. It exposes to a high risk of developing a secondary malignant neoplasm, a risk higher than that of developing a cancer in the general population [1]. Breast cancers (BCs) are the most common solid tumors among women survivors of childhood HL [2]. In the last decades, thanks to the use of smaller involved fields, lower radiation doses, and combined therapy using less toxic chemotherapy regimens, the incidence of secondary BC is expected to decline among female HL survivors [3]. Nevertheless, in this population the risk of BC still remains high [4], similar to that of *BRCA* mutations carriers, thus requiring a surveillance more intensive than that proposed to the general female population.

Several guidelines agree on recommending yearly mammography and breast magnetic resonance imaging (MRI) for screening BC after CRT even if there is a lack of uniformity for the specific radiation doses and time intervals to be considered [5]. A relevant and not negligible concern also regards who should actually follow this patients after completion of the therapy, if the pediatric oncologist, adult oncologist, or primary care providers, a confusion leading to

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an inadequate late-effect surveillance and to a lack of adhesion to screening programs.

The purpose of this chapter is to discuss the incidence of secondary malignancies after CRT, focusing on BC, to describe clinicopathological and imaging features of secondary BCs after CRT, and to define the best strategies for imaging surveillance for BC in these women. Even though in the literature the term *second* BC is sometimes used for those BCs newly diagnosed after CRT, all over the chapter the term *secondary* BC will be used (with reference to any primary neoplasm treated with CRT), to avoid any confusion with second BCs diagnosed after a first previous treated BC.

14.2 Secondary Malignancies After CRT

Thanks to effective therapies that mainly consist of associated radiation and chemotherapy, HL currently shows an excellent prognosis. In the last decades, these therapies improved dramatically to reduce toxicities and increase survival, mainly shifting from extended radiation fields to smaller target volumes, including only clinically involved lymph node regions and less toxic chemotherapy regimens, limiting the use of anthracycline-containing and alkylating agents. However, CRT represents the main concern for HL survivors to develop secondary malignancies that actually are the leading cause of death in this population.

The most common locations of secondary malignancies were reported to be the breast (18%), lung (15%), prostate (8%), skin (8%), and bone marrow (7%) [6]. A meta-analysis by Ezzeldin M. Ibrahim and coworkers on the risk of secondary BC in female HL survivors was published in 2012 [7], including 34 studies and 25,305 women diagnosed with HL at a median age of 27.3 years and with a median follow-up of 14.5 years. A total of 957 BCs were diagnosed at a median age of 35.0 years for a median interval of 17.7 years from HL diagnosis. Patients with HL turned out to have an about eightfold increased risk of BC, with a relative risk (RR) of 8.23 (95% confidence interval [CI] 5.43–12.47). A significant inverse correlation was found between RR and age at diagnosis and a positive relation to latency since HL treatment. Chaya S. Moskowitz and coworkers [8] reported a 35% risk of BC by age 50 for female HL survivors, comparable to the 31% risk of *BRCA1* mutation carriers.

Age at irradiation is the most important risk factor for a secondary BC. Women treated around puberty, i.e., at 10–16 years, have the highest risk, possibly due to the amplification of tumorigenic effect of radiation on the proliferating breast cells [2]. The risk of having a secondary BC increases as the time since irradiation progresses, starting 5–9 years post-CRT, peaking at 15–19 years, and being still elevated 35 years or more after treatment [4, 7].

Michael Schaapveld and coworkers [4] reported a cumulative incidence of any secondary cancer, including the myelodysplastic syndrome, of 33.2% (95% CI 31.1–35.3%) in a cohort of 3,905 HL survivors, as compared with the expected cumulative cancer incidence of 9.6% in the general population; at 40 years, the incidence was 48.5% (95% CI 45.4–51.5%). The cumulative incidence of BC at 30 years among women was 16.6% (95% CI 14.1–19.2%) versus 4.1% (95% CI 2.9–5.6%) cumulative incidence of lung cancer.

The risk of secondary BC is positively correlated with the radiation dose. Women receiving >37 Gy resulted to have approximately 4.5 times the risk of secondary BC compared with those receiving <4Gy [2]. Nevertheless, some authors highlighted that patients treated with higher radiation doses also had longer follow-up, possibly explaining the larger incidence of BC following high doses [7]. Also the field size influences the risk of developing a secondary BC. Mantle radiation therapy was associated with an almost three times higher BC risk compared to smaller radiation volumes [8, 9]. Importantly, a lower radiation dose to a larger field, such as whole lung irradiation for metastatic Ewing's sarcoma, has been shown to confer a risk similar to a higher dose to a relative smaller field [8]. Thus, irradiation dose and field interact with each other modeling the risk of developing secondary cancers. Interestingly, in the meta-analysis by Ezzeldin M. Ibrahim and coworkers [7], the RR of combined RT and any computed tomography examination was only slightly higher than that associated with RT only [7]. Moreover, early menopause subsequent to pelvic RT or chemo-toxic regimens, in particular alkylating agents, seems to

reduce the risk of secondary BC, highlighting the role of hormone stimulation in radiation-induced breast carcinogenesis [7].

Finally, other contributing factors such as family history of breast or ovarian cancer, BC predisposing genes, or a particular susceptibility to radiation and/or chemotherapy may favor the development of a second BC in HL survivors (see Chap. 12). Fortunately, a trend toward a less invasive radiation therapy is contributing to a declining incidence of secondary BC among female survivors of HL [3, 9], but the continuous increase in cancer survival rate makes the absolute number of survivors to be very high and follow-up care thus increasingly important.

14.3 Clinicopathological and Imaging Features of BCs After CRT

Compared to female general non-exposed population, secondary BCs after CRT present at a younger age (40 versus 61 years) on average [10]. They are mainly invasive ductal carcinomas, but ductal carcinomas in situ (DCIS) have been reported in up to 50% [11]; they are more commonly estrogen receptor (ER) negative, triple negative, and high grade, while human epidermal growth factor receptor 2 (HER2) amplification is present at a rate similar to that of the primary sporadic BCs [2].

These findings suggest that CRT supports a more aggressive phenotype and a subsequent poor prognosis. Bilateral BCs occur more often with respect to sporadic BCs (6–34% versus 0.3–3%) and in up to 50% of cases are synchronous [2]. As reported by Steven D. Allen and coworkers [12], the most frequent locations are the upper outer quadrants (67% versus 49% in historical controls of general population BCs) and, to a lesser extent, lower inner quadrants (11% versus 8%, respectively) [12] (Fig. 14.1). BCs in these patients resulted to be located within or at the margin of the radiation field [7, 11].

Imaging features have been more extensively described for mammography than for MRI and

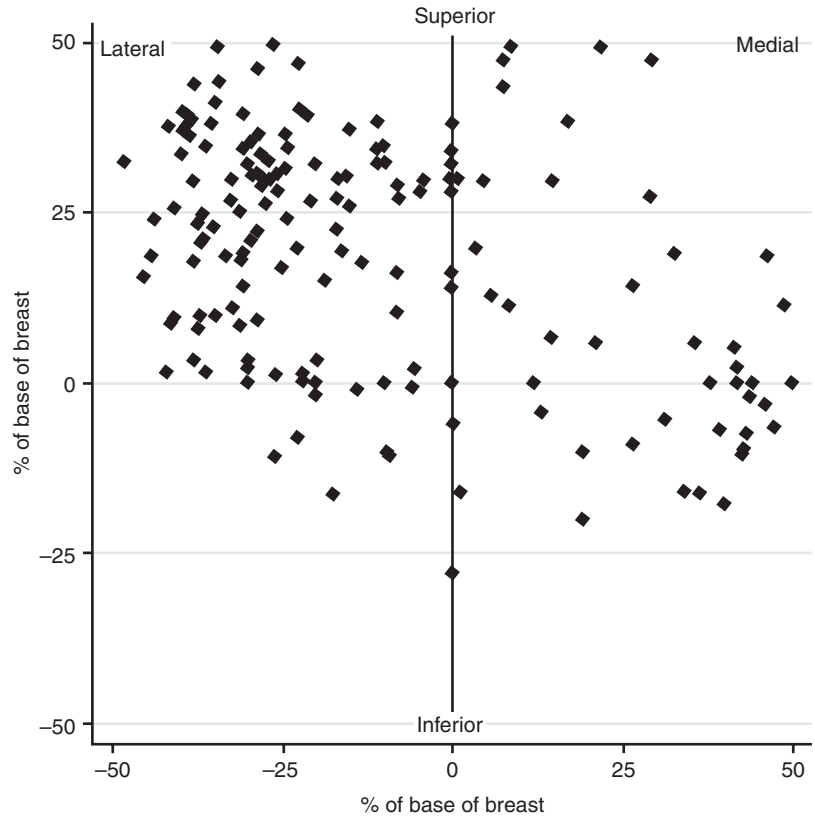

Fig. 14.1 Location of 192 secondary BCs after CRT visible on mammogram. Note the high number of BCs in the superior lateral quadrants. (Reproduced with permission from Allen et al., Radiology 2014 [12])

ultrasonography. Irregular masses were described to be the most common imaging feature (57% of tumors) at mammography, followed by microcalcifications (25% of tumors) [12]. High-density breast tissue was identified in most cases, also given the early onset of BC in those patients [13] (Figs. 14.2 and 14.3).

The sensitivity of mammography and MRI reported in the four major published studies [14–17] is shown in Table 14.1 together with the frequency of MRI false-negative cases, mainly due to DCIS with microcalcifications detected by mammography.

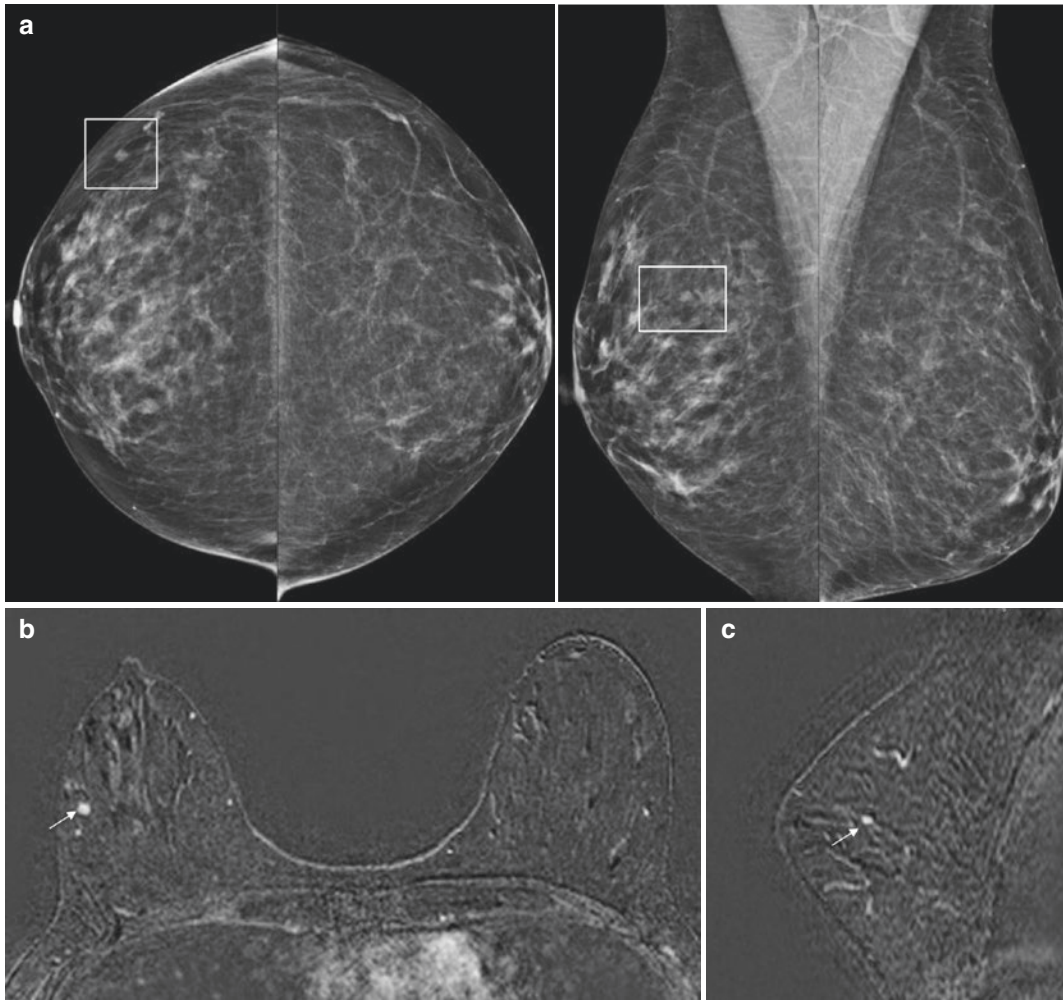

Fig. 14.2 47-year-old woman with previous Hodgkin lymphoma (stage IIa) treated at age 20 with CRT (mantle field + *inverted-Y* field, 36 Gy + 36 Gy) and chemotherapy. (**a**) Mammography (bilateral standard two view): at the upper outer quadrant of the right breast, a 5-mm mass lesion with circumscribed margins (*white boxes*) was detected. Subtracted MRI axial (**b**) and sagittal (**c**) images confirmed the 5-mm mass lesion at the upper outer quadrant. The patient underwent percutaneous needle biopsy and subsequent surgical excision: pathology demonstrated a 6-mm intermediate grade invasive ductal carcinoma

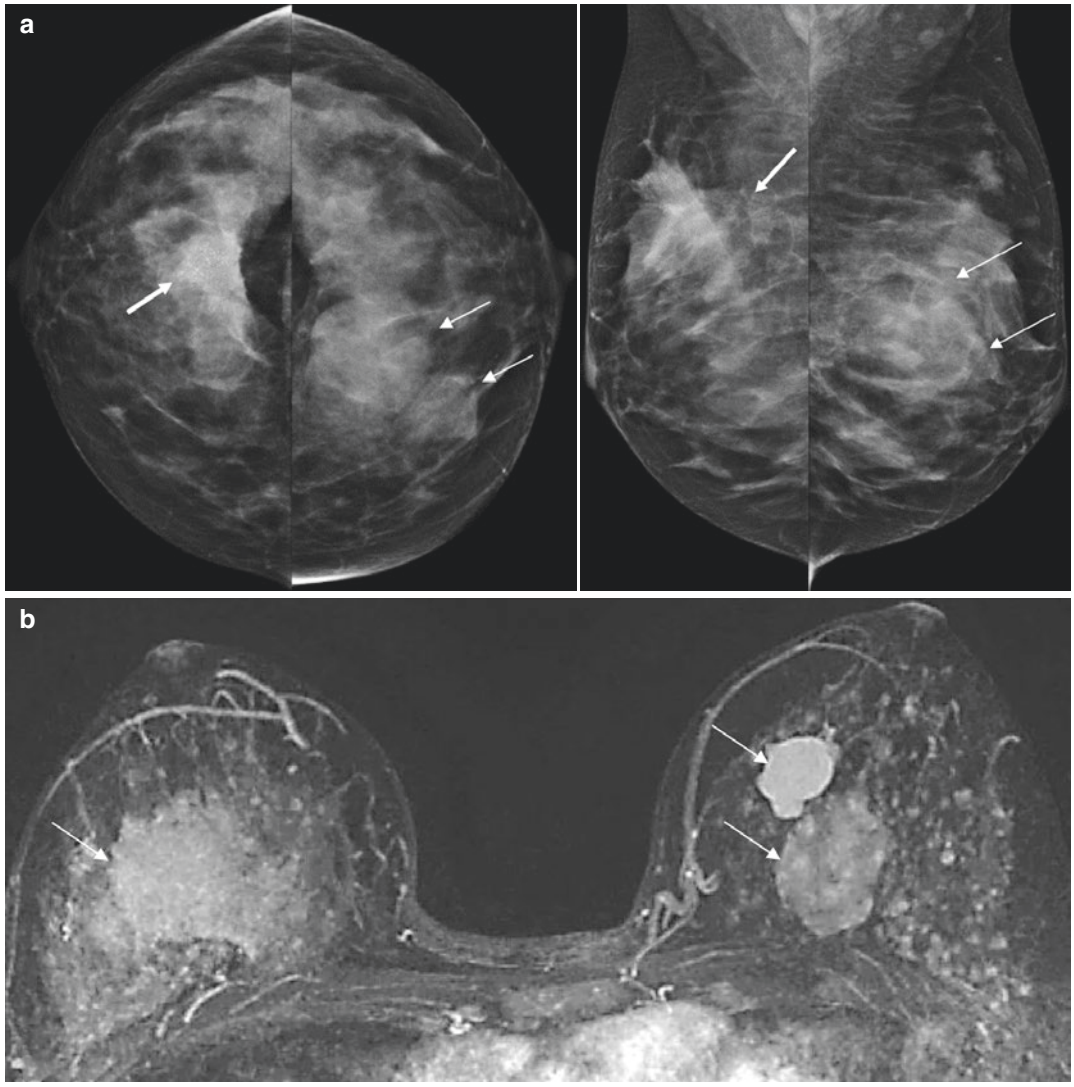

Fig. 14.3 32-year-old woman with previous non-Hodgkin lymphoma type B treated at age 14 with CRT (mediastinal field, 29 Gy) and chemotherapy. (**a**) Mammography (bilateral standard two view) shows at the upper quadrants of the right breast a 36-mm mass with irregular margins associated with pleomorphic microcalcifications (biopsy-proven invasive ductal carcinoma), at the left breast in the inner quadrants, two masses with circumscribed margins (both biopsy-proven B3 lesions). MRI: (**b**) axial maximum intensity projection; (**c**) right and (**d**) left sagittal maximum intensity projection images. A high background parenchymal enhancement with numerous non-specific foci is visible in the left breast. MRI confirmed in the right breast the large mass lesion with irregular margins and in the left breast the two mass lesions with circumscribed margins. The patient underwent bilateral mastectomy: pathology demonstrated a 40-mm high-grade invasive ductal carcinoma with DCIS component in the right breast and fibroadenomas associated to papillomatosis and multiple foci of low-grade cribriform DCIS in the left breast. (MRI images courtesy of Dr. Laura Martincich, Radiodiagnostics, Research Hospital (IRCCS) Candiolo Cancer Institute, Turin, Italy)

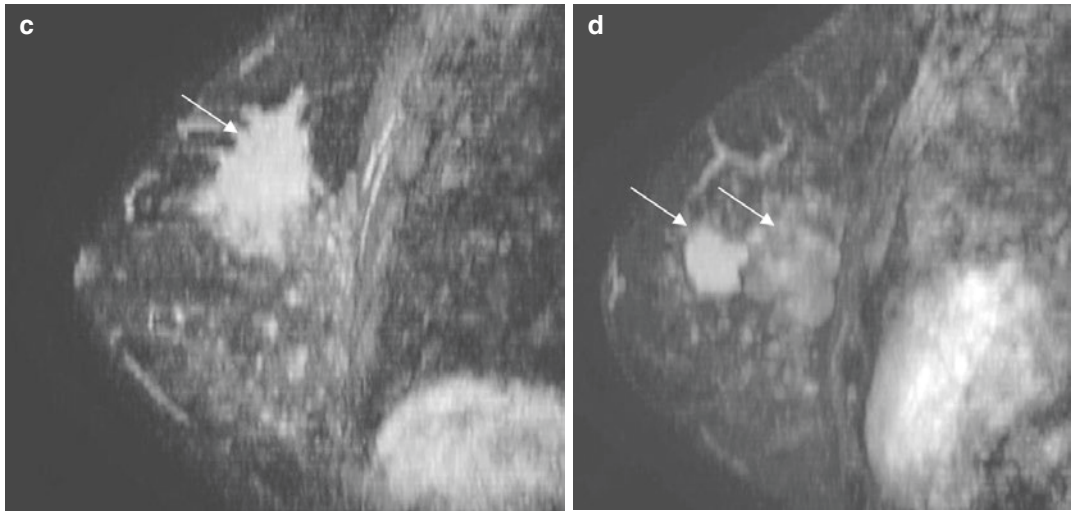

Fig. 14.3 (continued)

Table 14.1 Reported sensitivities of mammography and MRI for BC surveillance after RCT

First author, year [reference]	Number of patients	Cancers detected	MRI-only cancers	MRI sensitivity	MG sensitivity	MRI False negatives	MRI ICD	MRI + MG sensitivity
Tieu, 2014 [14]	96	10	3	80%	70%	2 DCIS	NA	100%
Freitas, 2013 [15]	98	13	12	92%	69%	2 DCIS	4.1%	NA
Ng, 2013 [16]	148	18	5	67%	68%	5 DCIS, 1 IDC	NA	94%
Sung, 2011 [17]	91	10	7	67%	67%	3 DCIS	4.4%	NA

Abbreviations: *MG* Mammography, *ICD* Incremental cancer detection rate, *DCIS* Ductal carcinoma in situ, *IDC* Invasive ductal carcinoma, *NA* Not available

14.4 Surveillance

International guidelines from the European Society of Breast Cancer Specialists (EUSOMA) [18], the American Cancer Society (ACS) [19], the Children's Oncology Group (COG) [20], and the National Comprehensive Cancer Network (NCCN) [21] all recommend annual mammography and breast MRI for screening after CRT. However, the specific radiation exposure and time intervals of testing differ among documents: COG refers to patients exposed to more than 20 Gy of chest radiation and starts at 25 years, while NCCN does not refer to radiation dose and starts 8–10 years after radiation (Table 14.2). A recent investigation [5] directly compared guideline recommendations, supporting the call for harmonization among them. The authors finally recommend to refer to COG guidelines, being the most comprehensive and also referenced by the NCCN guidelines: yearly mammography and MRI are recommended beginning 8 years after CRT or at 25 years of age, whichever occurs last.

The Italian College of Breast Radiologists of the Italian Society of Medical Radiology (SIRM) firstly introduces digital breast tomosynthesis (DBT) with synthetic two-dimensional reconstructions as an alternative to mammography, to be equally annually performed [1]. Authors also state that mammography or DBT and MRI can be performed at once (preferably during only one visit) or alternately every 6 months, considering

Table 14.2 Available recommendations for BC surveillance of women after CRT

Medical body [reference]	Patients population	Suggested surveillance	
		Time interval	Strategy
American Cancer Society [19]	Chest radiation between age 10 and 30 years of age	NA	Yearly MG + MRI
Children's Oncology Group [20]	Children, adolescents, and young adult cancer survivors exposed to more than 20 Gy of chest radiation	Starting 8 years after radiation or 25 years of age, whichever occurs last	Yearly MG + MRI Monthly breast self-exam beginning at puberty Yearly breast exam until 25 years of age then every 6 months
European Society of Breast Cancer Specialists (EUSOMA) [18]	Women who have had previous mantle radiotherapy before age 30 (e.g. for Hodgkin disease),	Starting 8 years after their treatment	Yearly MRI
Italian College of Breast Radiologists by SIRM [1]	Chest radiation ≥10 Gy before 30 years of age	25 years of age or 8 years after radiation	Yearly MG or DBT and MRI Dedicated interview about individual risk profile and potential of different breast imaging modalities
National Comprehensive Cancer Network-AYA [21]	Patients diagnosed with cancer at 15–39 years	Starting 8 years after radiation or 25 years of age, whichever occurs last	Yearly MG + MRI
National Comprehensive Cancer Network-Site [21]	Patients with osteosarcoma, acute lymphoblastic leukemia and Hodgkin lymphoma; age not listed	Starting 8–10 years after radiation or 40 years of age, whichever occurs first	Yearly MG + MRI
National Comprehensive Cancer Network-Survivorship/DPRR [21]	Cancers survivors; age not listed	Beginning at age 25: 8–10 years after radiation or 40 years of age, whichever occurs first	Yearly MG + MRI

Abbreviations: *MG* Mammography, *MRI* Magnetic resonance imaging, *SIRM* Italian Society of Medical Radiology, *DBT* Digital Breast Tomosynthesis, *AYA* Adolescent and Young Adult Oncology, *Site* Guidelines for treatment of cancer by site, *DPRR* Guidelines for Detection, Prevention, and Risk Reduction, *NA* Not available

local conditions, and that MRI has to be reported using the Breast Imaging reporting and Data System (BI-RADS) [22] both overall and for individual findings. Moreover, when the age for entering a population screening program is reached, the recommendation is to discuss with women their individual risk profile, to opt for the only mammography or DBT screening or for continuing the intensive protocol including MRI [1]. Notably, EUSOMA guidelines recommend caution in performing mammography before 35 years of age because of an unfavorable cost-benefit ratio [18].

Notably, in *BRCA* mutation carriers and also in women with a strong family history of BC with unknown mutational status, MRI has been demonstrated to outperform mammography and ultrasonography and to be able to work as a stand-alone method [23]. This is especially true for *BRCA1* mutation carriers, as shown by a recent individual patient data meta-analysis [24], and as the reader can extensively verify in Chaps. 9, 10, and 11. *Conversely, in women who underwent CRT, MRI sensitivity has been reported to be relatively lower (63–80%) and that of mammography relatively higher (67–70%) than those observed in women with hereditary predisposition, due to a higher incidence of DCIS with microcalcifications* [11] (Fig. 14.4) *and low neo-*

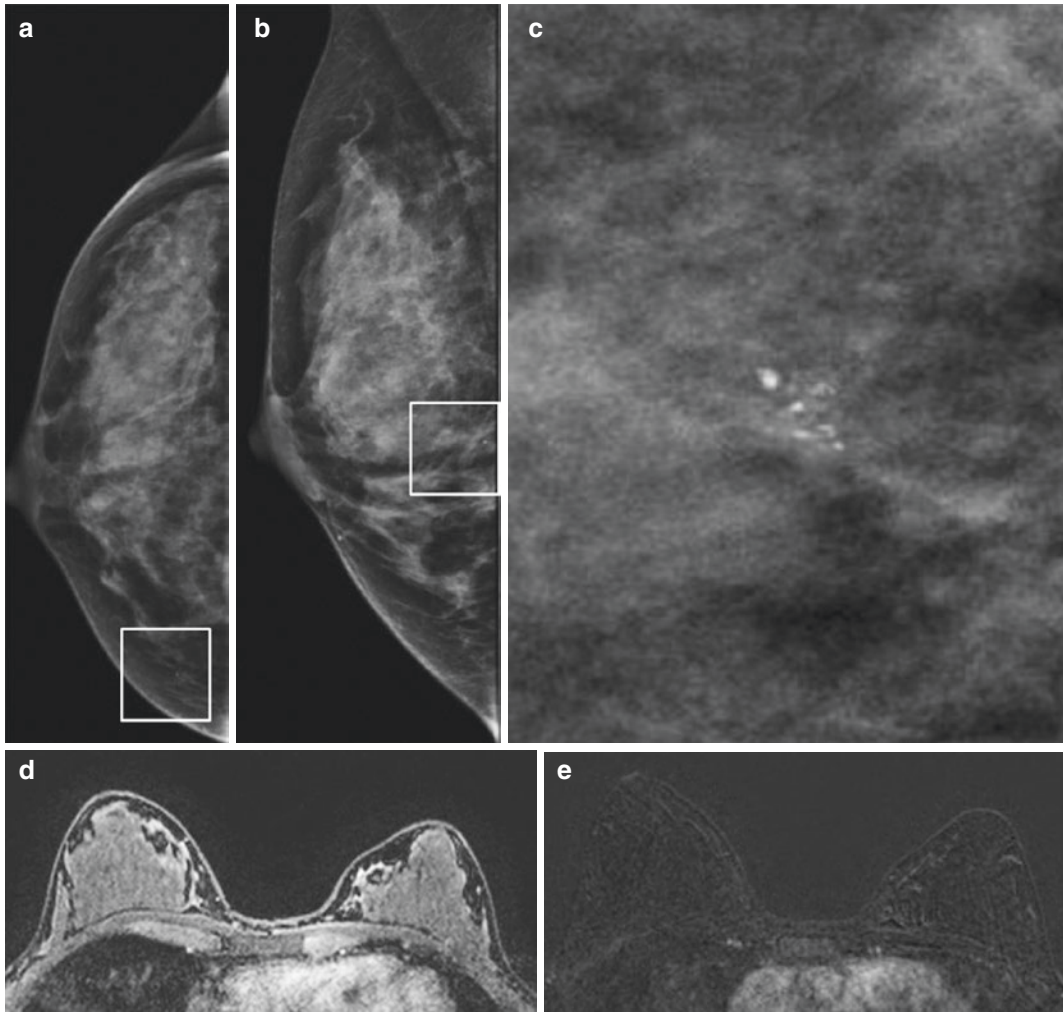

Fig. 14.4 28-year-old woman with previous Hodgkin lymphoma treated at age 13 with CRT (mantle field, 36 Gy) and chemotherapy. Mammography: right craniocaudal (**a**), oblique mediolateral (**b**), and magnification view (**c**). At the lower-inner quadrant, a 5-mm cluster of coarse heterogeneous microcalcifications was identified (*white boxes* in a and b). MRI: axial postcontrast (**d**) and subtracted (**e**) images. No suspicious findings were detected. The patient underwent percutaneous needle biopsy under stereotactic guidance and subsequent surgical excision: pathology demonstrated an 8-mm low-grade DCIS

angiogenesis. A sensitivity close to 95% can be reached only using mammography as an adjunct to MRI [1, 16] (Fig. 14.5). Of note, Sung et al. reported no relationship between breast density and modality of detection [17] (Fig. 14.6). Thus, *in women who underwent CRT, mammography has to be performed as an adjunct to MRI.*

While many guidelines exist for BC screening in women survivors of HL, there is concern about their applicability in clinical practice. A study from the United States published in 2009 [25] reported that among 551 women with previous CRT, 47% of those with 25–39 years of age never had a mammogram and only 37% had biennial screening mammography, the same percentages being 8% and 53% between 40 and 50 years of age. Importantly, *the screening rate was higher in the presence of a specific medical recommendation*. BCs in HL survivors resulted to be more likely detected by screening mammography, to be diagnosed at an earlier stage, and to less likely have axillary lymph node

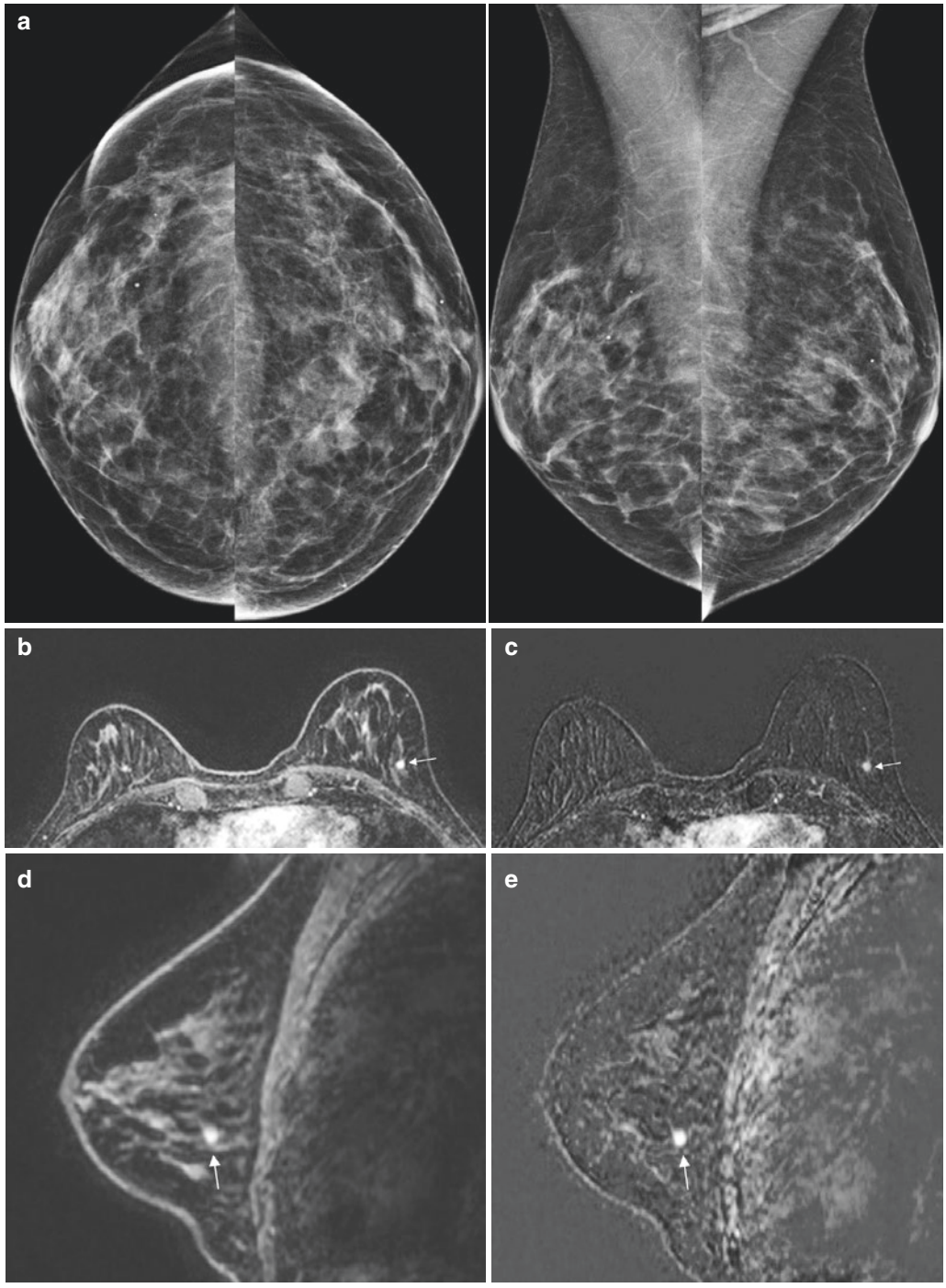

Fig. 14.5 55-year-old woman with previous Hodgkin lymphoma (stage IIa) treated at age 23 with subtotal nodal CRT (mantle field + *spade* field, 36 Gy + 36 Gy) and chemotherapy. Mammography, bilateral standard two view (**a**): no suspicious findings were identified in scattered areas of fibroglandular tissue. MRI, axial first postcontrast (**b**) and subtracted (**c**) images; sagittal first postcontrast (**d**) and subtracted (**e**) images: at the lower-outer quadrant of the left breast, a 5-mm lesion was detected; subsequent targeted ultrasonography (not shown) confirmed a 5-mm heterogeneous hypoechoic mass, which underwent percutaneous needle biopsy and surgical excision. Pathology demonstrated a 6-mm low-grade tubular invasive carcinoma

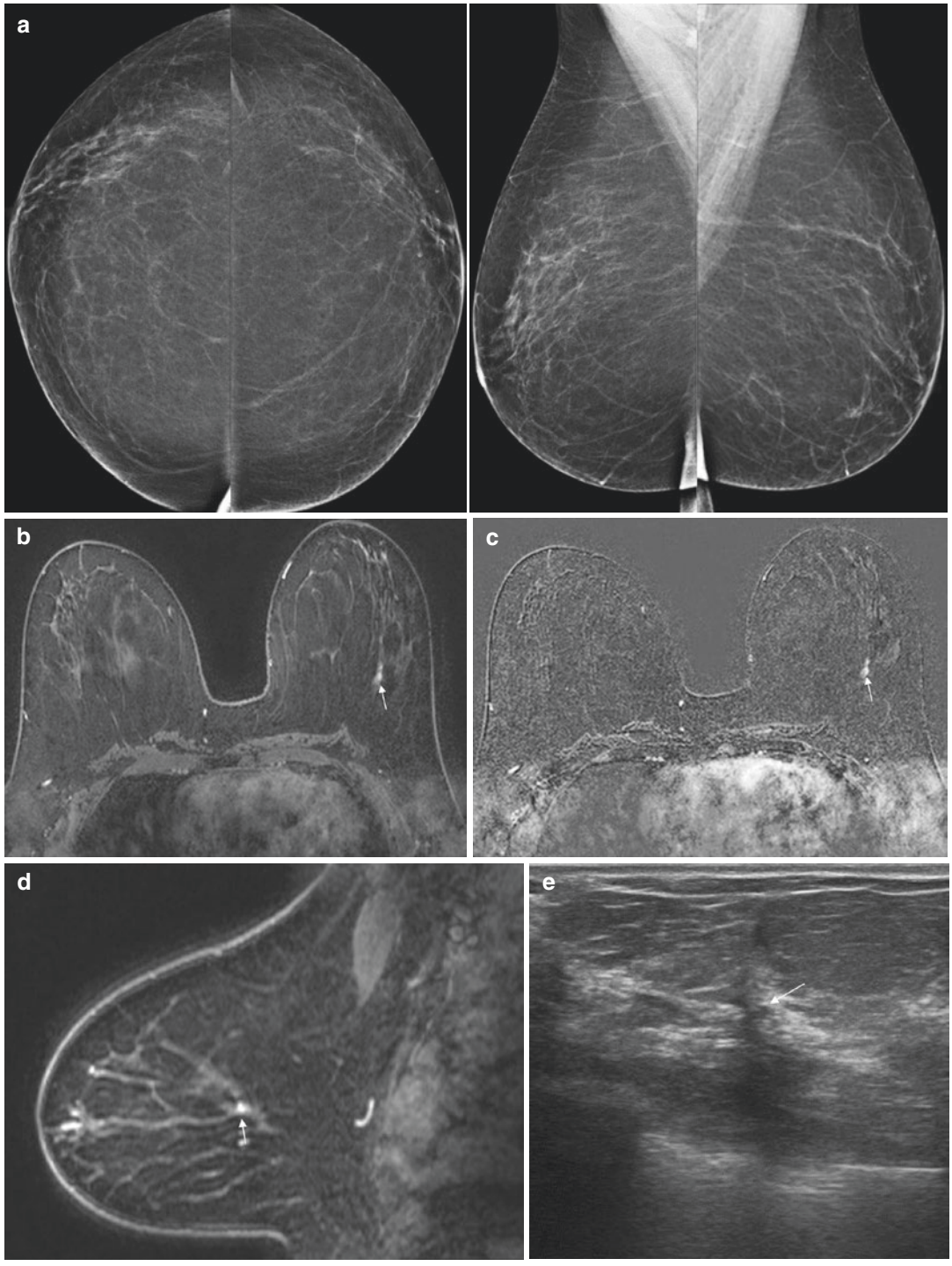

Fig. 14.6 46-year-old woman with previous Hodgkin lymphoma treated 22 years before, at age 24 with CRT (mantle field + *inverted-Y* field, 36 Gy + 36 Gy) and chemotherapy. Mammography, bilateral standard two view (**a**): no suspicious findings were detected in fatty breasts. MRI, axial first postcontrast (**b**) and subtracted (**c**) images, sagittal first postcontrast image (**d**): at the outer quadrants of the left breast, a 5-mm focus of enhancement was identified. Subsequent targeted ultrasonography (**e**) showed a heterogeneous hypoechoic mass (white arrow), which underwent percutaneous needle biopsy and surgical excision. Pathology demonstrated a 10-mm high-grade invasive ductal carcinoma

involvement compared to patients who had sporadic BC [25].

These results play in favor of a potential role of early diagnosis, that also is of particular concern for the management of these patients after a BC diagnosis. As a matter of fact, the management of patients who survived a tumor is different from the management of patients newly diagnosed with a primary tumor. Specifically, in women survivors of HL and affected by a secondary BC, conserving surgery may no longer be considered the option of choice because the breast tissue is no longer easy to handle, and because further irradiation would not be well tolerated and could cause adverse events, including radionecrosis. As a consequence, most women with secondary BC are managed with mastectomy [2]. The use of systemic adjuvant therapy is also limited. Elena B. Elkin and coworkers [26] reported an overall poorer survival in HL survivors than in patients with sporadic BC, but women with screen-detected BCs turned out to have almost half the risk of death of women whose BCs were patient- or clinician-detected as a result of symptoms.

There is a need for clear statements from medical bodies on who should follow and how to follow these patients after completion of CRT, whether the pediatrician, the oncologist, or the primary care provider, to drive them toward the most appropriate surveillance protocol.

14.5 Conclusions

Women who received CRT at a young age have a risk of secondary BC comparable to that of women carriers of a *BRCA* deleterious mutation. These cancers have been reported to be more aggressive and to have a poorer prognosis than sporadic cancers encountered in the general female population. Early diagnosis is, therefore, crucial also when considering particular issues in the therapeutic management of these women. Yearly mammography and breast MRI have to be recommended starting at least 8 years after the end of treatment.

However, we have no data about patient outcome, survival, or mortality reduction, the last one being very difficult to evaluate when considering the combination of BC added to lymphoma in the woman's history. Notably, David C. Hodgson and coworkers [27] developed a mathematical model to estimate the impact of early BC screening on mortality among young survivors of childhood HL. They investigated the marginal benefit of early-initiated screening starting at age 25 years on BC mortality compared with screening initiated at age 40. For survivors treated at 15 years of age, the absolute risk of BC mortality by age 75 years was predicted to decrease from 16.65% with no early screening to 16.28% with annual mammography, 15.40% (annual MRI), 15.38% (same-day annual mammography and MRI), and 15.37% (alternating mammography and MRI every 6 months). One BC death would be avoided for every 80 patients invited to have an MRI – including screening. Even though combinations of mammography and MRI were predicted to produce a 10% false-positive rate between age 25 and 39 years, the authors concluded that early MRI-based screening should reduce BC mortality among women who underwent radiation therapy for adolescent HL and that the magnitude of this benefit is superior to that reported for other accepted screening indications.

Clinical breast radiologists must investigate the patient's history and the individual risk profile and inform the woman on the potential of different imaging modalities for BC screening in this special setting. Efforts should be made to educate providers regarding surveillance for secondary malignancies in HL survivors, in particular, BC.

References

1. Mariscotti G, Belli P, Bernardi D et al (2016) Mammography and MRI for screening women who underwent chest radiation therapy (lymphoma survivors): recommendations for surveillance from the Italian College of Breast Radiologists by SIRM. Radiol Med 121:834–837
2. Koo E, Henderson MA, Dwyer M, Skandarajah AR (2015) Management and prevention of breast cancer after radiation to the chest for childhood, adolescent, and young adulthood malignancy. Ann Surg Oncol 22(Suppl 3):S545–S451

3. Giri S, Pathak R, Martin MG, Bhatt VR (2015) Incidence of breast cancer among female survivors of Hodgkin lymphoma: a US-population-based trend analysis from 1973 to 2011. Blood 126:1861–1863
4. Schaapveld M, Aleman BM, van Eggermond AM et al (2015) Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 373:2499–2511
5. Barthel EM, Spencer K, Banco D, Kiernan E, Parsons S (2016) Is the adolescent and young adult cancer survivor at risk for late effects? It depends on where you look. J Adolesc Young Adult Oncol 5(2):159–173
6. LeMieux MH, Solanki AA, Mahmood U, Chmura SJ, Koshy M (2015) Risk of second malignancies in patients with early-stage classical Hodgkin's lymphoma treated in a modern era. Cancer Med 4(4):513–518
7. Ibrahim EM, Abouelkhair KM, Kazkaz GA, Elmasri OA, Al-Foheidi M (2012) Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. BMC Cancer 12:197
8. Moskowitz CS, Chou JF, Wolden SL et al (2014) Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol 32:2217–2223
9. De Bruin ML, Sparidans J, van't Veer MB et al (2009) Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol 27:4239–4246
10. Henderson TO, Amsterdam A, Bhatia S et al (2010) Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 152(444–455):W144–W154
11. Cutuli B, Kanoun S, Tunon De Lara C et al (2012) Breast cancer occurred after Hodgkin's disease: clinico-pathological features, treatments and outcome: analysis of 214 cases. Crit Rev Oncol Hematol 81:29–37
12. Allen SD, Wallis MG, Cooke R, Swerdlow AJ (2014) Radiologic features of breast cancer after mantle radiation therapy for Hodgkin disease: a study of 230 cases. Radiology 272:73–78
13. Kwong A, Hancock SL, Bloom JR et al (2008) Mammographic screening in women at increased risk of breast cancer after treatment of Hodgkin's disease. Breast J 14:39–48
14. Tieu MT, Cigsar C, Ahmed S et al (2014) Breast cancer detection among young survivors of pediatric Hodgkin lymphoma with screening magnetic resonance imaging. Cancer 120:2507–2513
15. Freitas V, Scaranelo A, Menezes R, Kulkarni S, Hodgson D, Crystal P (2013) Added cancer yield of breast magnetic resonance imaging screening in women with a prior history of chest radiation therapy. Cancer 119:495–503
16. Ng AK, Garber JE, Diller LR et al (2013) Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. J Clin Oncol 31:2282–2288
17. Sung JS, Lee CH, Morris EA, Oeffinger KC, Dershaw DD (2011) Screening breast MR imaging in women with a history of chest irradiation. Radiology 259:65–71
18. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
19. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
20. Children's Oncology Group (2014) Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 4.0. https://childrensoncologygroup.org/index.php/survivorship-guidelines. Accessed 14 May 2020
21. National Comprehensive Cancer Network. NCCN guidelines. https://www.nccn.org. Accessed 14 May 2020
22. American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA
23. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Investig Radiol 46:94–105
24. Phi XA, Saadatmand S, De Bock GH et al (2016) Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 114:631–637
25. Oeffinger KC, Ford JS, Moskowitz CS et al (2009) Breast cancer surveillance practices among women previously treated with chest radiation for a childhood cancer. JAMA 301:404–414
26. Elkin EB, Klem ML, Gonzales AM et al (2011) Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study. J Clin Oncol 29:2466–2473
27. Hodgson DC, Cotton C, Crystal P, Nathan PC (2016) A mathematical model of BC development was used to evaluate the marginal benefit of early-initiated screening. J Natl Cancer Inst 108(7)

Electronic Data Capture Systems for Breast Cancer Research

15

Giovanni Di Leo, Daniela Sacchetto, and Filippo Santoro

Abbreviations

ACS	American Cancer Society
CDISC	Clinical data interchange standards consortium
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
DICOM	Digital imaging and communication in medicine
EDC	Electronic data capture
FTPS	File transfer protocol secure
GUI	Graphical user interface
HIBCRIT	High breast cancer risk Italian (study)
MIPA	Preoperative breast MRI in clinical practice: multicenter international prospective analysis
MRI	Magnetic resonance imaging
PACS	Picture archiving and communication system
PDF	Portable document format

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15.1 Introduction

Clinical trials form the basis of the evidence-based medicine. A clinical trial evaluates the efficacy of a new drug, a new surgical/interventional procedure, or a new diagnostic imaging or non-imaging tool. A typical approach to this aim is to randomize patients to the two arms of the study (new or experimental versus standard or control), although uncontrolled trials may be designed when randomization is not possible or necessary. Uncontrolled trials are more frequent in the imaging world, where a new diagnostic technique is typically compared to an established one. If the endpoint is limited to diagnostic performance, an intraindividual prospective design (with randomization of the order of performance of the diagnostic techniques) can be more efficient than a randomized interindividual design [1].

In Europe, it is a legal requirement to conduct clinical trials in accordance with the guidelines on *good clinical practice* coming from the *International Conference on Harmonization* [2]. Of note, after these guidelines were issued in 1996, a decline was observed in the number of trials being conducted by independent academic groups [3]. At the same time, trial costs increased by 85% and insurance costs from 70 million to 140 million euros. One possible reason is that reporting and documentation requirements are now so burdensome that the process has become unnecessarily complicated [4]. This is rather ironic,

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given that well-designed clinical trials should be amenable to very simple data handling and analysis [5]. Indeed, the flowchart established by the CONSORT (*Consolidated Standards of Reporting Trials*) statement [6] for carrying out a properly randomized controlled trial only has four steps, which supports the approach of keeping it simple.

Evolution in technology and risk management offers new opportunities to increase efficiency and focus on relevant activities. When the original *good clinical practice* guidelines were prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitated implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original guideline. Therefore, this text has been amended in 2016 [7] to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure protection of enrolled humans and reliability of trial results.

In this setting, instruments that are able to discharge researchers from administrative and operational tasks are welcome. The conduct of a clinical trial is typically coordinated by a *principal investigator*, together with co-investigators or local principal investigators in multicenter trials. Additionally, several other collaborators with different expertise are needed to cover all the aspects related to a trial. As an option, the principal investigator or the sponsor (if any) may also delegate the conduct of the trial to a *Contract Research Organization*.

The fundamental contribution to the trial documentation comes from the *case report form* (CRF), the record that reports all the patient data. The CRF is derived from the *source document*, which contains original data and records (e.g., hospital records, clinical and office charts, laboratory notes, subjects' diaries, radiological examinations, etc.). Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

In this chapter, we provide an overview of the current information technology systems to gather data in the framework of a multicenter clinical trial. These approaches are the technical basis for future multicenter trials concerning screening of high-risk women by imaging methods such as magnetic resonance imaging (MRI), both in terms of diagnostic performance and in terms of patient outcome. In particular, we describe the application of an ad hoc locally developed system used in a national multicenter study (HIBCRIT) [8] devoted to the surveillance of women at high risk for breast cancer and of a system adopted for an international large multicenter study of preoperative breast MRI, the MIPA study [https://www.eibir.org/initiatives/euroaim/evidence-based-radiology-wg/].

15.2 The Power of Paperless Systems

Traditionally, clinical research studies relied on collecting data by hands in paper CRFs, which were later entered into a database to create electronic records and perform statistical analysis. Clearly, this method was time-consuming, prone to misinterpretation, and basically inefficient especially for multicenter clinical trials, which collect paper CRFs through different centers, may be all over the world, with a real possibility of losing data. These limitations found a solution in the *electronic data capture* (EDC) systems, powerful tools reducing study times and costs and, importantly, enhancing the quality of collected data. Moreover, EDC systems allow multicenter studies across the world with real-time, incisive, and corrective monitoring.

Regulatory bodies in the USA and Europe address data protection and privacy, electronic data interchange, and the use of computerized systems in clinical trials in their regulations and directives [9, 10]. Criteria are defined under which electronic records and electronic signatures are considered to be trustworthy, reliable, and equivalent to paper records. It requires implementation of controls, including system

validations, audit trails, electronic signatures, and documentation for software and systems involved in processing electronic data to ensure the authenticity, integrity, and confidentiality of electronic records.

Generally, EDC systems use a web-based platform, accessible from any computer or mobile device connected to the Internet. The database is centralized, managed by a small group of qualified people with deeper administrative access for data monitoring. Local investigators of a multicenter trial can access the system at any time and at any location, with only the possibility to enter patient data of their own center, being blinded to the data entered by other institutions. Moreover, EDC systems support and validate data entry, can implement cross-check, and minimize missing data by preventing the user from going ahead without filling all the mandatory fields.

Shan et al. [11] reported a reduction of 60–80% of inconsistencies among the collected data, thanks to automatized controls that minimize common errors and missing values. Other authors have shown the superiority of capturing clinical data using EDC systems rather than with classical spreadsheets, both in terms of time and accuracy with the promise to reduce trial costs [12–14].

15.3 Overview of EDC Systems

The main components of EDC systems are as follows:

(a) An administrative module to develop the study, build CRFs, add users, and supervise role-based access and security
(b) A graphical user interface (GUI) for data entry
(c) A validation engine to execute edit checks and verify the validity of the data entered into the database
(d) A reporting module providing both standard and ad hoc reports.

Depending on the specific solution implemented by the manufacturer, each of these components can be self-managed by users or can require a technical external support.

There are a number of EDC systems available, both commercial and open-source. The most popular EDC systems and their main features are reported in Table 15.1. This list reflects the number of citations, the availability of online documentation, and our own experience. All the EDC systems presented are web-based and compliant with the *Guidance for Industry Part 11, Electronic Records; Electronic Signatures—Scope and Application*, a guidance document for submitting clinical trial results to the Food and Drugs Administration [10].

The main features of EDC systems are the followings:

- *Offline capability*—The possibility to use the system when disconnected from the Internet, resynchronizing once the connection is restored. This can be useful in a geographical area where network connectivity is poor (for instance, rural locations) or when it is important to give users the possibility to work disconnected from the network.
- *Randomization*—It is an integrated method to perform randomization.
- *User authentication*—The access to the system is controlled by login with username and password.
- *Clinical Data Interchange Standards Consortium* (CDISC) *certification*—A certification by a global, open, multidisciplinary, nonprofit organization that has established standards to support the acquisition, exchange, submission, and archive of clinical research data and metadata. CDISC standards are vendor-neutral, platform-independent, and freely available (https://www.cdisc.org/).
- *Ad hoc reporting*—Free predefined reports and further customized reports for a fee. In recent years, ad hoc reporting has become a must-have feature, allowing users to create their own reports.
- *Electronic patient-reported outcomes capabilities*—A methodology that allows patients to complete self-report symptoms or any adverse effect of a therapy. This can be

Table 15.1 List of the main electronic data capture systems and their features

EDC system	Vendor	License	Offline capability	Randomization	User authentication	CDISC certification	Ad hoc reporting	ePRO capabilities	Multi language	On demand export	PDF archiving	Document management	Electronic signature	Audit trail	Import/export
1. CleanWEB	Telemedicine Technologies S.A. Boulogne-Billancourt, France http://cleanweb.tentelemed.com	Commercial		Yes	Yes	Yes		Yes	Yes		Yes		Yes	Yes	X-ray, ECG
2. ClinPlus	DZS Software Solutions West Bound Brook, NJ, USA https://www.clinplus.com	Commercial		Yes[a]	Yes		Yes		Yes	Yes		Yes	Yes	Yes	
3. ClinicalStudio	Crucial Data Solutions, Inc. Reno-Tahoe, NV, USA http://www.clinicalstudio.com	Commercial		Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes	Images, ODM, SAS, XML, SPSS, Excel
4. Dados Prospective	Techna Toronto, Ontario https://www.dadosproject.com	Open source			Yes						Yes		Yes	Yes	Capture handwritten data from paper documents
5. DatatrakONE	DATATRAK International, Inc. Cleveland, OH, USA http://www.datatrak.com	Commercial		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		DICOM images CSV, SAS program and datasets
6. Express EDC	BioClinica Newtown, PA, USA http://www.bioclinica.com	Commercial		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		ECG, Central Safety Lab SAS, ODM, Microsoft Access

7. Forte EDC	Forte Madison, WI, USA https://forteresearch.com	Commercial			Yes		Yes						Yes		
8.InForm GTM	Oracle Corporation Redwood Shores, CA, USA http://oracle.com	Commercial	Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes		
9. MARVIN	XClinical GmbH Munich, Germany http://xclinical.com	Commercial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Images, X-rays, PDF and XML archiving
10. medrio	Medrio San Francisco, CA, USA http://medrio.com	Commercial	Yes	Yes[a]	Yes		Yes	Yes		Yes	Yes	Yes	Yes	Yes	
11. iMedNet	MedNet Solutions, Inc. Minnetonka, MN, USA http://www.mednetstudy.com	Commercial		Yes	Yes		Yes	Yes		Yes	Yes		Yes	Yes	DICOM images, SAS, CSV, Excel and ODM, XML
12. OpenClinica	OpenClinica Waltham, MA, USA www.OpenClinica.com	Open source	Yes	Yes[b]	Yes			Yes[b]		Yes	Yes		Yes	Yes	XML, SOAP, HTML, tab-delimited, Excel, and SPSS export
13. Oracle Remote Data Capture	Oracle Corporation Redwood Shores, CA, USA http://oracle.com	Commercial			Yes					Yes			Yes	Yes	
14. Rave	Medidata Solutions New York City, NY, USA https://www.mdsol.com	Commercial		Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	SAS, Excel

(continued)

Table 15.1 (continued)

EDC system	Vendor	License	Offline capability	Randomization	User authentication	CDISC certification	Ad hoc reporting	ePRO capabilities	Multi language	On demand export	PDF archiving	Document management	Electronic signature	Audit trail	Import/ export
15. REDCap	Vanderbilt University Nashville, TN, USA https://projectredcap.org	Open source[c]	Yes		Yes		Yes		Yes	Yes		Yes	Yes	Yes	Excel, PDF, SPPSS, Stata, R export
16. TrialMaster	OmniComm Systems Fort Lauderdale, FL, USA http://www.omnicomm.com	Commercial		Yes	Yes		Yes	Yes	Yes	Yes	Yes		Yes		SAS, CSV, SDTM, TAB, XML formats
17. Viedoc	PCG Clinical Services Uppsala, Sweden https://www.viedoc.com	Commercial		Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CSV, SAS program and datasets, PDF archive, CDISC ODM

EDC electronic data capture, *CDISC* clinical data interchange standards consortium, *ePRO* electronic patient-reported outcomes, *CSV* comma-separated values, *SAS* statistical analysis system, *ODM* operational data manager; XML, extensible mark-up language, *SOAP* simple object access protocol, *HTML* hypertext mark-up language, *SPSS* statistical package for social science, *SDTM* study data tabulation model, *DICOM* Digital imaging and communication in medicine

[a]Optional licensing

[b]OpenClinica Randomize/Participate, fully supported version

[c]Available at no cost only for REDCap Consortium Partners

achieved by using a mobile device (e.g., a tablet) or it can be web-based via *interactive web response* or phone-based with *interactive voice response*.

- *Multi-language*—Clinical trials are run all over the world, and although English is the standard for scientific publications, sometimes there is the need to collect data in the local language. A multi-language system allows CRF content to be automatically translated and, in some cases, allows simultaneous use of multiple languages.
- *On-demand export*—It is the ability to schedule data downloads in different formats (SAS, XLS, CSV, ASCII etc.) but should also provide data on demand to offer immediate availability.
- *Portable document format* (PDF) *archiving*—At the end of a trial, it is often necessary to provide an archive copy of the data collected during the trial. The PDF is a very popular format and very similar to a paper document. Reports including all queries and audits can be prepared and provided to each center participating in the trial.
- *Document management*—It is the capability to store documents related to the trial.
- *Electronic signature*—The electronic signature authorized by a researcher is the legally binding equivalent of the individual's handwritten signature.
- *Audit trail*—It is a record providing documentary evidence of the sequence of activities and/or changes that have affected, at any time, a specific operation, procedure, or event.
- *Import/export*—It is the capability to import/export different types of data, such as DICOM (digital imaging and communications in medicine), XLS (Excel), SAS (Statistical analysis system), etc.

Interestingly, only one EDC system listed in Table 15.1 (MARVIN, XClinical GmbH Munich, Germany) provides all the above-mentioned features, including the possibility to import/export images. All EDC systems provide electronic signature, while offline capability is available in only five. Most of EDC systems have a commercial license, while only two are open-source with obviously fewer features. Twelve of the 17 EDC systems of Table 15.1 are developed in the USA, likely reflecting a tighter control from the Food and Drugs Administration over clinical trials.

Notably, in a clinical trial, it is the responsibility of the principal investigator (or of the sponsor, when present) to ensure and document that the EDC system conforms to the established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation). Moreover, the principal investigator/sponsor should maintain *standard operating procedures* for using these systems. The standard operating procedures should cover system set up, installation, and use and should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.

15.4 EDC Systems in Imaging Research

EDC systems are still poorly used in breast imaging research and imaging research in general. They are stand-alone systems, not being interconnected to other *eHealth* applications. In particular, handling of images is still insufficiently supported. This is rather disappointing, as medical imaging is looming large today in clinical trials. Image-based surrogate endpoints provide eligibility, efficacy, and security evaluation by qualitative and quantitative disease finding in clinical studies [15]. In particular, there is a poorly structured way to capture DICOM data in EDC systems.

So far, storage or retrieval of DICOM-based data in the CRF is impossible, and interfaces for DICOM-based communication are unavailable. Images are transferred manually between the systems in roundabout ways. Manual interaction of study personnel is required, decreasing data quality, increasing processing time, and increasing costs.

The *Medical Imaging Resource Center* of the *Radiology Society of North America* is a sharing platform for teaching files and clinical trial data [16]. An open-source imaging platform for

sharing, management, processing, and distribution of images and related study data is offered with the *Extensible Neuroimaging Archive Toolkit* of the *Neuroinformatics Research Group* [17]. However, these solutions are rather specialized systems for certain diseases and disconnected from the EDC system.

There are few commercial systems such as *iMedNet EDC* (http://www.mednetstudy.com/technology/imednetedc) that support storing and viewing of DICOM data. However, particularly for investigator-initiated trials and academic research, commercial approaches are rarely adopted due to their high costs.

An example of ad hoc noncommercial EDC systems integrating images was developed by van Herk [18], who utilized *OpenClinica* (www.OpenClinica.com) and *Conquest* (http://ingenium.home.xs4all.nl/dicom.html) as EDC system together with the *Picture Archiving and Communication System* (PACS). However, with this system, DICOM objects must be already available in Conquest. Advanced DICOM viewing functionality is not provided, limiting user interaction conducting the trial. A similar architecture was proposed by Skripcak [19] connecting OpenClinica and Conquest with Lua scripts. DICOM data are integrated via a stand-alone client, which transfers images to the PACS and inserts references in the CRF via web service envelopes. However, images cannot be stored directly via the web, and a special client has to be installed on all systems. Finally, an entirely web-based solution integrating EDC, PACS, and DICOM viewer, implemented using the open-source projects OpenClinica, was developed by Haak and co-workers [20].

15.5 The HIBCRIT Study: An Ad Hoc Application

As explained in other chapters of this book, the *High Breast Cancer Risk Italian* (HIBCRIT) multicenter study [8]—coordinated by the Istituto Superiore di Sanità (ISS, Rome) with funds of the Italian Ministry of Health—compared since June 2000 clinical breast examination, mammography, ultrasound, and MRI in the surveillance of women at high risk of breast cancer (HIBCRIT-1). Considering the large number of measured variables by dozens of imaging and non-imaging specialists located in many different Italian institutions, as well as the high number of images obtained in several screening rounds, a bulk of data had to be stored for analysis. Thus, an effective EDC had to be developed to allow a more efficient conduct of the second phase of this study (HIBCRIT-2) that is currently ongoing.

The main objectives of such a system had to be the followings: 1) to consolidate the multicenter network already activated in the first phase of the project (HIBCRIT-1), 2) to extend the network to include additional institutions, 3) to update the shared protocol for screening women at high genetic-familial risk of breast cancer, 4) to develop a more advanced centralized platform of data collection, management, and analysis to serve as a basis for more extended screening projects.

Managing such a bulk of clinical data required a dedicated study-specific EDC, with high performance as well as software and hardware resources. The technology used for that task was not the most advanced available at that moment. Indeed, none of the EDC systems listed in Table 15.1 was chosen, as none of them allowed for a graphical representation of the investigated breasts, with a visual localization of the detected lesions. Thus, an *ad hoc* locally developed EDC was conceived and implemented, also taking into account future adaptation and extension to a larger setting. The implementation of this EDC was possible, thanks to a synergic effort of the service supplier and the experts coordinating the HIBCRIT study.

Analysis, design, and implementation can be summarized in the following steps:

1. Definition of the overall requirements
2. Set up of the hardware platform (storage, connectivity, and disaster recovery systems)

3. Set up of the database with its GUI
4. User technical documentation
5. Overall final testing
6. Deployment

Two information technologists worked on the project, one software engineer (for the EDC design) and one database manager (for the software implementation and integration). As schematically represented in Fig. 15.1, this system consisted of three main parts: (a) a *relational database,* for centralized collection of patient data (including a GUI for lesion localization) with predefined protocols for connecting all participating center to the database, (b) a repository for the storage of anonymized images, and (c) a website to allow the users to access the network-reserved documentation.

15.5.1 Relational Database

A database is an archive (or a set of archives), where information and data are structured and linked together according to specific modalities (*logical models*). Among the three classical logical models (hierarchical, relational, and network), the relational one is the most used. In the relational model, all information are grouped into relations [21]. The relational model has many advantages over other models, in what it (1) is based on solid mathematics [22], (2) allows the identification and elimination of data redundancy, and (3) allows data manipulation by an easy and human-readable language, the *structured query language*. The HIBCRIT database was set up using Microsoft Structured Query Language Server 2008 (Microsoft Corporation, Redmond, WA, USA), while the GUI was developed using Microsoft Access.

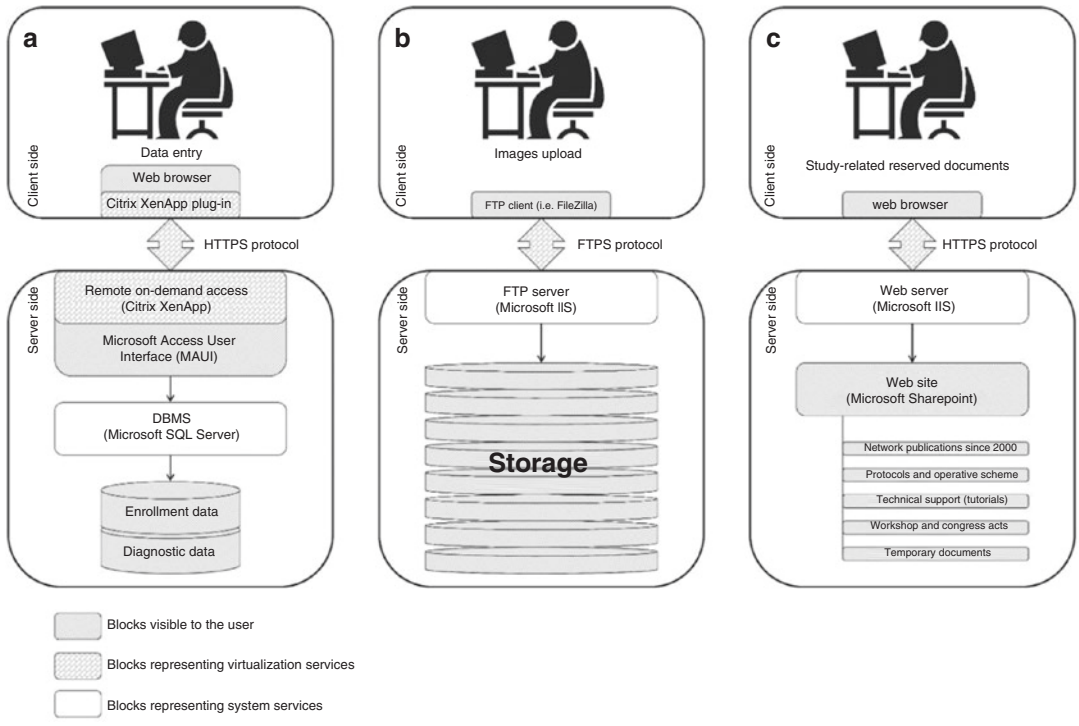

Fig. 15.1 Schematic representation of the electronic data capture system implemented ad hoc for the HIBCRIT-2 study

The relational database was composed by two macrosections, one devoted to the enrollment and the other to the multimodal imaging. In turn, these main blocks were divided in subsections, according to the scheme reported in Fig. 15.2.

The GUI was developed to allow data entry and to perform few, well-defined operations by the users. Checks for data consistency were also implemented. For example, the tables *Biopsy*, *Surgery*, and *Histopathology* in Fig. 15.3b were accessible only if the correspondent findings were described in the GUI reported in Fig. 15.4 in one of the imaging modalities.

In the first macrosection (*Enrollment*), the user could enter the patient personal data as well as family history, previous events of breast and/or ovarian cancer, and participation in primary and/or secondary prevention programs (Fig. 15.3a). The second macrosection (*Diagnostics*) contained detailed information concerning the results of clinical breast examination and imaging modalities. If invasive procedures such as fine-needle aspiration and core needle/vacuum-assisted/surgical biopsy were performed, a detailed description of the findings could be entered in the proper subsections, as well as the modalities which prompted the procedure (Fig. 15.3b). Data were automatically saved when exiting macrosections, but later modifications were still possible at this stage. When a given patient CRF was complete, confirmation of the final submission was prompted to prevent patients with missing information. After finalization, already entered data could not be further modified without a special permission by the system administrator.

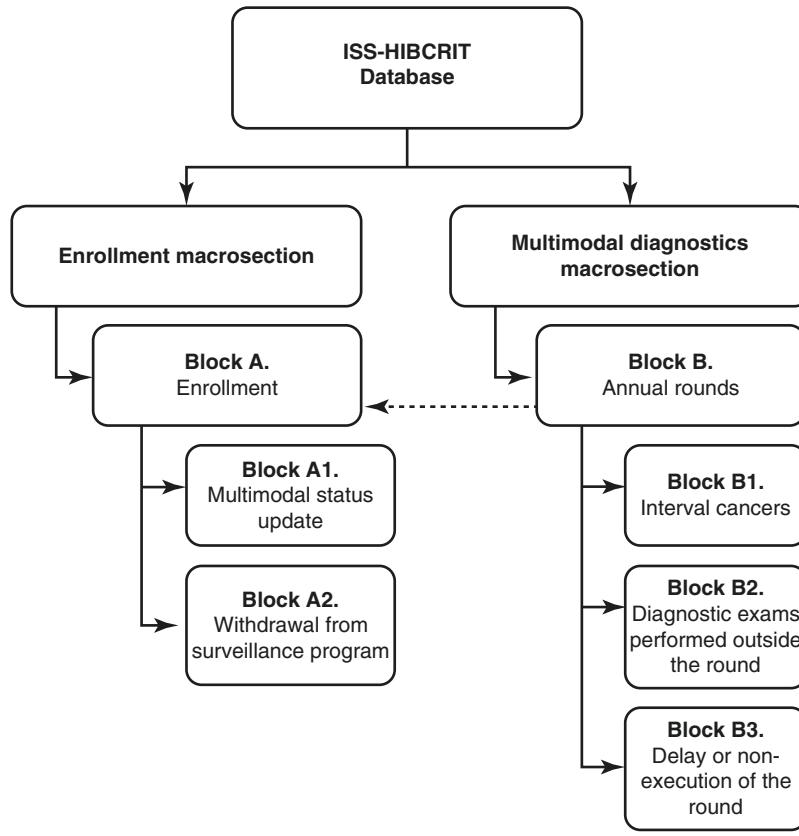

Fig. 15.2 Structure of the HIBCRIT-2 database

Fig. 15.3 Screenshot of the enrollment (**a**) and diagnostic (**b**) macrosections in the HIBCRIT-2 study. Several cross-checks were implemented. For example, the mammography table of the diagnostic macrosection was active only for women older than 35 years, while at second look, US and repeat MRI sections were accessible only if MRI findings were reported

15.5.2 Graphical User Interface for Lesion Localization

Regarding the multimodality diagnostic macrosection, a GUI was developed to report the location of the detected lesions (Fig. 15.4). It provided a schematic representation of the breasts (including nipples and axillary regions) and consisted of a grid where each pixel could be flagged to indicate the rough position of a lesion, coded by numbering and technique. The system granted a one-to-one correspondence between graphically reported data and relative description in the database.

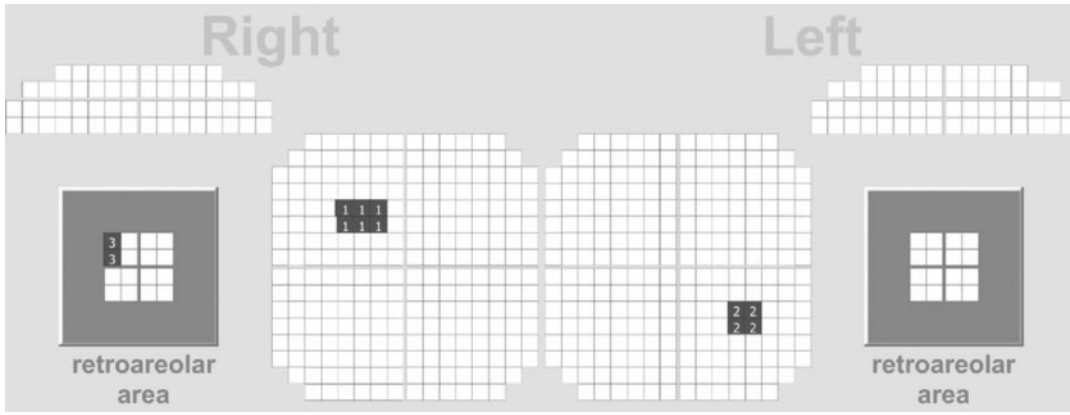

Fig. 15.4 Graphical user interface for localization of breast lesions revealed by any imaging technique in the HIBCRIT-2 study

15.5.3 Connecting Centers to the Database

After set up, remote workstations could securely access the GUI through web browser (*Internet Explorer, Firefox, Chrome*, or others) via *HyperText Transfer Protocol* over secure socket layer (HTTPS). Set up consisted of installation of both a security certificate (3-year validity) and *Citrix XenApp* client. The XenApp suite (formerly known as *Metaframe* server) developed by Citrix (Fort Lauderdale, FL, USA) is widely used for remote on-demand access to applications housed on a central server [23, 24].

The access to the database needed authentication using credentials provided to each participating center. The local principal investigator identified the operator(s) authorized to data entry for the creation of respective dedicated user area.

15.5.4 Image Repository

The storage of huge amounts of data required high-performance, reliable, and scalable equipment. Anonymized images were uploaded after encoding, so to ensure a one-to-one correspondence between database and image repository. An extension of the *File Transfer Protocol Secure* (FTPS) was used to upload the radiological images. On the server side, FTPS service was offered by *Microsoft Internet Information Services*; on the client side, any FTPS client could be used, although the open source *FileZilla FTPS* client (http://filezilla-project.org) was recommended. Database and repository were independent on one another, so to avoid the lock of data entry until the image upload was completed.

15.5.5 The Website

A website was implemented by using *Microsoft SharePoint* (Microsoft Corporation, Redmond, WA, USA). This website was reserved to the centers participating in the HIBCRIT study and to the *Ministry of Health* (as well as, upon request, to the *Regional Health Authorities*) and contained the whole documentation of the study.

15.5.6 The HIBCRIT-2 Study in Numbers

The patient enrollment started in April 2009. Twenty-six centers were progressively connected. By June 30th, 2012, 763 women had been enrolled for a total of 1,963 diagnostic rounds. In the image repository were stored the following:

- Mammography, for a total of 4,051 images and 6.5 GB
- Ultrasound, for a total of 2,866 images and 3.5 GB
- MRI, for a total of more than 1 million images and 410 GB

Overall, this EDC system costed as follows:

1. Analysis and design, 80 man-hours (€ 3,000)
2. Design and implementation of database, 160 man-hours (€ 4,000)
3. GUI development, 160 man-hours (€ 4,000)
4. System testing, 80 man-hours (€ 2,000)
5. GUI enhancement and bug correction, 320 discontinuous man-hours (€ 8,000)
6. Storage, approximately (€ 31,000)

The total gross cost was approximately € 51,000. The time needed for the development and implementation of this EDC system up to the activation of the first center was approximately 12 months.

15.6 The MIPA Study: An OpenClinica Application

OpenClinica (OpenClinica, Waltham, MA, USA) is the world's leading open-source EDC system for clinical data management and is compliant with the guidence of the Food and Drug Administration [10, 25–27]. It has a modular design with separate modules for study set up, data submission, monitoring, and extraction. It is a *do-it-yourself* tool in what the system administrator(s) can develop a clinical study database from an easy-to-use GUI.

Based on their access policy and permissions, individual users participating in a clinical trial can manage specific modules and/or functions. OpenClinica offers a complete online documentation, templates to create CRFs, forum, and examples. The administrator has total access to all subjects enrolled by all centers, exclusive of rights to extract patient data and the ability to modify the content of any CRF at any time. Although it does not require large technical skills, it is advisable that the system is managed by a professional technician (for instance, an engineer). The main steps involved in designing a clinical trial using OpenClinica are described below to demonstrate the power of this system.

The MIPA study (*Preoperative Breast MRI in Clinical Practice: Multicenter International Prospective Analysis*—ISRCTN41143178) is an ongoing prospective observational multicenter trial investigating the impact of preoperative MRI on the surgical management of patients newly diagnosed with breast cancer. It is a project involving 27 enrolling centers around the world and collecting a huge amount of data, regarding personal information, imaging (digital mammography, ultrasound, MRI), tissue sampling, planned and performed surgical treatment, final pathology, and 5 years of follow-up. In clinical studies like this, identifying an efficient EDC system is extremely important to allow the management of the whole study.

Considering the available resources, OpenClinica was identified as the best solution for the MIPA study. For the purpose of the study, OpenClinica was installed on a server cloud to improve the performance, its stability, and the data security. OpenClinica can be downloaded and easily installed by following the online documentation. After installing the package, the administrator can start to *build* the study. OpenClinica allows the management of more than one study simultaneously within the same installation. For the MIPA study, a pilot procedure was created to test all the CRFs, fix potential bugs, and optimize the whole process.

The MIPA study is organized in two main events, the baseline assessment and the follow-up. Baseline includes eight CRFs, namely:

1. Enrollment
2. Imaging studies 1 (digital mammography, ultrasound)
3. Imaging studies 2 (MRI)
4. Tissue sampling
5. Planned surgical treatment

6. Performed surgical treatment
7. Final pathology
8. Nonsurgical therapy

The follow-up event is a repetitive event, as it can be scheduled as many times as appropriate. As per the study protocol, it includes only one CRF for each of the 5 years of follow-up. Thus, for each patient, a total of 13 CRFs must be completed. The person in charge of the *data entry*, after adding a new subject, can complete all the CRFs or only some of them, especially when the data are not yet available (e.g., final pathology or follow-up). The user can edit a CRF easily, several times until it has not been marked as *complete*. Once a CRF is marked as complete, the user can still change the already entered data but must give an explanation (*reason for change*). Only when all the baseline CRFs of a given subject are complete, the event *Baseline* is complete. OpenClinica shows different status with different icons (Fig. 15.5).

OpenClinica allows to define different users with different roles/permissions. The main roles involved in the MIPA study are as follows:

- *Data manager*—can submit, monitor, manage, and extract data, view and build studies, and assign users
- *Data entry person*—can only enter patient data
- *Data monitor*—can monitor, manage, and extract data

The Administrator (the so-called superuser) is similar to the data manager but with the additional permission to switch among all the clinical trials (if any) implemented in the same installation.

The implementation of a new clinical trial is quite simple. OpenClinica offers an easy-to-use process based on excel files: each CRF is a spreadsheet where questions, answers, and rules are defined. When the excel file is uploaded into

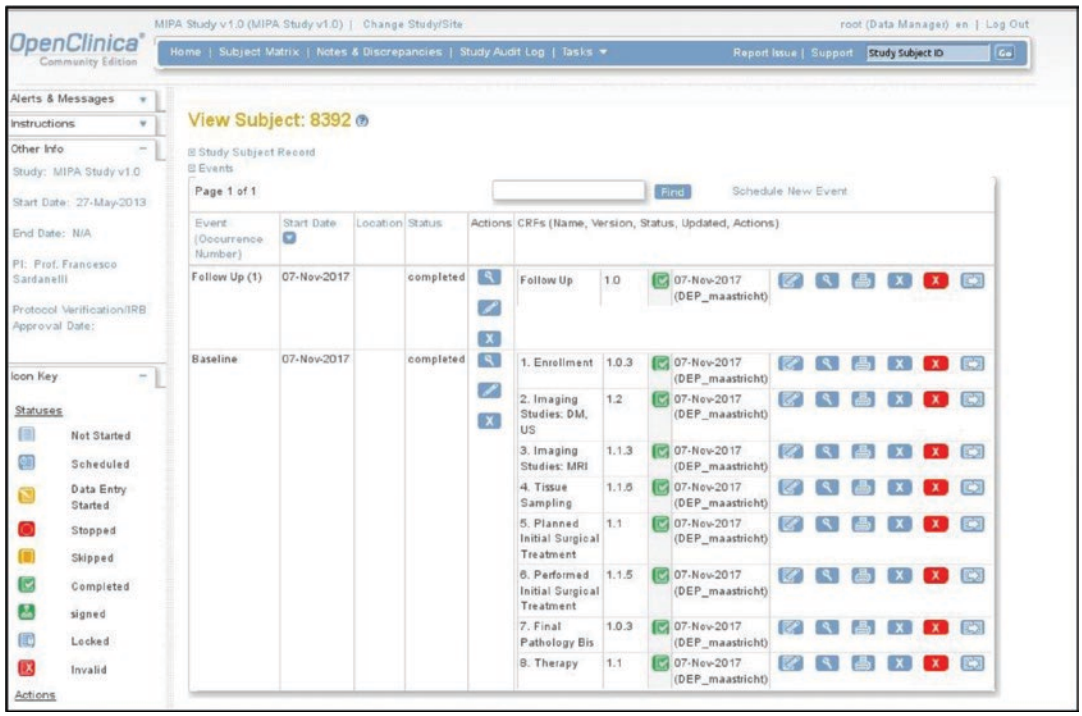

Fig. 15.5 This screenshot shows the eight CRFs of the *Baseline* event and only one CRF of the *Follow-up* event for the subject ID 8392 of the MIPA study

OpenClinica, the system checks the syntax and, if everything is ok, the CRF is ready to use. However, given the intrinsic complexity of the whole process, few trials proceed exactly as initially planned. As it happened in the MIPA study, changes may be implemented in the course of the trial: CRFs may need updating, new sites (and users) may be added, and new technologies may emerge.

Despite the several advantages of OpenClinica, managing the MIPA study with this system implied some limitations, especially regarding cross-checks among different CRFs. Splitting the CRF in several parts (eight CRFs for the Baseline event and one CRF per each year of follow-up) was essential to allow data entry users to handle the amount of data required, but it introduced the need to duplicate some data. For example, the specification of the lesion laterality is required in all CRFs of the Baseline event. As OpenClinica does not provide the possibility to implement inter-CRF cross-checks (only intra CRF checks are allowed), an ad hoc external tool had to be developed to cross-check datasets and to verify the data integrity and consistency. Another limitation is that exported data must be decodified as all questions and related answers are coded in alphanumeric words. As for data cross-checks, another ad hoc external tool had to be developed to make datasets easily interpretable by users different from those who have developed the CRFs (e.g., the statistician). These limitations were easily solved by including in the MIPA study team a data manager with technical skills to manage the study, to implement the CRFs, to perform the quality assurance checks, and to extract the datasets.

15.7 Conclusions

Large multicenter clinical trials such as those on breast cancer screening of high-risk women typically involve a huge amount of data and images to be collected, stored, and processed by the local and principal investigators. Relatively few years ago, this task was accomplished through paper CRF and by sending source documents and digital media (e.g., compact disk) via regular mail all over the world. Study monitoring also implied clinical trial monitors to move all around for data quality check. All these activities intrinsically implied big efforts and costs that could be covered only by industries.

In the current era of information technology revolution, these limitations may be easily overcome using EDC systems that greatly increase a trial feasibility. To date, clinical studies may be conceived larger than ever, with obvious advantages for the scientific community and, finally, for patients.

Authorities have acknowledged that standards and capabilities of electronic systems have improved, and features such as audit trails, automated date-and-time stamps, appropriate validation, and the ability to generate copies and retain records are standard components of many EDC systems. Thus, new regulations for a proper use were introduced, including legal binding of electronic signatures, that are equivalent in all to regular handwritten signatures. New regulations have also appeared concerning the processing of personal data and the protection of privacy in the electronic communications sector.

Several EDC systems, both commercial and open-source, have been developed to cover all aspects of a clinical trial, discharging investigators from administrative tasks and largely improving quality. Contract research organizations are still leading clinical research, especially on pharmaceuticals, with their expertise in reviewing and negotiating all required essential regulatory documents and the ability to identify activities along critical paths and completion of all site start-up activities for a study. However, it is more and more important for researchers to understand these tools in order to better interface with collaborators and with other experts. Especially, radiologists and imaging specialists carrying out spontaneous low-budget research should be aware of these systems, in order to be able to select the most appropriate one and cooperate in their start up.

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References

1. Sardanelli F, Di Leo G (2009) Biostatistics for radiologists. Springer, Milan, pp 150–153
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1996) Guideline for good clinical practice E6(R1). https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed 30 Jun 2020
3. Hemminki A, Kellokumpu-Lehtinen PL (2006) Harmful impact of EU clinical trials directive. BMJ 332:501–502
4. Grimes DA, Hubacher D, Nanda K et al (2005) The good clinical practice guideline: a bronze standard for clinical research. Lancet 366:172–174
5. Pocock SJ (2006) The simplest statistical test: how to check for a difference between treatments. BMJ 332:1256–1258
6. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357:1191–1194
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2016) Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf. Accessed 30 Jun 2020
8. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol 46:94–105
9. European Parliament (2002) Directive 2002/58/EC of the European parliament and of the council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0058:EN:pdf. Accessed 30 Jun 2020
10. U.S. Department of Health and Human Services Food and Drug Administration (2007) Guidance for industry—computerized systems used in clinical investigations. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070266.pdf. Accessed 30 Jun 2020
11. Shah J, Rajgor D, Pradhan S, McCready M, Zaveri A, Pietrobon R (2010) Electronic data capture for registries and clinical trials in orthopaedic surgery: open source versus commercial systems. Clin Orthop Relat Res 468:2664–2671
12. Staziaki PV, Kim P, Vadvala HV, Ghoshhajra BB (2016) Medical registry data collection efficiency: a crossover study comparing web-based electronic data capture and a standard spreadsheet. J Med Internet Res 18:e141
13. Walther B, Hossin S, Townend J, Abernethy N, Parker D, Jeffries D (2011) Comparison of electronic data capture (EDC) with the standard data capture method for clinical trial data. PLoS One 6:e25348
14. Dillon DG, Pirie F, Rice S et al (2014) Open-source electronic data capture system offered increased accuracy and cost-effectiveness compared with paper methods in Africa. J Clin Epidemiol 67:1358–1363
15. Miller CG, Krasnow J, Schwartz LH (2014) Medical imaging in clinical trials. Springer, London
16. Gentili A, Chung CB, Hughes T (2007) Use of the MIRC DICOM service for clinical trials to automatically create teaching file cases from PACS. Radiographics 27:269–275
17. Gao Y, Burns SS, Lauzon CB et al (2013) Integration of XNAT/PACS, DICOM, and research software for automated multi-modal image analysis. Proc SPIE Int Soc Opt Eng 8674: https://doi.org/10.1117/12.2007621
18. van Herk M (2014) Integration of a clinical trial database with a PACS. JPCS 489:12099
19. Skripcak T (2014) Lessons learned from integrating OpenClinica with other IT systems. https://community.openclinica.com/sites/fileuploads/akaza/cms-community/Tomas%20Skripcak%20-%20Lessons%20learned.pdf. Accessed 30 Jun 2020
20. Haak D, Page CE, Reinartz S, Krüger T, Deserno TM (2015) DICOM for clinical research: PACS-integrated electronic data capture in multi-center trials. J Digit Imaging 28:558–566
21. Date CJ (2012) Database design and relational theory: normal forms and all that jazz, 1st edn. O'Reilly Media, Sebastopol
22. de Haan L, Koppelaars T (2007) Applied mathematics for database professionals, 1st edn. Apress Media LLC, New York
23. VanderClute S (2003) How the information highway can help manage medical equipment. Biomed Instrum Technol Suppl:7–8
24. Cadick R (2004–2005) Implementing Citrix: weighing the pros and cons. Biomed Instrum Technol Suppl:23–24
25. Afrin LB, Kuppuswamy V, Slater B, Stuart RK (1997) Electronic clinical trial protocol distribution via the World-Wide Web: a prototype for reducing costs and errors, improving accrual, and saving trees. J Am Med Inform Assoc 4:25–35
26. Fegan GW, Lang TA (2008) Could an open-source clinical trial data-management system be what we have all been looking for? PLoS Med 5:e6
27. Ngari MM, Waithira N, Chilengi R, Njuguna P, Lang T, Fegan G (2014) Experience of using an open source clinical trials data management software system in Kenya. BMC Res Notes 7:845

16 Guidelines and Recommendations on High-Risk Breast Cancer Screening All Over the World: Agreements and Differences

Ayla Selamoglu and Fiona J. Gilbert

Abbreviations

ACS	American Cancer Society
BC	Breast cancer
CBE	Clinical breast examination
LTR	Lifetime risk
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OECD	Organization for Economic Cooperation and Development
US	Ultrasound, Ultrasonography
WHO	World Health Organization

16.1 Introduction

Following compelling evidence from many trials for the increased sensitivity of regular magnetic resonance imaging (MRI) screening compared to mammography for women with hereditary predisposition to breast cancer (BC), many countries have introduced regular surveillance for this group of women. Despite the same evidence being available, policy makers have adopted different eligibility criteria for high-risk screening, with variable starting and finishing ages and different imaging modalities to screen for BC. Reasons for the adoption of slightly different strategies for screening implementation are not always clear. The decision is sometimes based on the willingness of the policy makers to pay for this type of intervention. This chapter examines population screening policies in different countries and discusses the similarities and differences for high-risk screening. Our hypothesis is that countries with high expenditure on healthcare are more likely to implement a high cost screening program (albeit for a small proportion of the population). However, the number of MRI scanners may also influence the decision on whether or not to offer MRI screening. Another factor to consider is the policy maker's attitude to population breast screening.

16.2 Health Expenditure and MRI Scanners

Initially, we look at the amount spent in each country on healthcare, as a measure of their willingness to pay for health interventions.

Data derived from the World Health Organization (WHO) [1] on total health expenditure as a percentage of the gross domestic product for 2014 indicates which countries worldwide

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spend the most and least on healthcare per capita. The Organization for Economic Co-operation and Development (OECD) [2] lists countries worldwide from 2013 specifying MRI units as a total in hospitals and ambulatory care providers per 1,000,000 inhabitants. Analyses between the amount countries spend on healthcare and the number of MRI units in hospital and ambulatory care providers do not suggest a strong positive correlation between health expenditure and MRI units. Table 16.1 depicts health expenditure (USD) per capita and MRI units per 1,000,000 inhabitants. For example, Japan has an intermediate health expenditure of $3,703 per capita [1], but has the highest number of MRI units at 45.9 units per 1,000,000 inhabitants [2]. The second highest is the USA with 35.5 units per 1,000,000 inhabitants [2] where the health expenditure is the highest ($9,403 per capita), followed by Germany with 28.9 MRI units per 1,000,000 inhabitants [2] and $5,411 health expenditure per capita. As illustrated in Fig. 16.1, there is an only weak correlation between healthcare expenditure and MRI scanners per capita, with a strong outlier (Japan).

Table 16.1 Health expenditure and MRI units by country

Country	Health expenditure per capita (USD)	MRI units per 1,000,000 inhabitants
Australia	6,031	13.4
Austria	5,580	19.2
Canada	5,292	8.9
Germany	5,411	28.9
Ireland	4,239	13.3
Israel	2,910	3.5
Italy	3,258	25.2
Japan	3,703	45.9
New Zealand	4,896	11.3
Norway	9,522	Not available
Spain	2,658	15.3
The Netherlands	5,694	11.5
Turkey	568	9.9
United Kingdom	3,935	6.1
United States	9,403	35.5

16.3 High-Risk Screening Guidelines

The implementation of MRI as a tool for BC diagnosis was first tested in the 1980s, and since then, studies have reported its positive and negative aspects. As described in other chapters of this book, research into the use of MRI in high-risk screening cohorts of women reported that MRI was significantly more sensitive than mammography, ultrasound (US), or clinical breast examination (CBE). The use of MRI in screening programs makes earlier diagnosis a real possibility, especially in younger premenopausal women where there is a much higher likelihood of dense breast tissue. The USA has firstly implemented guidelines [3] for the surveillance of high-risk women with MRI; many countries worldwide

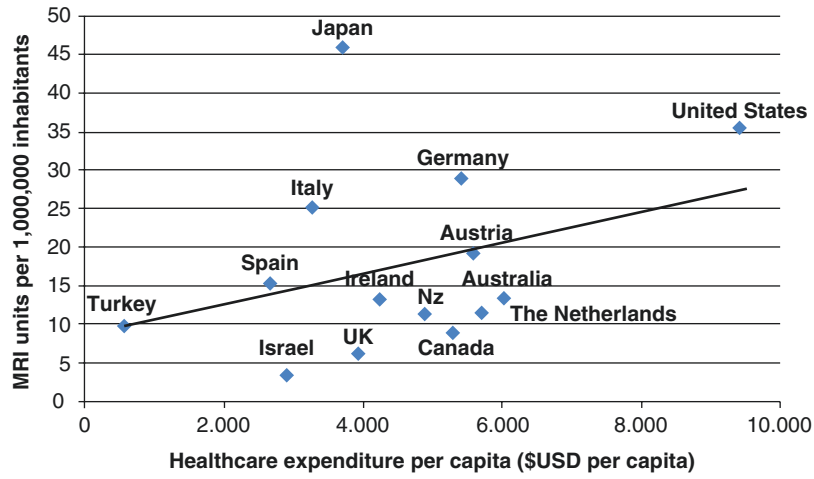

Fig. 16.1 Scatterplot of MRI units by health expenditure by country. There is a weak but significant correlation between the two series of data ($r = 0.340$, $R^2 = 0.115$). Notably, excluding the outlier (Japan), $r = 0.570$, $R^2 = 0.325$

Table 16.2 High-risk screening by country and age range

Country	Age range
Australia [4, 5]	50 years or under
Austria [6]	25 years and over
Belgium [7, 8]	30 years and over
Canada [9]	30–69 years
France [10]	30 years and over
Germany [11]	25 years and over
Ireland [12]	30–49 years (20–49 for *TP53* carriers)
Israel [13]	40 years and over
Italy [14]	25 years and over
Japan [15]	25 years and over
Malaysia [16]	30 years and over
New Zealand [17]	30 years and over
Norway [18]	25–70 years
Spain [19, 20]	25–70 years
Sweden [21]	25–74 years
The Netherlands [22]	25 years and over
Turkey [23]	25 years and over
United Kingdom [24]	30–60 years* (20 years and over for *TP53* carriers)
United States ACS [3]	30 years and over
United States NCCN [25]	25–75 years

*30–49 years: with MRI; 40–59 with mammography

have subsequently adopted their own versions with some similarities and some differences.

Table 16.2 lists in detail the recommendations for each country, the reference(s), the eligibility criteria, the age at which screening starts and stops, and the type(s) of imaging modality offered. The American Cancer Society (ACS) [3] advised that women from the age of 30 years with a high-risk of developing BC begin annual MRI screening as an adjunct to mammography and continue to do so as long as they are in good health. Eligibility criteria are as follows:

1. To have a known *BRCA1* or *BRCA2* mutation.[1]
2. To be first-degree relative (i.e., parent, sibling, child) with a *BRCA1* or *BRCA2* mutation carrier and have not had previous genetic testing themselves.
3. To have a history of radiation therapy to the chest between the ages of 10 and 30 years.
4. To have a lifetime risk (LTR) of BC of 20% to 25% or greater, based on one of several accepted risk assessment tools dependent on family history (e.g., Gail, Claus, or Tyrer-Cuzick models).
5. To be affected by Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or have a first-degree relative with one of these syndromes.

The American Cancer Society [3] also recommended against MRI screening for those women with a LTR of BC lower than 15%. It is also suggested that there is no valid evidence to recommend for or against annual MRI screening for those women who fall within the moderately increased risk cohort with an LTR between 15% and 20%, or who may have an increased risk due to certain factors outlined as follows:

1. To have a personal history of BC, ductal carcinoma in situ, lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia.
2. To have dense breasts (i.e., extremely or heterogeneously dense breasts) as observed on mammogram.

A recent review summarized these and other guidelines on the surveillance of *BRCA* mutation carriers issued by major North American bodies [26].

16.4 High-Risk Criteria

BC surveillance programs worldwide all have similar—yet somehow different—definitions both of what constitutes a high risk for BC and of the criteria required to entitle women to receive certain healthcare services within that country. In the UK, the National Institute for Health and Care Excellence (NICE) [24] has published a set of guidelines titled *Familial breast cancer, classification, care and managing breast cancer, and related risk in people with a family history of*

[1]All along this chapter, the term *mutation* as referred to *BRCA1*, *BRCA2*, *TP53*, or other genes associated with an increased BC risk has to be read as *deleterious mutation*.

breast cancer. The NICE guidelines [24] state that women who have not had genetic testing but have a greater than 30% probability of being a *BRCA* or *TP53* mutation carrier are considered at high risk, compared to the ACS definition that is also considered as high-risk first-degree relatives (i.e., parent, sibling, child) of *BRCA1* or *BRCA2* mutation carriers with no previous genetic testing, or with a LTR higher than 20% [3]. The ACS further recommended that questionnaire tools dependent on family history (e.g., Gail, Claus, or Tyrer-Cuzick) are to be used to assess LTR and that women who are affected by Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes, or have a first-degree relative with one of these syndromes, or have a history of radiation therapy should also be considered high risk [3], whereas the NICE guidelines make no recommendations for including these women [24].

16.5 Lifetime Risk Thresholds

Countries also vary in LTR thresholds, and certain countries define LTR based on dependent factors such as genetic, family, and medical history. In Canada [9], Italy [14], Turkey [23], and the USA [3, 25], guidelines have established that women with an LTR of 20–25% or greater are categorized as high risk. In Austria [6], women with an LTR of 20% or greater are considered high risk, without any range of uncertainty. In Germany [11], women with an LTR greater or equal to 30% are considered at high risk. In Spain [19, 20], an LTR ranging from 15% to 50% is taken into consideration, greatly depending on underlying factors based on genetic status as well as family and medical history. In Sweden [21], a similar yet more constricted range from 17% to 30% LTR is considered for determining the high-risk condition.

Conversely, other countries who have not established an LTR threshold take into account various factors based on genetic and family history to consider women as high risk. The Australian [4, 5] and Belgian [7, 8] guidelines are similar in that they indicate that women who are aged 50 years or lower with a strong family history of breast or ovarian cancer, or with known genetic mutations, or with Ashkenazi Jewish ancestry are defined as high risk. This includes three or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer, or one first- or second-degree relative diagnosed with BC at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger. In Ireland [12] and Israel [13], women with known *BRCA1*, *BRCA2*, or *TP53* mutations are considered high risk. In Malaysia [16], factors including family history, genetic mutations, personal history of invasive ductal or lobular carcinoma, or ductal carcinoma in situ, or benign breast disease with atypical hyperplasia are considered before classifying women as high risk. In New Zealand [17], risk categories developed by the Australian [4, 5] guidelines are followed; however, priority is also given to women of Māori and Pacific Islander descent, considering their higher incidence and mortality from BC, encouraging these women to be screened. Therefore, specific Māori healthcare services have been implemented to improve the Māori cancer experience such as employing Māori staff, setting up cultural practices, and staff alerting Māori patients to their entitlements (*e.g.*, transport, benefits, home help, and equipment) [4, 5]. In Norway [18], only women with a known *BRCA1* or *BRCA2* mutations are considered as high risk.

16.6 Age Ranges for Invitation to the Screening

Several countries worldwide have different age ranges for high-risk surveillance. The Department of Health in Australia has advised that women under the age of 50 who are at high risk of developing BC are recommended for annual MRI surveillance [4, 5]. The National Comprehensive Cancer Network (NCCN) in the USA [25] and European countries such as Austria [6], Germany [11], Italy [14], Spain [19, 20], and the Netherlands [22] all recommend beginning MRI surveillance at age 25 and above. Upper limits

are indicated in the Netherlands where MRI surveillance ends at age 60, in Germany where surveillance was extended to 70 years for mutation carriers and discontinued after age of 50 in non-carriers, and in Spain where annual breast MRI was extended to 70 for BRCA mutation carriers. Other countries such as Belgium [7, 8], Canada [9], France [10], Malaysia [16], New Zealand [17], and the American Cancer Society in the USA [3] all recommend beginning MRI screening for high-risk women at age 30, where Canada [9] suggests discontinuing screening at age 69, while the other countries have no upper age limit. Countries which recommend MRI screening to high-risk women beginning from the age of 20 are Ireland [12], Turkey [23], and the UK [24], where Turkey [23] has no upper age limit. Both Ireland [12] and the UK [24] begin screening at 20 for *TP53* mutation carriers and 30 for *BRCA1* and *BRCA2* mutation carriers; the UK [24] distinguishes the upper age limit according to the risk level and mutations, while Ireland [12] sets it at age 50. Israel [13] is the only country that suggests beginning MRI high-risk surveillance later on in life—at age 40—and to continue it as long as the screened women are in good health.

16.7 Imaging Modalities Recommended

Imaging modalities also vary in the surveillance programmes of countries worldwide. The guidelines for high-risk women in Australia [4, 5] and Israel [13] recommend annual MRI alone, without further requirements for any additional imaging, unless specified in consultation by a general practitioner or specialist. Many other countries including Austria [6], Belgium [7, 8], Canada [9], Ireland [12], Malaysia [16], Norway [18], Spain [19, 20], Sweden [21], the Netherlands [22], the UK [24], and the ACS in the USA [3] all indicate that MRI should be performed in adjunct to mammography annually. In addition to MRI and mammography, a CBE is also included as part of the high-risk surveillance guidelines for countries such as France [10], Italy [14], New Zealand [17], and Spain [19, 20] and in the NCCN guidelines [25] in the USA. Turkey [23] also recommends the addition of US to MRI and mammography. Germany [11, 27] and the NCCN have specific high-risk guidelines to recommend CBE and advise to consider US annually or semiannually, with MRI and mammography annually. In contrast, in Asia where the incidence of BC is the lowest in the world, countries such as Japan [15] and South Korea do not have any established surveillance and screening system for high-risk women: Japan relies on general but non-binding recommendations for the use of MRI annually (Table 16.3).

There is a general agreement worldwide that the frequency of MRI surveillance should be annual for women in the high-risk cohort. Austria [6] is the only country that has a slightly different definition of frequency, stating that MRI surveillance in high-risk women could take place annually, simultaneously with mammography, or alternating it every 6 months with mammography.

An international survey recently [28] assessed the schemes offered in high-risk clinics in different countries. An e-mailed survey was distributed to high-risk clinics affiliated with the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), Centre for Cancer Genetic Epidemiology, University of Oxford, Cancer Research, UK. A total of 22 centers from 16 countries answered. Surveillance schemes proposed before and after risk-reducing surgery overwhelmingly included breast imaging (primarily MRI) from 18 to 30 years and CBE at 6–12-month intervals. For ovarian cancer, all but six centers offered semiannual/annual gynecological exam, transvaginal US, and CA-125 assessment. After risk-reducing mastectomy, most centers offered only annual CBE examination, while four centers offered annual MRI (primarily for substantial residual breast tissue). After risk-reducing salpingo-oophorectomy, only four centers offered specific gynecological surveillance. The authors noted that the existing guidelines for breast/ovarian cancer detection in *BRCA* mutation carriers are being applied before risk-reducing surgery but are not globally harmonized, and most centers offer no specific surveillance post risk-reducing surgery, an issue that requires evidence-based and long-term prospective data on the most effective scheme to be applied.

Table 16.3 Summary of guidelines for high-risk breast cancer screening by country

Country [reference(s)]	Reference guideline	High-risk definition	Imaging modality	Age range (years)	Frequency
Australia [5, 7]	https://canceraustralia.gov.au/clinical-best-practice/breast-cancer/screening-and-early-detection/mri-high-risk-women http://www.health.gov.au/internet/main/publishing.nsf/Content/mri-breast-services-q-and-a	MRI scan of both breasts for the detection of cancer, if a dedicated breast coil is used; the request for scan identifies that the woman is asymptomatic and is ≤50 years of age, and the request for the scan identifies the following: (A) That the patient is at high risk of developing BC, due to one of the following: • ≥ three first DRs or second DRs on the same family side diagnosed with BC or OC • Two first DRs or second DRs on the same side of the family diagnosed with breast or ovarian cancer, if any of the following applies to at least one of the relatives: – Has been diagnosed with bilateral BC – Had onset of BC < 40 – Had onset of OC < 50 – Has been diagnosed with BC or OC at the same or at different times – Has Ashkenazi Jewish ancestry – Is a male who has been diagnosed with BC • One first DR or second DR diagnosed with BC at age ≤ 45, plus another first DR or second DR on the same family side with bone or soft tissue sarcoma at age ≤ 45 (B) A genetic testing has identified the presence of a high-risk BC gene mutation	MRI	≤50	Annually
Austria [11]	C.F. Singer, et al. 2015. The Central European Journal of Medicine	Females who fulfil ≥1 of the following criteria are considered at high risk: (A) Existence of >20% individual LTR to develop BC (B) Presence of a known germline mutation or presence of an unclassified variants in *BRCA1* or *BRCA2* (C) History of mantle field irradiation before 30 For them, annual mammography and MRI can be performed simultaneously every 12 months or alternating, every 6 months. If applicable, surveillance should be initiated at age 25 or 5 years prior to the age at which the youngest affected family member has developed the cancer. Annual mammography should be withheld until age 35 because of the exquisite radiosensitivity of breast tissue in mutation carriers and because of the decreased sensitivity that is observed in the relatively dense breast tissue that is characteristic for young age	MRI and mammography (no mammography before 35 years of age)	≥25 or 5 years prior to the age of the youngest affected family member	Annually, simultaneously or alternating every 6 months

Belgium [8, 12]	https://kce.fgov.be/fr/publication/report/d%C3%A9pistage-du-cancer-du-sein-comment-identifier-les-femmes-expos%C3%A9es-%C3%A0-un-risque-ac#.VIlwvXuKQk4 (Interpreted with Google Translate)	**KCE guidelines 2012** In high-risk women, a yearly mammography at 40–49 year is recommended. From age 50 to 69, high-risk women may participate in organized BC screening program with mammography every 2 year *(weak recommendation, very weak level of evidence)* In women with proven high risk, yearly mammography and MRI are recommended from age 30 or 5 years prior to age of the youngest affected family member *(strong recommendation, very weak level of evidence)*. The use of US can be considered, for example, to shorten the interval or as complementary examination in case of positive MRI or mammography *(weak recommendation, weak level of evidence)*	MRI	≥30 or 5 years prior to age of youngest affected family member	Annually
	http://www.domusmedica.be/ (Interpreted with Google Translate)	***Domus medica* guidelines 2016. Which women must be referred for screening?** **Recommendations** • Do not refer women <40 for screening mammography *(good practice point)* • Consider referring women with moderate higher risk aged 40–49 for yearly mammography *(good practice point)* • Refer women with moderate higher risk aged 50–69 for 2 yearly mammography *(Grade 1B)* • Refer women with moderate higher risk aged 70–74 in good health for two-yearly mammography *(Grade 1B)* • Do not refer women with moderate higher risk for screening MRI or US *(good practice point)* **High-risk women have a more favorable condition for repayment of mammography, US, and MRI in the presence of ≥1 of the following conditions:** • Two first DR or second DR diagnosed with BC < 50, ≥1 of them being first DR • Three first DR or second DR diagnosed with BC < 60, ≥1 of them being first DR • ≤ 4 relatives diagnosed with BC at any age, ≥1 of them being first DR • ≤ 4 paternal relatives diagnosed with BC < 60 • Personal history of BC or ductal or lobular atypical hyperplasia • OC in personal history or in a first DR or second DR • Genetic disease with high cancer risk (as Li-Fraumeni syndrome, Cowden disease) • *BRCA1*- of *BRCA2*-positive, personal or a first DR • Bilateral BC (within 2 years) in a first DR or second DR • BC in a male in a first DR or second DR • Sarcoma in a first DR or second DR, diagnosed <45 • Glioma of adrenal cortical cancer diagnosed in childhood in a first DR or second DR • Treatment with chest radiation therapy in personal history	Mammography	40–49	Annually

(continued)

Table 16.3 (continued)

Country [reference(s)]	Reference guideline	High-risk definition	Imaging modality	Age range (years)	Frequency
Canada [14]	Cancer Care Ontario https://www.cancercare.on.ca/pcs/screening/breastscreening/OBSP/highrisk/	Women ages 30 to 69 who are confirmed to be at high risk of developing breast cancer get screened once a year with a mammogram and breast magnetic resonance imaging (MRI) (screening breast ultrasound if MRI is not medically appropriate) Women ages 30 to 69 can get screened through the high-risk OBSP if they have a referral from their doctor, valid Ontario Health Insurance Plan number, no acute breast symptoms, and fall into one of the following risk categories: • Are known to have a gene mutation that increases their risk for breast cancer (e.g., *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*) • Are first DR of someone who has a gene mutation that increases their risk for breast cancer (e.g., *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*), have already had genetic counselling, and have chosen not to have genetic testing • Have been assessed at a genetics clinic (using the IBIS or BOADICEA tools) as having a 25 percent or greater lifetime risk of breast cancer based on personal and family history • Have had radiation therapy to the chest to treat another cancer or condition (e.g., Hodgkin lymphoma) before age 30 and at least 8 years ago	Mammography + MRI (+ eventually US if MRI is contraindicated)	30–69	Annually
France [10]	https://www.e-cancer.fr/content/download/250888/3470608/file/Depistage_des_cancers_recommandations_et_conduites_a_tenir_mel_20181114.pdf (Interpreted with Google Translate)	*Women with previous of breast cancer or ductal carcinoma in situ* Clinical examination every 6 months for 2 years following end of treatment, then every year; annual two-view or one-view mammography ± ultrasound	CBE + Mammography		Semi-annually Annually
		Women with antecedents atypical ductal or lobular hyperplasia Annual mammography ± ultrasound for 10 years. After 10 years, if the patient is older than 50 years, the patient returns to organized screening, if is younger than 50 years, mammography ± ultrasound every 2 years up to 50 years	Mammography ± US		Annually according to age
		Women with previous high-dose thoracic radiation therapy (Hodgkin lymphoma) Clinical examination every year after age 20 and MRI ± ultrasound after age 30, from 8 years after ending radiation therapy, and annual one-view mammogram (mediolateral oblique) and possible ultrasound	CBE MRI ± US Mammography	>20 >30 >30	Annually Annually Annually
		Women with suspected (Eisinger score ≥ 3) or confirmed BRCA1/2 mutation Genetic test with consultation and specific follow-up (MRI, Pelvic ultrasound…)	MRI		

Germany [19]	Bick et al. (2019)	[…] Program was offered to all eligible women from age 25 (or 5 years before the earliest breast cancer diagnosis in the family if earlier, but not before age 18) to 55. The program consists of annual MRI supplemented by clinical exam and ultrasound every 6 months. In accordance with the German regulations, an individual decision whether to include mammography at a screening round was made based, e.g., on age, risk profile, and findings on MRI. At the beginning of the program, mammography was in most cases offered annually starting at age 30. With growing evidence of the relatively small contribution of mammography to the detection of breast cancer if MRI is available, this was gradually changed to offering mammography only every 1 to 2 years starting at age 40. In 2013, the 6-month interval ultrasound was discontinued *in BRCA1/2*-negative women, and the starting age of the program was increased to 30 for these women. Surveillance was extended until age 70 for mutation carriers and discontinued after age of 50 in non-carriers	CBE US MRI Mammography	≥25 ≥25 ≥25 ≥40 or 5 years prior to age of youngest affected family member (but not before 18 years) Up to 70 for mutation carriers	Semi-annually Semi-annually Annually Annually or biennially
Ireland [13]	Health Information and Quality Authority (2013) Health Technology Assessment of High-Risk Breast Cancer Surveillance	Surveillance is cost-effective compared to no surveillance for women aged <50 with an identified high-penetrance genetic mutation. For women aged <50 with either high familial risk or no identified genetic mutation or those at moderate risk, surveillance is not cost-effective by traditional standards when compared to no surveillance For women aged <50 with identified high-penetrance genetic mutations other than *TP53*, annual MRI from age 30 to 49 is recommended. The addition of annual digital mammography from age 40 to 49 could be offered to maintain accordance with current international practice For the subgroup with a *TP53* mutation, annual MRI surveillance from age 20 to 49 is recommended	MRI	30–49 20–49 with *TP53* mutation	Annually
		For women at high familial risk with no identified genetic mutations, annual digital mammography from ages 40 to 49 is preferable to existing ad hoc surveillance For women at moderate risk, annual digital mammography from ages 40 to 49 is preferable to existing ad hoc surveillance An organized surveillance program will improve equity of access; it should have quality key performance indicators	Mammography	40–49	Annually
Israel [16]	http://en.cancer.org.il/template_e/default.aspx?PageId=7749	Women who are at high risk who have a mother or sister affected by BC should be tested once a year, starting from the age of 40 or according to their physician's recommendation. *BRCA1/2* gene mutation carriers are entitled to a breast MRI scan	MRI	≥40 years	Annually
			Mammography	≥50 years	Biannually

(continued)

Table 16.3 (continued)

Country [reference(s)]	Reference guideline	High-risk definition	Imaging modality	Age range (years)	Frequency
Italy [23]	https://www.aiom.it/wp-content/uploads/2018/11/2018_LG_AIOM_Breast_ENversion.pdf	In women at high risk because of family history of breast cancer or *BRCA1* and/or *BRCA2* mutation, instrumental examinations should start at the age of 25 or 10 years before the age of tumor onset in the youngest family member Breast magnetic resonance imaging with gadolinium (CE-MRI) and with annual screening frequency is indicated in high-risk women, defined as follows: • *BRCA1* or *BRCA2* mutation • Lifetime risk of 20–25% according to common risk prediction models • Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome • Prior chest radiotherapy between 10 and 30 years of age	MRI	≥25 or 10 years prior to youngest affected family member	Annually
Japan [15]	Murakami et al. 2019	Currently, in Japan, women of average risk for breast cancer are advised to undergo mammography every 2 years beginning at age 40 years. However, no suitable surveillance system for women at high risk of developing breast cancer has yet been established […] Although the Guidebook for Diagnosis and Treatment of Hereditary Breast and Ovarian Cancer Syndrome 2017, an initiative spearheaded by Japan's Ministry of Health, Labor, and Welfare, recommends annual contrast-enhanced MRI examination for women aged ≥25 years who have a BRCA mutation, currently, this screening study is not covered by the national health insurance program	MRI	≥25	Annually
Malaysia [17]	CPG-Management of Breast Cancer, 2010 (second edition)	In Malaysia, the Ministry of Health follows the Clinical Practice Guidelines for screening and management of BC. According to this guideline, women with a personal history of BC, lobular carcinoma or ductal carcinoma in situ, atypical hyperplasia, carriers of *BRCA1* or *BRCA2* mutation, or first DRs with BC are identified as being at high risk. For them, screening should be done from the age of 30 years with both MRI and mammography	MRI + Mammography	≥30 years	Annually
The Netherlands [27]	Richtlijnen Database https://richtlijnendatabase.nl/richtlijn/borstkanker/screening/screeningsmiddelen/mri.html (Interpreted with Google Translate)	Screening by MRI should be reserved for women at very high risk, specifically the *BRCA1/2* mutation carriers Screening with mammography is indicated in women from the general population between 50 and 75 years, with a screening interval of 2 years In connection with an increased risk of interval carcinoma in women between 30 and 50 years old, a screening interval of 1 year is recommended In connection with an increased risk of tumor induction in young women, in particular, gene mutation carriers, a starting age of 30 years is advised Screening for breast cancer in women over 75 years of age is not recommended	Mammography + MRI	25, 35, or 45 depending on causes, up to 60 for women with LTR ≥ 50%	Annually

New Zealand [18]	National Breast Cancer Tumour Standards Working Group, 2013	The National Breast and Ovarian Cancer Centre (now Cancer Australia) defines as being at potential or known high-risk women who are BC susceptibility gene mutation carriers (*e.g.*, *BRCA1* or *BRCA2*) and women who have a strong family history with at least two first DRs affected, plus other features. LTR of BC should be >25%, covering <1% of the female population […]	Mammography + MRI	≥30 years	Annually
		BRCA carriers have annual breast MRI and consider annual mammography from 10 years prior to the age of onset for the youngest affected family relative. Mammography is not recommended before age 30 Good practice points: • Women with *TP53*, *PTEN*, and *CDH-1* (E-cadherin) gene mutations are managed similarly to BC susceptibility gene mutation carriers • Mammography is not recommended under 30 years of age, because of the low sensitivity of the test and the risk of radiation-induced cancer (NHS Cancer Screening Programmes 2013; Pijpe et al. 2012; expert opinion) • Women with *TP53* mutations are especially at risk of radiation-induced malignancy so should not have mammograms (whole body MRI may be considered) • Women are encouraged to report any breast changes promptly to their clinician • Women have a CBE every 6–12 months from 10 years prior to the age of onset for the youngest-affected family relative or starting at age 25–30 (Genetic Health Service New Zealand 2012) • Standard: Women at high risk of developing BC are considered for annual breast MRI in addition to mammography (over the age of 30 years) and CBE	CBE	25–30 years of age or 10 years prior to youngest-affected relative	6–12 months
Norway [25]	Norwegian Institute of Public Health Inferred from https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2018/diagnostic-accuracy-clinical-effectiveness-and-budget-impact-of-screening-brca1_2-mutation-carriers-by-mri-rapport-2018.pdf	The current screening strategy in Norway for women with *BRCA1* and *BRCA2* mutations is annual MRI and mammography from the age of 25 to 70	Mammography + MRI	25–70	Annually

(continued)

Table 16.3 (continued)

Country [reference(s)]	Reference guideline	High-risk definition	Imaging modality	Age range (years)	Frequency
Spain [20, 21]	http://www.sedim.es/nueva/wp-content/uploads/2015/01/Cap%C3%ADtulo_7_Otras-Indicaciones-de-RM.pdf (Interpreted with Google Translate)	In the group of patients with a family history without proven genetic mutations, the risk accumulated fluctuates from 15% to 50%, depending on other associated factors. Three levels of risk are identified: 1. Carriers of genetic mutations with an accumulated vital risk of 50–85% 2. First DRs of the previous subjects, in whom the mutational status is not known, with an LTR of 30–50%, or subjects with ≥3 first DRs or second DRs affected by BC and/or OC or BC in the male (30–50% risk) 3. Subjects with two first DRs or second DRs affected with BC and/or OC or a male relative affected by BC (15–30% risk)	MRI Mammography CBE BSE	25–70 30–35 to 70 >25 >18	Annually Annually 6–12 months
	Llort et al. 2015	Screening recommendations in *BRCA* mutation carriers: BSE, starting at age 18; CBE every 6–12 months, starting at age 25; annual breast MRI from age 25 to 70; annual mammogram from age 30–35 to 75			
Sweden [4]	https://www.cancercentrum.se/stockholm-gotland/cancerdiagnoser/brost/vardprogram/gallande-vardprogram/10.-utredning-uppfoljning-och-omhandertagande-av-personer-med-misstankt-arftligt-okad-risk-for-brost-och-aggstockscancer/ (Interpreted with Google Translate)	Recommendations for greatly increased risk (mutation carrier *BRCA1* or *BRCA2*) […] Annual imaging (breast) diagnostics from 25 to about 74 years of age, including breast MRI up to about 55 years of age (++++ for sensitivity compared to mammography alone, +++ for diagnosis in more favorable stage A) […]	Mammography + MRI	25–74	Annually
		PALB2 Moderate–strongly elevated risk. Annual imaging including MRI from age 30 […]	Imaging including MRI	≥30	Annually
		TP53 Significantly increased risk. Annual imaging of breasts from the age of 20. *TP53* mutation carriers should, if possible, avoid ionizing radiation during follow-up and treatment, especially at younger ages and should be screened alternately with MRI and ultrasound from the age of 20 […]	MRI + US alternatively	≥20	Annually
		PTEN Probably greatly increased risk (uncertain risk estimates). Follow-up with mammography + MRI from the age of 30–35: Information on the possibility of risk-reducing surgery […]	Mammography + MRI	From 30–35	Annually
		CDH1 Probably greatly increased risk of lobular breast cancer (uncertain risk estimate). Follow-up with mammography + MRI from the age of 30–35: risk-reducing surgery can be considered based on current family history […]	Mammography + MRI	From 30–35	Annually
		STK11 Probably greatly increased risk (uncertain risk estimates). Follow-up with mammography + MRI from the age of 25: risk-reducing surgery may be considered based on current family history	Mammography + MRI	≥25 (for both modalities)	Annually

Turkey [6]	Aribal et al. (2012) The Journal of Breast Health (Interpreted with Google Translate)	Annual MRI recommended (proven by non-randomized studies and observational studies) in the case of: *BRCA* gene mutation carriers; persons not tested, with first DRs being *BRCA* gene mutation carriers; persons with LTR > 20–25% (statistical models based on family history) Annual MRI recommended (based on expert consensus thought) in the case of chest radiation therapy from age 10 to 30; Li-Fraumeni syndrome and first DRs; Cowden and Bannayan-Riley-Ruvalcaba syndrome and first DRs Insufficient evidence for recommending MRI screening in the case of: LTR about 15–20% (statistical models based on family history); previous lobular carcinoma in situ or atypical lobular hyperplasia, atypical ductal hyperplasia; dense or heterogeneous mammographic density; previous personal invasive BC or ductal carcinoma in situ MRI scan not recommended (expert consensus) in the case of LTR < 15%	MRI	≥25 years	Annually
United Kingdom [9]	NICE Guidelines https://www.nice.org.uk/guidance/cg164/chapter/1-recommendations	Offer annual MRI surveillance to women: • Aged 30–49 who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier • Aged 30–49 with a known *BRCA1* or *BRCA2* mutation • Aged 20–49 who have not had genetic testing but have a greater than 30% probability of being a *TP53* carrier • Aged 20–49 with a known *TP53* mutation Consider annual MRI surveillance for women aged 50–69 years with a known *TP53* mutation	MRI	30–49 30–49 20–49 20–49	Annually
		Offer annual mammographic surveillance to women: […] • Aged 40–59 at high risk of BC but with a 30% or lower probability of being a *BRCA* or *TP53* carrier • Aged 40–59 who have not had genetic testing but have a > 30% probability of being a *BRCA* carrier • Aged 40–69 with a known *BRCA1* or *BRCA2* mutation	Mammography	40–59 40–59 40–69	Annually Annually Annually

(continued)

Table 16.3 (continued)

Country [reference(s)]	Reference guideline	High-risk definition	Imaging modality	Age range (years)	Frequency
United States [3, 22]	American Cancer Society (ACS) https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html	Women who are at high risk for BC should get an MRI and a mammogram every year. This includes women who: • Have a LTR ≥ 20–25%, according to risk assessment tools that are based mainly on family history (e.g., Claus model) • Have a known *BRCA1* or *BRCA2* gene mutation • Have a first DR (parent, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation and have not had genetic testing themselves • Had chest radiation therapy between the ages of 10 and 30 • Have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or have first DRs with one of these syndromes If MRI is used, it should be in addition to, not instead of, a screening mammogram For most women at high risk, screening with MRI and mammograms should begin at age 30 years and continue for as long as a woman is in good health. But because the evidence is limited about the best age at which to start screening, this decision should be based on shared decision-making between patients and their healthcare providers, taking into account personal circumstances and preferences	MRI + Mammography	>30 years	Annually
	National Comprehensive Cancer Network (NCCN) https://www.nccn.org/	*BRCA1/2* Breast awareness starting at age 18 years Clinical breast exam, every 6–12 months, starting at age 25 years Breast screening: • Age 25–29 years, annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present • Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast • Age > 75 years, management should be considered on an individual basis • For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above […]	CBE	≥25 years	Annually or semi-annually
			MRI	25–29	Annually
			MRI + Mammography (consider tomosynthesis)	30–75	Annually

		Li-Fraumeni (TP53) Breast awareness starting at age 18 years Clinical breast exam, every 6–12 months, starting at age 20 years Breast screening: • Age 20–29 years, annual breast MRI screening with contrast • Age 30–75 years, annual breast MRI screening with contrast and mammogram with consideration of tomosynthesis • Age > 75 years, management should be considered on an individual basis For women with a *TP53* pathogenic/likely pathogenic variant who are treated for breast cancer and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram should continue as described above […]	CBE	≥20 years	Annually or semi-annually
			MRI	20–29	Annually
			MRI + Mammography (consider tomosynthesis)	30–75	Annually
		Cowden Syndrome—PTEN Hamartoma Tumor Syndrome Breast awareness starting at age 18 years Clinical breast exam, every 6–12 months, starting at age 25 years or 5–10 years before the earliest known breast cancer in the family (whichever comes first) Breast screening: • Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast starting at age 30–35 years or 5–10 years before the earliest known breast cancer in the family (whichever comes first) • Age > 75 years, management should be considered on an individual basis For women with a *PTEN* pathogenic/likely pathogenic variant who are treated for breast cancer, and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above	CBE	≥25 depending on family history	Annually or semi-annually
			MRI + Mammography (consider tomosynthesis)	From 30–35 depending on family history	Annually

1st DR first-degree blood relative, *2nd DR* second-degree blood relative, *BC* breast cancer, *CBE* clinical breast examination, *BSE* breast self-examination, *LTR* lifetime risk, *MRI* magnetic resonance imaging (contrast-enhanced), *OC* ovarian cancer, *US* ultrasound

16.8 Conclusions

Mammography and MRI are recommended to be mostly annually offered to women who are known to be carriers of a *BRCA* deleterious mutation or at 50% risk of being a mutation carrier. This recommendation is given mainly in those countries offering mammography screening to their average-risk female population. Variations in the recommendations for high-risk women regard eligibility for screening and the age at which screening should start or stop. No country offers annual US with mammography without MRI unless there is a contraindication to MRI.

International cooperation is needed to harmonize recommendations for screening women at high risk for BC and to extend these recommendations in other countries. In countries now starting the organization of BC screening programs, attention to the high-risk subgroup could be paid since the planning stages, taking into account the economic sustainability of earlier age invitation and of additional screening for high-risk women.

References

1. WHO | World Health Organization. https://www.who.int/. Accessed 30 Jun 2020
2. OECD (2016) Magnetic resonance imaging (MRI) units (indicator). https://www.oecd-ilibrary.org/social-issues-migration-health/magnetic-resonance-imaging-mri-units/indicator/english_1a72e7d1-en. Accessed 30 Jun 2020
3. American Cancer Society (2017) American Cancer Society recommendations for the early detection of breast cancer. https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html. Accessed 30 Jun 2020
4. MRI for high risk women | Cancer Australia. https://canceraustralia.gov.au/clinical-best-practice/breast-cancer/screening-and-early-detection/mri-high-risk-women. Accessed 30 Jun 2020
5. MRI (Magnetic Resonance Imaging) breast services Q&A (questions and answers). https://www1.health.gov.au/internet/main/publishing.nsf/Content/mri-breast-services-q-and-a. Accessed 30 Jun 2020
6. Singer CF, Tea MK, Pristauz G et al (2015) Clinical Practice Guideline for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families. Wien Klin Wochenschr 127:981–986
7. KCE (2012) Dépistage du cancer du sein: comment identifier les femmes exposées à un risque accru – Quelles techniques d'imagerie utiliser? https://kce.fgov.be/fr/publication/report/dépistage-du-cancer-du-seincomment-identifier-les-femmes-exposées-à-un-risque-ac#.VIlwvXuKQk4. Accessed 30 Jun 2020
8. Domus Medica – Richtlijnen. https://domusmedica.be/richtlijnen. Accessed 30 Jun 2020
9. Ontario Breast Screening Program Screening for Women at High Risk – Cancer Care Ontario. https://www.cancercare.on.ca/pcs/screening/breastscreening/OBSP/highrisk. Accessed 30 Jun 2020
10. Institut National du Cancer Dépistage des cancers: recommandations et conduites à tenir. https://www.ecancer.fr/content/download/250888/3470608/file/Depistage_des_cancers_recommandations_et_conduites_a_tenir_mel_20181114.pdf. Accessed 30 Jun 2020
11. Bick U, Engel C, Krug B et al (2019) High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat 175(1):217–228
12. Health Information and Quality Authority (2013) Health technology assessment of high risk breast cancer surveillance
13. The Israel Cancer Association – Breast Cancer. http://en.cancer.org.il/template_e/default.aspx?PageId=7749. Accessed 30 Jun 2020
14. Associazione Italiana di Oncologia Medica Breast Neoplasms Guidelines. https://www.aiom.it/wp-content/uploads/2018/11/2018_LG_AIOM_Breast_ENversion.pdf. Accessed 30 Jun 2020
15. Murakami W, Tozaki M, Nakamura S et al (2019) The clinical impact of MRI screening for BRCA mutation carriers: the first report in Japan. Breast Cancer 26:552–561
16. Ministry of Health Malaysia (2010) Management of breast cancer, 2nd edn. Academy of Medicine Malaysia
17. National Breast Cancer Tumour Standards Working Group (2013) Standards of service provision for breast cancer patients in New Zealand – provisional. https://www.health.govt.nz/system/files/documents/pages/standards-of-service-provision-breast-cancer-patients-jan14.doc. Accessed 30 Jun 2020
18. Tjelle T, Torkilseng E, Movik E et al (2018) Diagnostic accuracy, clinical effectiveness and budget impact of screening BRCA1/2 mutation carriers by MRI. A health technology assessment. Norwegian Institute of Public Health
19. Camps-Herrero J Capítulo 7. Otras indicaciones de resonancia magnética mamaria. In: Radiología Básica de la Mama. Sociedad Española de Diagnóstico por Imagen de la Mama
20. Llort G, Chirivella I, Morales R et al (2015) SEOM clinical guidelines in hereditary breast and ovarian cancer. Clin Transl Oncol 17:956–961
21. Regionalt Cancercentrum Stockholm Gotland Utredning, uppföljning och omhändertagande av personer med misstänkt ärftligt ökad risk för bröst- och

äggstockscancer. https://www.cancercentrum.se/stockholmgotland/cancerdiagnoser/brost/vardprogram/gallande-vardprogram/10.-utredning-uppfoljning-och-omhandertagande-av-personer-med-misstankt-arftligt-okad-risk-for-brost-och-aggstockscancer/. Accessed 30 Jun 2020
22. Federatie Medisch Specialisten Borstkanker – MRI. In: Richtlijnendatabase. https://richtlijnendatabase.nl/richtlijn/borstkanker/screening/screeningsmiddelen/mri.html. Accessed 30 Jun 2020
23. Arıbal E, Tunçbilek N, Çelik L (2012) Turkish Radiologic Society Breast Imaging Group Standards for breast cancer screening. J Breast Heal 8:3–10
24. National Institute for Health and Care Excellence (2013) Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clin Guidel. [CG164]. https://www.nice.org.uk/guidance/cg164/chapter/Recommendations. Accessed 30 Jun 2020
25. National Comprehensive Cancer Network (2019) Genetic/familial high-risk assessment: breast and ovarian. https://www.nccn.org. Accessed 30 Jun 2020
26. Elezaby M, Lees B, Maturen KE et al (2019) BRCA mutation carriers: breast, and ovarian cancer screening guidelines and imaging considerations. Radiology 291:554–569
27. Meindl A, Ditsch N, Kast K et al (2011) Hereditary breast and ovarian cancer. Dtsch Aerzteblatt Online 108:323–330
28. Madorsky-Feldman D, Sklair-Levy M, Perri T et al (2016) An international survey of surveillance schemes for unaffected BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 157:319–327

A Soft Option for Primary Prevention: Drugs and Agents

17

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Abbreviations

BC	Breast cancer
CI	Confidence interval
ER	Estrogen receptor
HBOC	Hereditary breast and ovarian cancer
HER2	Human epidermal growth factor receptor 2
OC	Ovarian cancer
OR	Odds ratio
OrC	Oral contraceptives
PR	Progesterone receptor
RR	Relative risk
SERMs	Selective estrogen receptor modulators

17.1 Introduction

Despite the advances in breast cancer (BC) diagnosis and therapy and the consequent reduction in terms of mortality of this disease, its social impact remains unacceptable. BC is the most commonly diagnosed malignancy among females, and several alternative strategies in order to decrease its incidence are still necessary.

The idea of primary prevention of BC dates back to history, and several progresses were made in understanding the underlying mechanisms of cancer development. The epithelial carcinogenesis is a multistep, multipath, and multiyear disease of progressive genetic and associated tissue damage [1]. The process starts with genetic events which lead to a progressive dysplastic cellular transformation with genotypic and phenotypic alterations, deregulated cell growth, and premalignancy status and finally to invasion of the basement membrane which establishes cancer [2]. The objective of primary cancer prevention is to intercept these processes in order to inhibit progression to the invasive stage. At present, strategies for primary prevention of BC encompass lifestyle factors, such as avoidance of obesity, maintaining physical activity, and moderation of alcohol intake, as well as surgical and medical therapeutic interventions. Research to improve therapeutic cancer prevention needs to include improvements in the prediction of benefits and harms and improvements in the safety profile of existing agents by experimentation with doses and schedules. Moreover, it is fundamental that these therapies can be directed toward the target most likely to benefit as high-risk populations.

In this chapter, we firstly define the population of women with an increased BC risk to whom these therapeutic interventions could be proposed. Then, we review the most important

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therapeutic agents for which there is a potential for being used as a risk reduction approach in these women.

17.2 Women with an Increased Risk for BC: Risk Factors and Germline Mutations

Several approaches seem to be able to identify women with a BC risk higher than that of the general female population. An increased BC risk is conferred by multiple factors such as a relevant family BC history, a personal history of atypical ductal or lobular hyperplasia, lobular or ductal carcinoma in situ, or known deleterious *BRCA1* or *BRCA2* mutation, the last condition typically implying a so-called high risk [3]. A promising modality seems to be the identification of phenotypic markers, such as mammographic breast density. In addition, tissue acquisition methods, such as random periareolar fine-needle aspiration or ductal lavage, might help in the assessment of risk and response to preventive therapies by identification of pathological and molecular markers [4].

However, advancing age is actually considered the strongest individually identified risk factor and together with family history provides one of the major clues to recognize hereditary BCs. Family history of BC or ovarian cancer (OC), especially if diagnosed at a young age or involving multiple family members, may suggest a hereditary cancer syndrome [5]. Women with hereditary breast and ovarian cancer (HBOC) syndrome represent a selected group with increased lifetime risk for developing these and other cancers. They include genetic alterations of various susceptibility genes such as *TP53*, *ATM*, *PTEN* or *MSH2*, *MLH1*, *PMS1*, *PMS2*, *MSH3*, and *MSH6* and, in particular, *BRCA1* and *BRCA2* [6]. Approximately 5% to 10% are directly due to an inherited germline genetic mutation [7]. The lifetime risk of BC in *BRCA1* or *BRCA2* mutation carriers is 45–80%, while the lifetime risk for OC is 45–60% for *BRCA1* mutation carriers and 11–35% for *BRCA2* mutation carriers [8] (Table 17.1).

BCs with *BRCA1* germline mutations can often be distinguished from non-*BRCA1*-related cancers. They frequently do not express estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [9]. This phenotype is referred to as the *triple-negative phenotype* and accounts for around 15% of all BCs. In contrast, *BRCA2*-related BCs appear to be different, in that they are frequently ER-positive [10] (Table 17.2). Importantly, the histologic and biologic characteristics of *BRCA*-related BCs, especially when being triple negative, significantly influence therapeutic and risk reduction strategies.

17.3 Chemoprevention

Despite prophylactic surgeries to decrease BC and OC risk are the most effective preventive approaches that could be offered to *BRCA* mutation carriers, they may not be the appropriate choice for some women, and chemoprevention may be offered to decrease their risk. Cancers arising in high-risk patients may be very heterogeneous among the different molecular subtypes and biological features. In this scenario, various preventive strategies are gaining importance, very different from each other and deeply related to the final target represented by the histological type of cancer and ultimately influencing incidence and outcome. However, hormones play a significant role in almost 70% of cases [11], and the main current strategies of chemoprevention do target hormonally responsive BCs.

The two major classes of antiestrogenic drugs, *selective estrogen receptor modulators* (SERMs) and *aromatase inhibitors*, have been recently used for their activity in BC prevention.

17.3.1 SERM: Tamoxifen

Four historical large trials [12–15] were undertaken on the effects of *tamoxifen*, the first SERM used for BC risk reduction, and long-term follow-up data are available. They have shown an overall 43% risk reduction in ER-positive invasive BC,

Table 17.1 Lifetime cancer risks in *BRCA* mutation carriers

Risk (%) of developing cancer by age										
	30 years		40 years		50 years		60 years		70 years	
Current age	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
BC, BRCA1										
20 years	1.8	1.4 to 2.2	12	9.5 to 14	29	24 to 35	44	37 to 52	54	46 to 63
30 years	–		10	8.2 to 13	28	23 to 34	44	36 to 52	54	45 to 63
40 years	–		–		20	16 to 25	38	31 to 45	49	41 to 58
50 years	–		–		–		22	18 to 27	37	30 to 44
60 years	–		–		–		–		19	15 to 24
BC, BRCA2										
20 years	1	0.78 to 1.4	7.5	5.8 to 9.8	21	17 to 26	35	20 to 42	45	38 to 53
30 years	–		6.6	5.1 to 8.6	20	16 to 26	35	28 to 42	45	38 to 53
40 years	–		–		15	12 to 19	30	24 to 36	42	34 to 49
50 years	–		–		–		18	15 to 22	32	26 to 38
60 years	–		–		–		–		17	14 to 20
OC, BRCA1										
20 years	1	0.68 to 1.8	3.2	2.3 to 5.1	9.5	7.3 to 13	23	18 to 28	39	34 to 44
30 years	–		2.2	1.6 to 3.4	8.7	6.7 to 12	22	18 to 27	39	34 to 43
40 years	–		–		6.7	5.2 to 8.9	20	17 to 24	38	33 to 41
50 years	–		–		–		15	12 to 17	34	29 to 36
60 years	–		–		–		–		22	20 to 23
OC, BRCA2										
20 years	0.19	0.09 to 0.47	0.7	0.37 to 1.5	2.6	1.5 to 4.5	7.5	5.1 to 11	16	12 to 20
30 years	–		0.52	0.28 to 1	2.4	1.5 to 4.2	7.4	5.1 to 11	16	12 to 20
40 years	–		–		1.9	1.2 to 3.2	7	4.8 to 10	16	12 to 20
50 years	–		–		–		5.2	3.7 to 7.2	14	17 to 11
60 years	–		–		–		–		9.8	7.8 to 11

BC, breast cancer; OC, ovarian cancer. Source [8]

Table 17.2 Features unique to *BRCA1* carriers and *BRCA2* carriers

Mutation	Onset of breast cancer	Onset of ovarian cancer	Frequent tumor features
BRCA1	Risk begins to increase considerably by age 40	Risk begins to increase by age 36–39, with a 2–3% risk by age 40	High-grade, ER-negative, PR-negative, HER2-negative, basal phenotype
BRCA2	Risk begins to increase considerably by age 45	Risk begins to increase by age 44–46, with a 2–3% risk by age 50	High-grade, ER-positive, PR-positive, HER2-negative, luminal phenotype

ER, estrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor 2. Sources [10]

but no effect on ER-negative disease [16]. Moreover, a recent meta-analysis by Jack Cuzick and coworkers [17] confirmed an overall significant risk reduction of 38% compared with placebo. Thus, in addition to its indication in adjuvant therapy, in the US tamoxifen is also approved by the Food and Drug Administration for the reduction of BC incidence in healthy women with an increased BC risk. Despite extraordinary preventive efficacy evidence, only limited data are available on the specific use of these agents in patients with *BRCA* mutations [18–22].

BRCA mutation carriers with BC have elevated risks for developing contralateral breast tumors. In one of the largest prospective series of *BRCA* mutation carriers, the mean cumulative lifetime risks for contralateral BC were estimated to be 83% for *BRCA1* mutation carriers

and 62% for *BRCA2* mutation carriers [23]. Patients with *BRCA* mutations who have intact contralateral breast tissue (and who do not undergo oophorectomy or receive chemoprevention) have an estimated 40% risk for contralateral BC at 10 years [24]. Case-control studies from the Hereditary Breast Cancer Clinical Study Group reported that the use of tamoxifen was associated with a 45% to 60% reduction in the risk for contralateral tumors among *BRCA* mutation carriers with BC [25, 26]. Data were not consistent as regards the protective effects of tamoxifen in the subset of *BRCA* mutation carriers who also underwent oophorectomy. In addition, no data were available on the ER status of the tumors. An evaluation of the subset of healthy individuals with a *BRCA* mutation in the Breast Cancer Prevention Trial revealed that the BC risk was reduced by 62% in those with a *BRCA2* mutation receiving tamoxifen relative to placebo [27]. However, an analysis of 288 women who developed BC during their participation in this trial showed that tamoxifen use was not associated with a reduction in BC risk in those with a *BRCA1* mutation probably due to the greater likelihood for development of ER-negative tumors. This analysis was limited by the very small number of individuals with a *BRCA* mutation diagnosed with BC (n = 19; 7% of participants).

A very recent meta-analysis addressed whether adjuvant tamoxifen treatment for BC is associated with reduced contralateral BC risk among *BRCA* mutation carriers with primary unilateral BC. Pooled relative risks (RRs) were calculated for contralateral BC along with 95% confidence intervals (CIs). Four non-overlapping studies were evaluated, and tamoxifen was found to be significantly associated with reduced risk of contralateral BC among *BRCA* mutation carriers (summary RR = 0.56, 95% CI 0.41–0.76) [28]. Similar findings were observed in *BRCA1* mutation carriers (summary RR = 0.47, 95% CI 0.37–0.60) and *BRCA2* mutation carriers (summary RR = 0.39, 95% CI 0.28–0.54) [28].

17.3.2 SERM: Raloxifene

Raloxifene, a second-generation SERM, has reduced the incidence of BC in preclinical models and in various clinical trials aimed to evaluate its effects for preventing osteoporosis and heart disease [20, 29]. Results of several previous trials led researchers to conduct a comparative, randomized phase III study of raloxifene versus tamoxifen (Study of Tamoxifen and Raloxifene (STAR) or NSABP-P2 trial) in more than 19,000 postmenopausal women at increased risk for BC [21]. Initial data showed the same efficacy as tamoxifen on infiltrating carcinomas but insufficient activity against in situ tumors. A recent update seems to show a small decrease in the efficacy on infiltrating and a small gain on in situ tumors, with an ultimate approximation of their efficacy [22]. However, no data are currently available on the use of raloxifene for BC prevention in *BRCA* mutation carriers.

17.3.3 Aromatase Inhibitors

A possible alternative to SERMs could be the use of aromatase inhibitors. The significant reduction in contralateral BCs found in adjuvant aromatase inhibitor clinical trials [30] has raised interest in these agents for primary prevention, in particular, because they may be associated with a less adverse effect profile, specifically thrombophilic events and endometrial cancer, as compared with SERMs. There have been two landmark studies on aromatase inhibitors for BC primary prevention. The National Cancer Institute of Canada Clinical Trials Group Mammary Prevention 3 (MAP.3) trial which utilized *exemestane* [31] and the IBIS-II with *anastrozole* [32] have shown that these agents were associated with a greater magnitude of BC risk reduction as compared to SERMs.

There are no completed prospective studies evaluating the preventive role of aromatase inhibitors in women with *BRCA* mutations. However, there is an ongoing French study evaluating

letrozole versus placebo in women with *BRCA* mutations [33]. It is noteworthy that a recent study evaluating the role of anastrozole in high risk who were carriers of *BRCA* mutations has shown a reduction in cancer incidence with the use of this and other inhibitors [34].

17.3.4 Any Evidence for Chemoprevention in *BRCA* Mutation Carriers?

In summary so far, in high-risk populations such as *BRCA* mutation carriers, we have not enough evidence of a sound effect of the very well-known chemopreventive compounds. Tamoxifen, however, appears as a very promising chemopreventive drug to be further studied, at least in subjects prone to endocrino-responsive BC, such as *BRCA2* mutation carriers. With respect to the evidence on the effect of oral contraceptives (OrC) on cancer risk in women with a known *BRCA* gene mutation, case-control studies have demonstrated that OrC reduced the risk of OC by 45% to 50% in *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers [35]. Notably, risks appeared to decrease with longer duration of OrC use [36]. In a meta-analysis conducted in a large number of *BRCA* mutation carriers (1,503 patients affected with OC and 6,315 without), the use of OrC significantly reduced the risk of OC by approximately 50% for both *BRCA1* and *BRCA2* mutation carriers [37]. These findings have been confirmed by another more recent meta-analysis which showed an inverse association between OC and use of OrC [38].

Studies on the effect of OrC use on BC risk among *BRCA* mutation carriers have reported conflicting results, mainly due to many differences in the study design (e.g., criteria for defining the "control" population, family history, demographics, and formulations/duration of OrC used). In one case-control study, the use of OrC was associated with a modest but statistically significant increase in BC risk only among *BRCA1* mutation carriers [39]. In this population, the BC risk was significantly associated with ≥5 years of OrC use, BC diagnosed before age 40, and use of "old-generation" (before 1975) OrC [39]. In another case-control study, among *BRCA2* mutation carriers, the use of OrC for at least 5 years was associated with a significantly increased risk for BC (odds ratio [OR] 2.06; 95% CI 1.08–3.94) and independently from OrC use (before or after 1975) [40]. Two other case-control studies, however, have reported no significant associations of OrC use (especially low-dose formulations after 1975) with the risk for BC in *BRCA* mutation carriers. Interestingly, in the latter study, the use of low-dose OrC for at least 1 year was associated with significantly decreased risk for BC among *BRCA1* mutation carriers (OR, 0.22; 95% CI, 0.10–0.49) [41, 42]. The two meta-analyses previously mentioned showed that OrC use is not significantly associated with a higher BC risk in *BRCA* mutation carriers [37, 38].

In summary, the current evidence is that *the use of OrC (particularly the more recent formulations after the year 1975) is clearly associated with a significant decrease in OC risk, while the effects on BC risk are somehow variable through the studies and may be overall considered as a moderate, not statistically significant increase*.

17.3.5 The Problem of ER-Negative BCs

Estrogen receptor-negative and triple-negative BCs are types of aggressive tumors that account for approximately 30% and 15% of total BCs, respectively [43]. Notably, a high rate of BCs arising in *BRCA1* mutation carriers is triple negative [44], and several cancers that arise in high-risk populations are generally nonhormonally responsive. For these reasons, preventive strategies for nonhormonal breast malignancies are needed. A great number of novel chemopreventive agents are currently under investigation in order to evaluate their efficacy in this particular cohort of patients, and they include retinoids, poly(ADPribose) polymerase (PARP) inhibitors, EGFR-tyrosine kinase inhibitors, metformin, cyclooxygenase-2 (COX-2) inhibitors, bisphosphonates, and peroxisome proliferator-activated receptor (PPAR) inhibitors (Table 17.3). Due to

Table 17.3 Class, specific mechanisms, and agents actually involved in the treatment and prevention of ER-negative breast cancer

Class of biomolecules or molecular mechanisms	Targets	Drugs or agents
Nuclear receptor	Retinoid acid X receptor (RXr) Vitamin D Receptor (VDR) Peroxisome proliferator-activated receptor (PPAR)	Fenretinide (4-HPR) 9 cis-retinoic acid (Targretin) Vitamin D3 analogues Troglitazone, rosiglitazone, pioglitazone
Membrane receptors and signal transduction	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) Tyrosine kinase Human epidermal growth factor receptor-1 (HER-1) or -2 (HER-2) Insulin-like growth factor receptor (IGF-R) or insulin-like growth factor 1 receptor (IGF-1) or insulin-like growth factor binding protein 3 (IGFBP3)	Statins Gefitinib Trastuzumab (Herceptin), lapatinib, gefitinib, erlotinib Metformin
Anti-inflammatory and antioxidant	Cyclooxygenase (COX)-2	Celecoxib, rofecoxib, NSAIDs
Angiogenesis	Vascular endothelial growth factor (VEGF)	Bevacizumab
DNA modulation	BRCA1, BRCA2	PARP inhibitors

4-HPR, N-(4-hydroxyphenyl) retinamide; ER, estrogen receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; PARP, poly (ADP-ribose) polymerases

their lack of proven efficacy or to an unacceptable risk-benefit ratio for healthy subjects, several of these agents are currently on standby. Thus, only the most promising agents (retinoids, bisphosphonates, and metformin) are described further.

Retinoids

Retinoids (either natural or synthetic compounds structurally related to vitamin A) have for long been studied for their chemotherapeutic effect and for their chemopreventive potential in BC setting. They are relative safe compounds with principally cutaneous and ocular light side effects. In particular, from the dermatological standpoint, the main side effects of retinoids are mucocutaneous dryness, skin atrophy, and skin vulnerability. As far as the eye is concerned, retinoids can induce conjunctivitis on one side but also interfere with some mechanisms of vision and, in particular, with dark adaptation. However, they are able to regulate cell growth, differentiation, and apoptosis in both ER-positive and ER-negative BC cells. An important phase III trial, recently updated [45], suggested a possible role of *fenretinide* as a preventive agent acting at different levels of breast carcinogenesis and, in particular, in young women. This protective effect was suggested also in women with a high probability of carrying a *BRCA* mutation.

Bisphosphonates

Bisphosphonates are commonly used in patients with BC to reduce skeletal-related events in metastatic disease and to mitigate bone loss associated with cancer therapy in early-stage disease. The most used antiresorptive agents are ibandronate [46, 47], risedronate [48, 49], and zoledronic acid [50–52], and all of them have been shown to mitigate aromatase inhibitor-associated bone loss in a series of trials. The studies on bisphosphonates point to direct antitumor effects involving antiangiogenic, antiproliferative, and proapoptotic mechanisms [53], and beneficial effects in the prevention of BC recurrence have been documented. Moreover, two large cohort studies reported reductions in BC incidence of around 30% in bisphosphonate users [54, 55] with similar benefits for ER-negative BCs, suggesting their possible role in BC prevention in high-risk populations including women with HBOC syndrome.

Metformin

Epidemiological studies have strongly suggested that metformin can reduce cancer risk and mortality in subjects with diabetes mellitus. A recent meta-analysis [56] on 47 independent studies showed that in diabetic subjects, metformin reduced the overall cancer incidence by 31%, while mortality was reduced by 34%. Finally, several early-phase BC clinical trials tested the effects of metformin on tissue biomarkers and tried to determine whether these observations apply to nondiabetic populations. One of our recent studies [57] suggests a heterogeneous effect of metformin on BC proliferation (Ki67) depending on insulin resistance and other factors reflecting altered energy balance, with a trend to a decreased proliferation in women with elevated HOMA[1] index and an opposite trend in women with normal insulin sensitivity. Moreover, metformin seems to be also able to increase apoptosis (determined by TUNEL[2] assay in invasive tumor tissue, in particular, in patients with a metabolic imbalanced condition) [58].

The antineoplastic mechanisms of action of metformin involve several pathways through which the drug acts in direct or indirect mode. In particular, metformin regulates the AMPK/mTOR pathway which is implicated in the control of protein synthesis and cell proliferation [59]. It is confirmed that metformin produces a significant repression of cell proliferation, and it has been found that this effect is different in human BC cell lines if related to either positive or negative ERs. In fact, a complete cell growth repression in ER-positive cell lines has been detected, while only a partial inhibition was detected in ER-negative phenotypes [60]. These data suggest that, although ER-negative cells are not as sensitive as ER-positive ones, both of them show a reduction in cell growth under metformin treatment. Although chemoprevention with metformin in healthy non-diabetic subjects has to be further validated, the choice of metformin appears much suited for chemoprevention of *BRCA2*-associated BCs, and further investigations are recommended in selected cohorts of high-risk women like those with familial BC risk or mutation carriers.

[1]Homeostatic model assessment (HOMA): a method used to quantify insulin resistance and beta-cell function.

[2]Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL): a method for detecting DNA fragmentation.

17.4 Lifestyle Changes and Natural Compounds

Lifestyle changes do offer an important strategy for cancer prevention [61]. They generally include diet and nutrition modifications as well as a regular and suitable physical activity. Recent attention has been given to the use of natural products in a preventive setting, especially in trying to counteract drug's side effects, in addition to making a possible preventive approach [62]. Moreover, chemoprevention of BC by natural products is potentially advantageous, as these compounds have few side effects and low toxicity compared to synthetic compounds. Most of these natural products involve apoptotic factors, while others affect signaling pathways such as Akt/mTOR and EGFR/HER2. Generally, several of these compounds show inhibitory effects on every step of carcinogenesis, in tumor growth, angiogenesis, proliferation, invasion, and metastasis. Thus, natural products might be preventive agents that can reduce side effects and improve the effect of drugs in human BC, while maintaining high selectivity and low toxicity.

Some of the most promising compounds include catechins such as epigallocatechin gallate (EGCG), a green tea extract, curcumin, berberine, carotenoids, omega-3 fatty acids, resveratrol, soy isoflavones, and vitamin D [63, 64]. However, *none of these dietary agents has been yet shown to consistently prevent BC*, in particular, in high-risk subjects. So, in spite of the fact that natural products are a promising alternative strategy for cancer prevention, their potential efficacy in the prevention of BC and possibly, in general, of ER-negative and triple-negative BC, in particular, should be determined in the near future.

17.5 Conclusions

The success of several recent clinical trials in the preventive setting in selected high-risk populations suggests that BC chemoprevention can be an effective strategy. New pathways, biomarkers, and agents are actively searched in the subgroup of cancers in high-risk subjects and have been recently put under investigation in order to improve effectiveness and reduce toxicity of preventive drugs. These strategies, accompanied by reasonable lifestyle, nutrition changes, and a personalized surveillance program (including MRI), could be a decisive step toward a better personalized BC prevention in high-risk women.

References

1. O'Shaughnessy AJ, Kelloff GJ, Gordon GB et al (2002) Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development. Clin Cancer Res 8:314–346
2. Braakhuis BJ, Tabor MP, Kummer JA et al (2003) A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 63:1727–1730
3. Amir E, Freedman OC, Seruga B, Evans DG (2010) Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst 102:680–691
4. Fabian CJ, Kimler BF, Mayo MS, Khan SA (2005) Breast-tissue sampling for risk assessment and prevention. Endocr Relat Cancer 12:185–213
5. Cazzaniga M, Bonanni B (2016) Pharmacoprevention for hereditary breast and ovarian cancer. Minerva Ginecol 68:517–535
6. Kobayashi H, Ohno S, Sasaki Y, Matsuura M (2013) Hereditary breast and ovarian cancer susceptibility genes. Oncol Rep 30:1019–1029
7. Palma MD, Domchek S, Stopfer J et al (2008) The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high risk breast cancer families. Cancer Res 68:7006–7014
8. Paul A, Paul S (2014) The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. Front Biosci 19:605–618
9. Johannsson OT, Idvall I, Anderson C et al (1997) Tumour biological features of BRCA1-induced breast and ovarian cancer. Eur J Cancer 33:362–371
10. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329–1333
11. Althuis MD, Fergenbaum JH, Garcia-Closas M et al (2004) Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomark Prev 13:1558–1568
12. Powles TJ, Ashley S, Tidy A et al (2007) Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 99:283–290
13. Fisher B, Costantino JP, Wickerham DL et al (2005) Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 97:1652–1662
14. Veronesi U, Maisonneuve P, Rotmensz N et al (2007) Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 99:727–737
15. Cuzick J, Forbes JF, Sestak I et al (2007) Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99:272–282
16. Cuzick J, Powles T, Veronesi U et al (2003) Overview of the main outcomes in breast-cancer prevention trials. Lancet 361:296–300
17. Cuzick J, Sestak I, Bonanni B (2013) Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 381:1827–1834
18. Cummings SR, Eckert S, Krueger KA et al (1999) The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 281:2189–2197
19. Lippman ME, Cummings SR, Disch DP et al (2006) Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. Clin Cancer Res 12:5242–5247
20. Martino S, Cauley JA, Barrett-Connor E et al (2004) Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 96:1751–1761
21. Vogel VG, Costantino JP, Wickerham DL et al (2006) Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295: 2727–2741
22. Vogel VG, Costantino JP, Wickerham DL et al (2010) Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev Res 3:696–706
23. Mavaddat N, Peock S, Frost D et al (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 105:812–822
24. Metcalfe K, Lynch HT, Ghadirian P et al (2004) Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 22:2328–2335

25. Gronwald J, Tung N, Foulkes WD et al (2006) Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 118:2281–2284
26. Narod SA, Brunet JS, Ghadirian P et al (2000) Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 356:1876–1881
27. King MC, Wieand S, Hale K et al (2001) Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286:2251–2256
28. Xu L, Zhao Y, Chen Z, Wang Y, Chen L, Wang S (2015) Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in BRCA1 and BRCA2: a meta-analysis. Breast Cancer 22:327–334
29. Barrett-Connor E, Mosca L, Collins P et al (2006) Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 355:125–137
30. Dowsett M, Cuzick J, Ingle J et al (2010) Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28:509–518
31. Reinert T, Barrios CH (2017) Overall survival and progression-free survival with endocrine therapy for hormone receptor-positive, HER2-negative advanced breast cancer: review. Ther Adv Med Oncol 9:693–709
32. Goss PE, Ingle JN, Alés-Martínez JE et al (2011) Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 364: 2381–2391
33. Cuzick J, Sestak I, Forbes JF et al (2014) Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383:1041–1048
34. McLaughlin JR, Risch HA, Lubinski J et al (2007) Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 8:26–34
35. Sénéchal C, Reyal F, Callet N et al (2016) Hormonotherapy for breast cancer prevention: what about women with genetic predisposition to breast cancer? Bull Cancer 103:273–281
36. Narod SA, Risch H, Moslehi R et al, Hereditary Ovarian Cancer Clinical Study Group (1998) Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 339:424–428
37. Iodice S, Barile M, Rotmensz N et al (2010) Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 46:2275–2284
38. Moorman PG, Havrilesky LJ, Gierisch JM et al (2013) Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol 31:4188–4198
39. Narod SA, Dube MP, Klijn J et al (2002) Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 94:1773–1779
40. Haile RW, Thomas DC, McGuire V et al (2006) BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomark Prev 15:1863–1870
41. Lee E, Ma H, Kean-Cowdin R et al (2008) Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiol Biomark Prev 17:3170–3178
42. Milne RL, Knight JA, John EM et al (2005) Oral contraceptive use and risk of early-onset breast cancer in carriers and non-carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomark Prev 14:350–356
43. Foulkes WD, Smith IE, Reis-Filho JS (2010) Triple-negative breast cancer. N Engl J Med 363:1938–1948
44. Peshkin BN, Alabek ML, Isaacs C (2010) BRCA1/2 mutations and triple negative breast cancers. Breast Dis 32:25–33
45. Veronesi U, Mariani L, Decensi A et al (2006) Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer. Ann Oncol 17:1065–1071
46. Body JJ, Diel IJ, Lichinitzer M et al (2004) Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 90:1133–1137
47. Lester JE, Dodwell D, Purohit OP et al (2008) Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res 14:6336–6342
48. Markopoulos C, Tzoracoleftherakis E, Polychronis A et al (2010) Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial. Breast Cancer Res 12:R24
49. Van Poznak CH, Hannon RA, Mackey JR et al (2010) Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol 28:967–975
50. Brufsky A, Bundred N, Coleman R et al (2008) Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist 13:503–514
51. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al (2008) Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840–849
52. Hines SL, Sloan JA, Atherton PJ et al (2010) Zoledronic acid for treatment of osteopenia and

osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy. Breast 19:92–96
53. Daniele G, Giordano P, De Luca A et al (2011) Anticancer effect of bisphosphonates: new insights from clinical trials and preclinical evidence. Expert Rev Anticancer Ther 11:299–307
54. Rennert G, Pinchev M, Rennert HS (2010) Use of bisphosphonates and risk of postmenopausal breast cancer. J Clin Oncol 28:3577–3581
55. Chlebowski RT, Chen Z, Cauley JA et al (2010) Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 28:3582–3590
56. Decensi A, Puntoni M, Goodwin P et al (2010) Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res 3:1451–1461
57. Bonanni B, Puntoni M, Cazzaniga M et al (2012) Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. J Clin Oncol 30:2593–2600
58. Cazzaniga M, DeCensi A, Pruneri G et al (2013) The effect of metformin on apoptosis in a breast cancer presurgical trial. Br J Cancer 109:2792–2797
59. Boyle JG, Salt IP, McKay GA (2010) Metformin action on AMP-activated protein kinase: a translational research approach to understanding a potential new therapeutic target. Diabet Med 27: 1097–1106
60. Phoenix KN, Vumbaca F, Claffey KP (2009) Therapeutic metformin/AMPK activation promotes the angiogenic phenotype in the ERalpha negative MDA-MB-435 breast cancer model. Breast Cancer Res Treat 113:101–111
61. Reddy L, Odhav B, Bhoola KD (2003) Natural products for cancer prevention: a global perspective. Pharmacol Ther 99:1–13
62. D'Incalci M, Steward WP, Gescher AJ (2005) Use of cancer chemopreventive phytochemicals as antineoplastic agents. Lancet Oncol 6:899–904
63. Petric RC, Braicu C, Raduly L et al (2015) Phytochemicals modulate carcinogenic signaling pathways in breast and hormone-related cancers. Onco Targets Ther 8:2053–2066
64. Grant WB (2009) A critical review of Vitamin D and Cancer: A report of the IARC Working Group. Dermatoendocrinol 1:25–33

18 Surgical Options for Primary Prevention: Prophylactic Mastectomy and Oophorectomy

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Abbreviations

BCT	Breast-conserving therapy
CBC	Contralateral breast cancer
EOC	Epithelial ovarian cancer
HBOC	Hereditary breast and ovarian cancer syndrome
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IBTR	Ipsilateral breast tumor recurrence
MRI	Magnetic resonance imaging
NSM	Nipple-sparing mastectomy
PMRT	Postmastectomy radiation therapy
RRSO	Risk-reducing salpingo-oophorectomy
SLN	Sentinel lymph node

18.1 Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) occurs in families and increases the risk of breast cancer, ovarian cancer, or both in an autosomal dominant pattern. Approximately 5 to 10% of breast cancers is hereditary, and *BRCA* mutations occur in 2.0 to 4.7% of breast cancer patients [1, 2]. It is estimated that the cumulative risk of female breast cancer to the age of 70 is 46–65% for *BRCA1* and 43–45% for *BRCA2* mutation carriers (Table 18.1) [3, 4]. Ovarian cancer occurs in approximately 39% of *BRCA1* and 11% of *BRCA2* mutation carriers. Male breast cancer occurs in about 1.2% of *BRCA1* and 6.8% of *BRCA2* mutation carriers; however, this risk is lower than that of an average female in the general population [5]. Additionally, HBOC patients with breast cancer treated with breast-conserving therapy (BCT) are at considerable risk of developing an ipsilateral breast tumor recurrence (IBTR) or contralateral breast cancer (CBC). Apart from *BRCA1* and *BRCA2*, many other gene mutations have been found to contrib-

Table 18.1 Risk of breast and Ovarian cancer in BRCA mutation carriers

Risk	*BRCA1* mutation	*BRCA2* mutation	Reference
Primary breast cancer	46–65%	43–45%	[3, 4]
Ipsilateral breast tumor recurrence) following breast-conserving therapy	11.6% (8 years) 12.1% (10.5 years)		[39] [40]
Contralateral breast cancer	23% (8 years) 18.4% (11 years)		[39] [41]
Male breast cancer	1.2%	6.8%	[5]
Ovarian cancer	39%	11%	[3, 4]

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ute or are suspected to contribute to HBOC, e.g., *ATM*, *PTEN*, and *TP53*. These are comprehensively reviewed in Chap. 3. Current gene-panel sequencing allows multiple genes to be tested simultaneously; however, these results must be interpreted with caution because there is lack of data on cancer penetrance associated with some of these mutations [6].

There are three strategies to manage the risk of breast and ovarian cancer in high-risk individuals: chemoprevention, screening, and prophylactic surgery.

The first option, *chemoprevention*, has been shown to reduce the risk of breast cancer in postmenopausal women. Unfortunately, chemoprevention drugs are poorly tolerated in young women because of their side effects, and they have not been proven to be effective [7]. The reader can find more details on this topic in Chap. 17.

The second option is *screening*. Ovarian cancer screening cannot be recommended as a substitution for bilateral risk-reducing salpingo-oophorectomy (RRSO), because it is not sensitive enough [8, 9]. Six-monthly transvaginal ultrasound and serum CA-125 measurement can be performed in women who are postponing RRSO, from the age of 30 to 35 years. On the other hand, breast cancer screening with regular magnetic resonance imaging (MRI), commencing age 25–30 years, and mammography, from age 30 years, is effective and should be recommended for all women from HBOC families [8–10]. However, although screening allows an earlier detection of breast cancer, it does not reduce the risk of its occurrence, nor does it eliminate the risk of mortality. Additionally, because *BRCA1*-associated breast cancers are frequently triple-negative, high-grade cancers [11], even small screen-detected cancers usually require chemotherapy as part of their treatment, and they impact on patient survival.

The third option for managing risk in individuals from HBOC families is *prophylactic surgery*. The advantage of surgery over screening is that it almost eliminates the risk of developing cancer. In healthy women, the adverse events of a more extensive axillary surgery and adjuvant cancer treatments can be avoided, and the risk of mortality is reduced—thus ending a regime of costly and emotionally charged breast screening. However, prophylactic surgery is not a panacea; it can result in surgical and emotional complications, and can have effects on long-term general health. Prophylactic surgery can also be considered in HBOC patients who develop cancer: however, the benefit gained from prophylactic surgery needs to be balanced with the risk of recurrence or death from the index cancer. In this chapter, we consider suitable patients for prophylactic mastectomy and oophorectomy, and discuss evolving surgical techniques that can improve quality of life following prophylactic surgery.

18.2 Prophylactic Surgery in Women Who Do Not Have Breast Cancer

Healthy women from HBOC families will frequently have attended genetic counselors and will frequently have had genetic testing performed. They may be aware of their risk of developing cancer and have commenced breast screening. They may now want to consider prophylactic surgery.

It should be remembered that prophylactic surgery is a significant undertaking, and candidates must be medically suitable. Individuals who are at high risk of complications should be discouraged from having prophylactic surgery. This includes elderly women as well as those with cardiovascular disease, significant respiratory disease, and diabetes. It also includes women who are smokers or obese, although these risks may be modified. Individuals who are at risk of HBOC may be overwhelmed with decisions about screening or prophylactic surgery. Younger women need to consider the effects of interventions on their fertility and body image. Older women may feel their risk of cancer is no longer as high and may prefer to avoid prophylactic surgery. Decision-making tools can help. For instance, healthy *BRCA* mutation carriers can calculate their probability of developing cancer and surviving it, with or without prophylactic surgery in combination with MRI screening [12]. This online model estimates that when

prophylactic mastectomy and oophorectomy are performed immediately after diagnosing a *BRCA* mutation, life expectancy gains can be up to 10 years in *BRCA1* mutation carriers and 4 years in *BRCA2* carriers [13]. However, an individual's risk of developing HBOC can only be crudely estimated using online models, and the beneficial effects of MRI and prophylactic surgery can be overestimated [14].

18.2.1 Bilateral Risk-Reducing Mastectomy

Breast cancer risk reduction. A recent review considered the effects of risk-reducing mastectomy in women who have not had cancer from families with HBOC syndrome [15]. The risk of breast cancer was reduced by 90% or more in four observational studies comparing women who underwent prophylactic mastectomy with similar women who did not have surgery. The results of these series were originally published between 1999 and 2004, and most subsequent studies have confirmed their findings. Bilateral mastectomy is widely promoted by healthcare bodies, including the Society of Surgical Oncology [8, 9, 16]. There is a wide international variation in prophylactic mastectomy rates and in subsequent breast reconstruction rates. These are both higher among patients in North America and Western Europe, compared to patients in Eastern Europe and Israel [17–19].

Complications and surgical development. Complications may occur following risk-reducing mastectomy; in one case series of high-risk patients, 49.6% of women undergoing risk-reducing mastectomy and reconstruction had a complication. These were frequently cosmetic, such as capsular contraction, and resulted in reoperation in most patients [20]. With evolving surgical techniques and experience, outcomes are improving for *BRCA* mutation carriers who undergo mastectomy. The final cosmetic results following nipple-sparing mastectomy (NSM) and implant-based reconstruction are now more realistic and acceptable (Fig. 18.1). In a recent series of 177 NSMs in 89 *BRCA* mutation carriers (26 in patients with breast cancer, 63 prophylactic), there were no recurrences or occurrences of breast cancer at a median follow-up of 26 months [21]. Subsequent excision of the nipple-areola complex was performed in 6% of them because of nipple involvement or necrosis. The low complication rate included skin debridement because of desquamation in 7.3% and implant removal in 3.4%. In a series of 397 NSMs in 201 *BRCA* mutation carriers (51 in patients with breast cancer, 150 prophylactic), 4 cancer events occurred with a mean follow-up of 32.6 months: 3 in breast cancer patients and 1 following prophylactic mastectomy [22].

Psychosocial consequences. Prophylactic mastectomy may have either positive or negative consequences at both the psychological level and the social level. Among 522 women with a family history of breast cancer who underwent bilateral prophylactic mastectomy 14.5 years before, 70% were satisfied with the procedure and 74% were less concerned about developing breast cancer [23]. A recent systematic review of 22 studies concluded that patients have high rates of satisfaction following bilateral prophylactic mastectomy [24]. Overall, 70% were satisfied with their outcome and 95% did not report any regrets. More than 60% of patients in this review had favorable responses related to their body image and sexual well-being, although more than 70% experienced negative somatosensory function. Recently, it has been shown that women undergoing prophylactic mastectomy who retain the nipple-areolar complex have an improved body image and sexual functioning compared to patients who had a skin-sparing mastectomy [25].

18.2.2 Risk-Reducing Salpingo-Oophorectomy (RRSO)

Ovarian cancer risk reduction and associated mortality. RRSO is effective in preventing ovarian cancer. The risk of ovarian and pelvic high-grade serous cancers was reduced in 7 studies investigating the efficacy of RRSO in *BRCA* mutation carriers [15]. On meta-analysis, this risk was reduced by approximately 80% [26].

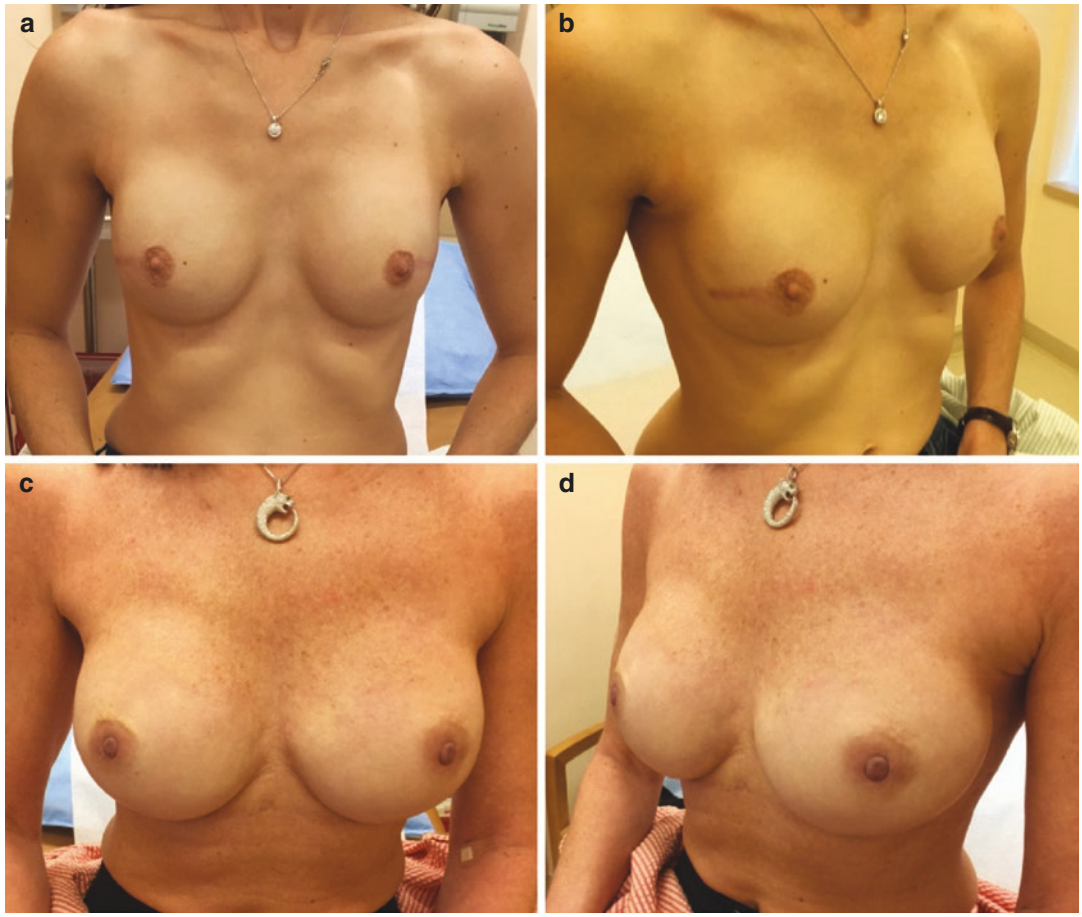

Fig. 18.1 **a**–**d**. Long-term cosmetic results in 2 patients following bilateral nipple-sparing mastectomy and implant-based reconstruction

RRSO is promoted in guidelines for *BRCA1* and *BRCA2* mutation carriers between the age of 35 and 40 years [8, 27]. RRSO can probably be delayed for several years in *BRCA2* mutation carriers because their risk of ovarian cancer is lower and less likely before the age of 50 years. The prospective Prevention and Observation of Surgical Endpoints (PROSE) study investigated the effects of prophylactic surgery in 2,482 *BRCA* mutation carriers, identified in 21 genetic centers [28]. Forty percent had RRSO performed, and at a median follow-up of 3.7 years, they had reduced all-cause mortality (hazard ratio [HR] 0.40; 95% confidence interval [CI] 0.21–0.61), breast cancer-specific mortality (HR 0.44; 95% CI 0.26–0.076), and ovarian cancer-specific mortality (HR 0.25; 95% CI 0.08–0.75).

Breast cancer risk reduction. It is more difficult to evaluate the effects of RRSO on breast cancer risk, because most studies included patients who already had breast cancer. Five studies excluded *BRCA* mutation carriers with prior breast cancer. When RRSO was performed before the onset of menopause, the risk of breast cancer was reduced by half [15]. A recent nationwide Dutch study has re-examined this topic and attempted to eliminate other causes of potential bias. As well as excluding *BRCA* mutation carriers with previous breast cancer or ovarian cancer, prophylactic mastectomy resulted in patient censoring, and the group that did not undergo surgery were allocated time prior to surgery [29]. The investigators then failed to find a reduction in breast cancer risk in patients who had RRSO

performed. We should keep this in mind when we discuss RRSO in terms of reducing breast cancer risk with patients; this may no longer be considered a definite benefit.

Long-term effects of RRSO. Prophylactic salpingo-oophrectomy is a relatively straightforward procedure that can be performed laparoscopically, as a day-surgery case. There are psychosocial benefits to performing RRSO in *BRCA* mutation carriers. In one study, 80% of *BRCA* mutation carriers who had RRSO had a reduced cancer-related concern, and 95% were satisfied with their decision [30]. However, the sudden onset of an induced menopause can have significant effects in *BRCA* mutation carriers [31]. Some of these symptoms can be relieved with short-term hormone replacement therapy, and this strategy has not been shown to be harmful following RRSO. Unfortunately, there are several negative long-term health effects associated with premature surgical menopause. These include increased cardiovascular disease and osteoporosis, and may include accelerated cognitive decline in elderly women. These important consequences should be considered by women contemplating prophylactic salpingo-oophrectomy.

18.3 Prophylactic Surgery in HBOC Patients with Ovarian Cancer

Before performing prophylactic surgery on HBOC patients, the risk of mortality from their index cancer needs to be considered carefully. Unfortunately, the overall prognosis of ovarian cancer in HBOC patients is poor, and prophylactic breast surgery is generally not appropriate.

In a series of 1,421 patients diagnosed with epithelial ovarian cancer (EOC), 177 (12.5%) were found to be *BRCA1* or *BRCA2* mutation carriers [32]. The 10-year actuarial survival of mutation carriers with stage III/IV serous cancers and no residual cancer was 29%. Similarly, in another series, the overall 10-year survival rate for 135 *BRCA* mutation carriers with EOC was 17% [33]. Because of poor survival rates, only 12 patients (8.9%) developed breast cancer at a median of 50.5 months following the diagnosis of EOC; all had early (stage 0–II) breast cancer.

Using an international registry of 509 *BRCA* mutation carriers with ovarian cancer, 20 (3.9%) developed breast cancer within 10 years [34]. The actuarial risk of developing breast cancer at 10 years was 7.8%, and this was conditional on surviving ovarian cancer and other causes of mortality. Improved survival was only observed with MRI or mastectomy in women who had survived 10 years following ovarian cancer and those with stage I or II cancer.

In summary, because of the poor survival associated with ovarian cancer in HBOC patients, prophylactic breast surgery is not usually appropriate. The exceptions to this may include women with early-stage ovarian cancer and long-term survivors of ovarian cancer.

18.4 Prophylactic Surgery in HBOC Patients with Breast Cancer

Individuals from families with HBOC syndrome and a documented gene mutation, who are undergoing breast surveillance, may be diagnosed with breast cancer. In this case, the diagnosis of HBOC syndrome may be straightforward. However, it is important to recognize a potential HBOC syndrome, in all patients diagnosed with breast cancer (see, for instance, Case 1 and Case 2). This allows prompt genetic testing to be performed, so that prophylactic surgery can be considered at the same time as their cancer surgery. There are several guidelines available to help clinicians decide which patients are appropriate candidates for genetic testing. The American Society of Breast Surgeons (ASBS) has recently revised its consensus guideline on hereditary genetic testing for patients with and without breast cancer [35]. It now recommends that genetic testing should be made available to all patients with a personal history of breast cancer, and to patients without a history of breast cancer who meet NCCN guidelines. It recommends that patients who had genetic testing performed prior to 2014 may benefit from having this repeated.

Often, the first decision to be made by HBOC patients with breast cancer is what type of surgery to have. The prognosis of the index breast cancer must be considered; extensive prophylactic surgery may not be appropriate in locally advanced breast cancer, when the risk of recurrence is high. Most early breast cancer patients can be adequately treated with BCT or a unilateral mastectomy. However, these strategies may result in a high risk of IBTR or CBC in HBOC patients, and bilateral mastectomy may be more appropriate. It is not surprising that the surgical decisions made by breast cancer patients are influenced by whether they know if they have HBOC syndrome at the time of their diagnosis. At the Mayo Clinic in the United States, bilateral mastectomy was chosen by 82.5% (52/63) who knew they were *BRCA* mutation carriers at diagnosis of stage 0–III breast cancer, compared to 29% (27/93) who did not realize they were *BRCA* mutation carriers [36]. It is important to note that the high rate of bilateral mastectomy in patients who did not have a *BRCA* mutation represents an increasing phenomenon in patients diagnosed with unilateral breast cancer [37].

We have realized for 15 years that HBOC patients have increased rates of IBTR and CBC when treated with BCT or a unilateral mastectomy, compared to patients with sporadic breast cancer [38]. However, the design of early studies was often biased, and patients did not receive adequate treatment by today's standards (e.g., data on margins was unavailable, axillary surgery was often omitted, and patients did not receive antiestrogen treatment). Larger multi-institutional studies have revisited the risk of IBTR in *BRCA* mutation carriers treated with BCT and of CBC in *BRCA* mutation carriers who underwent BCT or had a unilateral mastectomy (Table 18.1).

Lori J. Pierce and coworkers [39] reported on 655 *BRCA* mutation carriers treated with BCT or mastectomy in patients from 9 institutions. The rate of IBTR was 11.6% (35/302) in patients treated with BCT after a median follow-up of 8.2 years. This was significantly greater than the 3.1% IBTR rate (11/353) in mastectomy patients with a median follow-up of 8.9 years. The rate of CBC during follow-up was 23.0% (148/643) in BCT and unilateral mastectomy patients. Kelly A. Metcalfe and coworkers [40] reported on *BRCA* mutation carriers ≤ 65 years of age with stage I and II breast cancer, treated between 1975 and 2008 at 10 genetic clinics. The risk of IBTR was 12.1% (48/396) in patients treated with BCT at a mean follow-up of 10.5 years. The risk of CBC was 18.4% (149/846) in patients treated with BCT or unilateral mastectomy, with a mean follow-up of 11.1 years [41]. Although recently published, these multicenter studies are retrospective and contain breast cancer patients treated four decades ago. Additionally, despite efforts to reduce its causes, bias cannot be eliminated. *However, we can conclude that early-stage HBOC patients with breast cancer treated with BCT or a unilateral mastectomy are at a clear disadvantage in terms of IBTR and CBC. These patients may benefit more from bilateral mastectomy*.

Case 1

*A 37-year-old female presented to the symptomatic breast clinic with a left breast lump she noticed 3 weeks previously. She was healthy and did not have a family history of breast cancer, although a paternal aunt had been diagnosed with ovarian cancer at 47 years. Mammogram, ultrasound, and biopsy confirmed an invasive ductal carcinoma, grade 2, measuring approximately 2 cm (Fig. 18.2**a–b**). The tumor was strongly estrogen- and progesterone-receptor positive and human epidermal growth receptor 2 (HER2) negative, and had a Ki-67 of 10%.*

*She underwent left breast wide local excision (Fig. 18.2**c**) and sentinel lymph node biopsy. The pathologic analysis confirmed a 20mm invasive ductal carcinoma, grade 2, with clear resection margins and 3 negative sentinel lymph nodes. This was a stage IA breast cancer (T1c N0). Oncotype DX (Genomic Health, Redwood City, CA, USA) testing confirmed a low-risk 21-gene recurrence score of 13; therefore, the benefits of adjuvant chemotherapy above tamoxifen alone were minimal.*

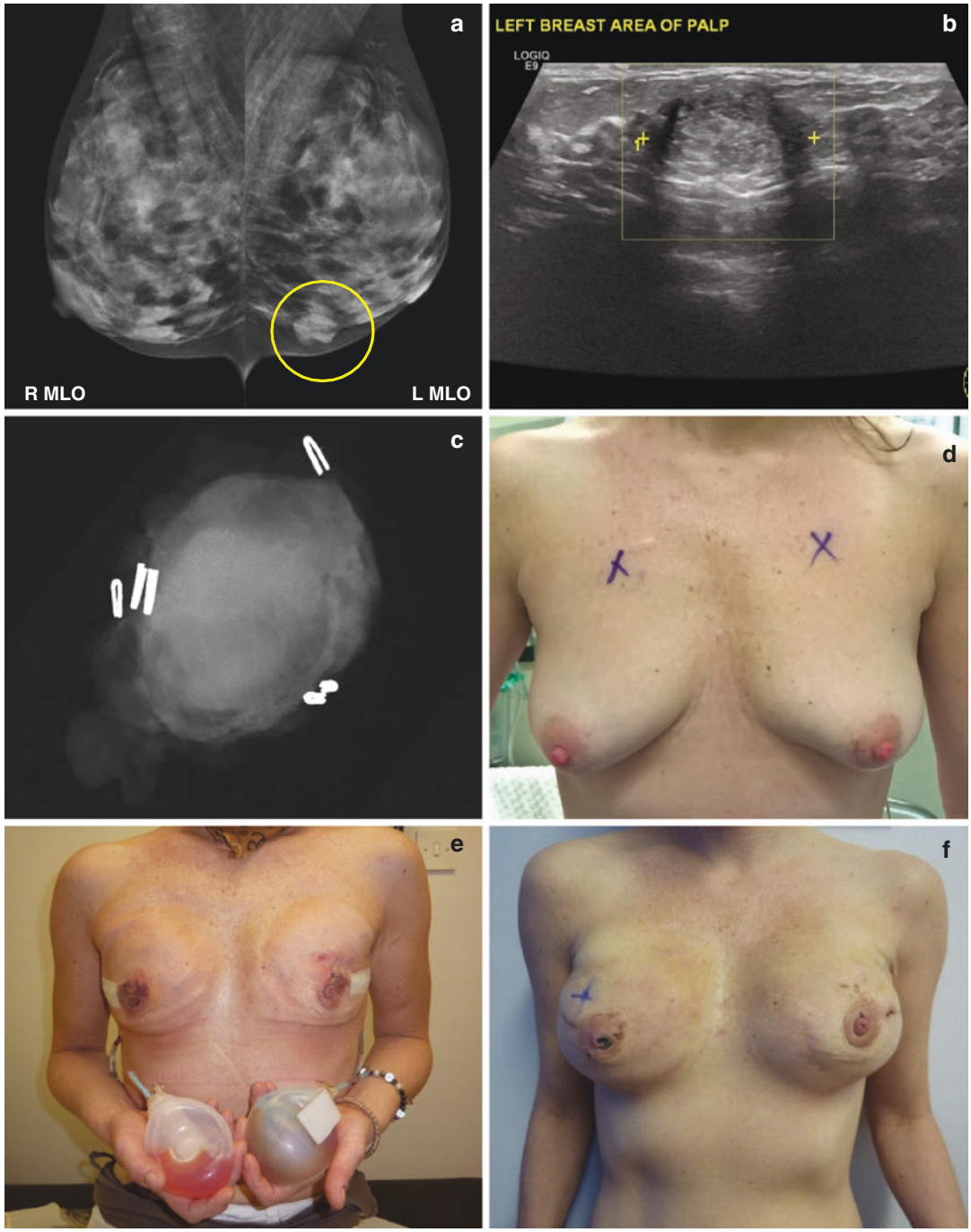

Fig. 18.2 Breast cancer treatment in a 37-year-old *BRCA2* mutation carrier (*Case 1*). (**a**) Mediolateral mammogram views with left breast cancer highlighted. (**b**) Ultrasound view of left breast cancer. (**c**) Specimen X-ray performed following wide local excision of left breast cancer. (**d**) Appearance following left breast wide local excision. (**e**) One week following bilateral nipple-sparing mastectomy with drains still in place. (**f**) Six weeks following surgery, with tissue expanders fully inflated

Genetic testing revealed that this patient was a BRCA2 *mutation carrier, with a heterozygous frameshift mutation. She received genetic counseling and chose to undergo bilateral prophylactic mastectomy rather than completing breast-conserving therapy by proceeding to left whole-breast radiotherapy. Bilateral nipple-sparing mastectomy with immediate tissue expander reconstruction was performed (Fig. 18.2**d–f**). Pathology revealed no residual cancer in the left breast, and a benign right breast and sentinel lymph nodes. Prophylactic oophorectomy is currently being considered by this patient.*

A key question in this scenario is the following: Is there a survival advantage to bilateral mastectomy in HBOC patients with breast cancer?

Several retrospective studies have found an association between improved survival and contralateral mastectomy in *BRCA* mutation carriers, although these studies contain many confounding factors [42–44]. Kelly A. Metcalfe and coworkers found that patients who underwent bilateral mastectomy had improved survival [43]. However, these patients were also significantly younger, were treated later in the study, had smaller tumors, and were more likely to receive chemotherapy and undergo oophorectomy. Commentators have questioned if higher income or better medical insurance was a factor, by increasing access to bilateral mastectomy. Additionally, breast MRI surveillance was not performed in patients with remaining breast tissue. Therefore, these studies do not prove that there is a survival advantage in HBOC patients who undergo bilateral mastectomy. This is not surprising because of the relatively low risk of breast cancer recurrence at 10 years and the short follow-up time of patients in these studies. In the Early Breast Cancer Trialists' Collaborative Group overview [45], a reduction in the 15-year breast cancer mortality was only found when there was a 10% or more difference in local recurrence at 5 years follow-up.

However, other factors should be considered when discussing treatment options in HBOC patients with breast cancer.

Not all HBOC patients with breast cancer choose to undergo bilateral mastectomy. Older patients, perhaps with a *BRCA2* mutation and an estrogen-sensitive breast cancer, may prefer BCT. They may feel their risk of IBTR and CBC is lower than that of a younger *BRCA* mutation carrier. In *BRCA* mutation carriers treated with BCT, the risk of IBTR was reduced with adjuvant chemotherapy [39, 40]. Lower rates of CBC have been observed in *BRCA* mutation carriers over 50 years of age with breast cancer compared to patients age < 50 years [46]. Concerns have previously been raised about the effect of adjuvant radiotherapy as part of BCT in *BRCA* mutation carriers [47]. Although there is a theoretically increased risk of second malignancies, e.g., radiation-induced sarcomas, this has not been observed in clinical studies.

Mastectomy and breast reconstruction techniques are continually evolving, resulting in improved quality of life in breast cancer patients, including those with HBOC. NSM is increasingly used to treat suitable patients with early breast cancer, and its role has been established in *BRCA* patients with breast cancer [21, 48]. Using the BREAST-Q patient-reported outcome instrument, patients who underwent NSM and reconstruction had improved psychosocial scores and sexual well-being, compared to patients who had skin-sparing mastectomy and nipple reconstruction [49]. It is reassuring that a meta-analysis has found similar oncologic outcomes with NSM compared to modified-radical or skin-sparing mastectomy [50].

Case 2

*A 38-year-old female presented to the symptomatic breast clinic after noticing a right breast lump. She was healthy, but had a significant family history of breast and ovarian cancer. These included her mother who had bilateral breast cancer at the age of 38 and 39 years, a maternal aunt with ovarian cancer aged 67 years, and a male maternal cousin with breast cancer aged 30 years. Mammogram, ultrasound, and biopsy revealed two invasive ductal carcinomas, grade 2, measuring approximately 2.2 cm each (Fig. 18.3**a**). The tumors were estrogen- and progesterone-receptor positive, and HER2 equivocal, with a Ki-67 of 50%.*

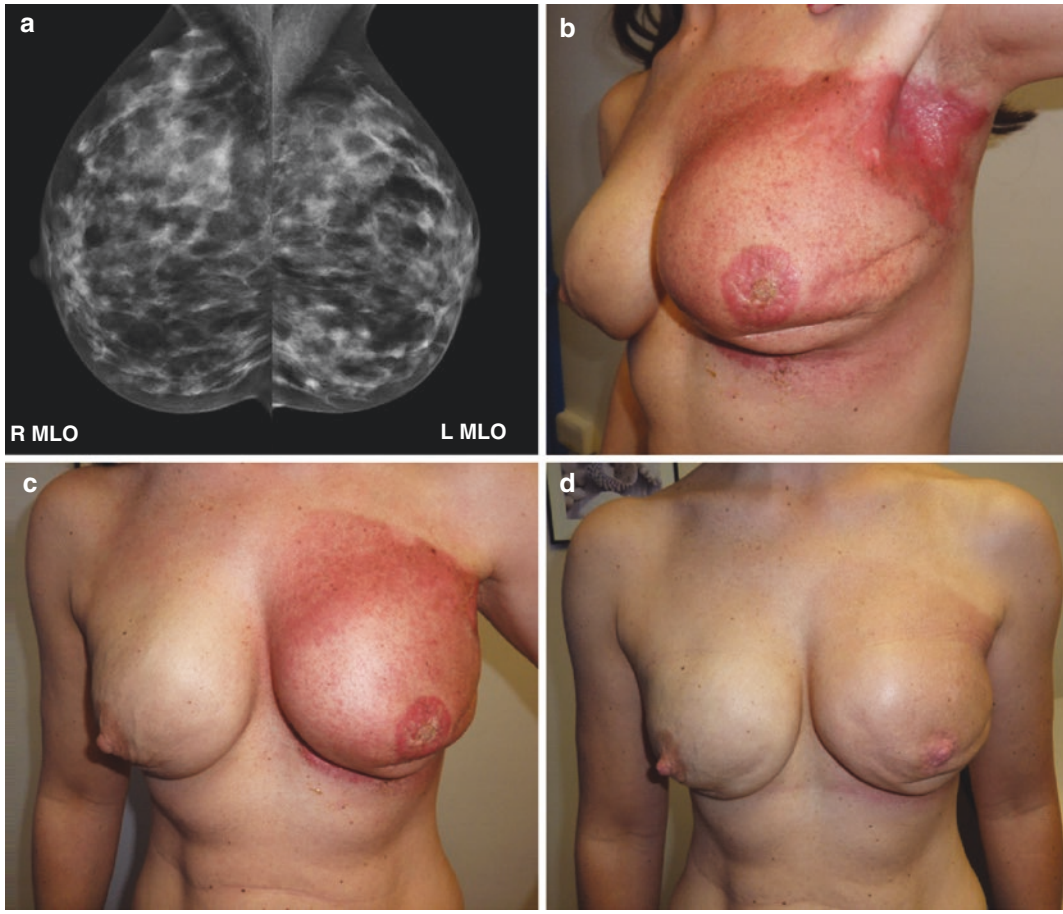

Fig. 18.3 Challenges in breast cancer treatment in a 38-year-old *BRCA2* mutation carrier (*Case 2*). (**a**) Mediolateral mammogram views. (**b, c**) Skin reaction 1 week following postmastectomy radiation therapy to left reconstructed breast following bilateral nipple-sparing mastectomy. Fully inflated tissue expanders are in place. (**d**) Improvement in skin reaction left reconstructed breast, 2 months following postmastectomy radiation therapy

*Because of her family history, she requested bilateral mastectomy. Bilateral NSM and SLN biopsy were performed. The pathology of the right side revealed an invasive grade 2, mixed ductal, and lobular carcinoma, measuring 45 mm, with 1 of 2 SLNs containing a micrometastasis. Histological examination of the left side revealed a mammographically occult invasive ductal carcinoma, grade 2, measuring 32 mm, with all 3 SLNs containing macrometastases. The left breast cancer was estrogen- and progesterone-receptor positive, and HER2 equivocal, with a Ki-67 15%. A completion axillary lymph node dissection was performed on the left side and revealed micrometastasis in a further 1/22 lymph nodes. The symptomatic right breast cancer was stage IIB (T2 N1mi), and the unsuspected left breast cancer was stage IIIA (T2 N2a). A positron emission tomography/computed tomography scan was performed to rule out metastatic breast cancer, following which our patient received adjuvant chemotherapy and PMRT to the left chest wall. PMRT was delivered to the fully inflated left tissue expander, and the local reaction to radiotherapy can be seen in Fig. 18.3**b**, **c**. This greatly settled during the following 2 months (Fig. 18.3**d**), and exchange of the tissue expanders to permanent implants will be performed 6 months following completion of PMRT.*

Genetic testing revealed that our patient was a BRCA2 mutation carrier, with a heterozygous frameshift mutation. She is currently considering the merits of having a prophylactic oophorectomy.

The increasing use of NSM has led to challenges for clinicians. In one series, Briar L. Dent and coworkers [51] found an increased risk of mastectomy flap necrosis and hematoma in patients who had prior cosmetic breast augmentation or reduction compared to those without prior cosmetic breast surgery. In contrast, M.J. Frederick and coworkers [52] found that complications following NSM were not related to prior breast surgery, but increased in patients who received radiotherapy prior to NSM. In an expanded series, the same institution found that additional independent risk factors for complications following NSM were postmastectomy radiation therapy (PMRT), smoking, age > 55 years, breast volume > 800 cm^3, and the use of a periareolar incision [53]. Although complications occurred in irradiated breasts, it is encouraging that nipple loss and reconstructive failure were uncommon.

A recent joint panel of medical, surgical, and radiation oncologists has re-examined the evidence for PMRT and issued a guideline statement [54]. There is strong evidence that PMRT reduces the risk of recurrence and mortality in patients with T1 or T2 tumors (less than 5 cm) and 1 to 3 positive lymph nodes. The importance of this is that more breast cancer patients with HBOC syndrome will require PMRT following mastectomy and reconstruction. Investigators continually seek strategies to improve the risk profile for patients with a breast reconstruction who require PMRT. For two-stage prosthetic reconstruction, when radiation therapy is delivered to the tissue expander rather than the permanent implant, the aesthetic results and capsular contracture rates are improved, although reconstructive failure rates are higher [55].

18.5 Conclusions

HBOC syndrome occurs in families and follows an autosomal dominant pattern of inheritance. The risks of breast cancer, ovarian cancer, or both are greatly increased in women who carry a deleterious gene mutation. The most common gene mutations associated with HBOC are *BRCA1* and *BRCA2* mutations.

Strategies to manage the risk of HBOC have been extensively studied, and are comprised of chemoprevention, screening, and risk-reducing surgery. Chemoprevention has been successfully used in postmenopausal women, but the side effects have proven intolerable for young women at risk of HBOC. Ovarian screening with ultrasound and CA-125 measurement has limited sensitivity and is only recommended for women deferring RRSO. Breast screening with MRI and mammography can detect cancers earlier than mammography alone, and should be performed in patients at risk for HBOC. However, although small breast cancers can be detected with screening, *BRCA1*-associated breast cancers are frequently high grade and triple negative. This means that even early breast cancers normally require chemotherapy and breast cancer fatalities can occur.

The best way to prevent cancer from occurring in individuals at risk of HBOC is by performing risk-reducing surgery. Prophylactic mastectomy has reduced the occurrence of breast cancer by 90% or more in recent studies. RRSO is 80% effective in preventing ovarian cancer. Because of its success in preventing cancer, prophylactic surgery is widely recommended by healthcare bodies. Although it is associated with morbidity and loss of femininity, NSM and better-quality reconstructive techniques have improved the acceptability of prophylactic breast surgery. Most women are less fearful about developing cancer after risk-reducing surgery, and the majority do not regret their decision. A recent study, which attempted to eliminate bias, has cautioned us that the RRSO might not actually reduce the risk of developing breast cancer. This must be kept in mind when counseling patients, especially those who are reluctant to pursue risk-reducing mastectomy. Potential RRSO candidates must be made aware of the long-term risks of increased cardiovascular disease, osteoporosis, and cognitive decline.

Prophylactic surgery is an important concept in the treatment of appropriate patients diagnosed with HBOC-associated cancer. Cancer patients must be carefully evaluated before offering risk-reducing surgery, because it will not improve the survival of patients with advanced index cancers or those with life-limiting medical comorbidities. Prophylactic breast surgery is only suitable for patients with early-stage ovarian cancer or for long-term disease-free survivors following ovarian cancer treatment. Conversely, most HBOC-associated breast cancer patients are diagnosed at an early stage, and the prospect of survival is good. Therefore, bilateral mastectomy is a prudent option because of the high risk of IBTR and CBC. Recently, the benefit of PMRT has been established in patients with breast cancers less than 5 cm in size and with 1 to 3 positive lymph nodes. Because more patients are now receiving PMRT following NSM and reconstruction, strategies to reduce the increased risk of radiation-induced complications are more important. Bilateral mastectomy is not mandatory for all patients with early-stage HBOC-associated breast cancer. BCT is an acceptable option for older *BRCA* mutation carriers with hormone-sensitive breast cancer who want to avoid more extensive surgery and whose risk of developing CBC is lower.

The improvement in access to quicker and less expensive genetic testing has meant that more individuals at risk of HBOC syndrome, or patients with HBOC-associated cancers, are candidates for prophylactic surgery. Perhaps in the future, genetic engineering or gene therapy will eliminate the occurrence of HBOC-associated cancers. For now, prophylactic surgery is king.

References

1. Anglian Breast Cancer Study Group (2000) Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 83:1301–1308
2. Malone KE, Daling JR, Doody DR et al (2006) Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Res 66:8297–8308
3. Chen S, Iversen ES, Friebel T et al (2006) Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J Clin Oncol 24:863–871
4. Antoniou A, Pharoah PD, Narod S et al (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130
5. Tai YC, Domchek S, Parmigiani G, Chen S (2007) Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 99:1811–1814
6. Easton DF, Pharoah PD, Antoniou AC et al (2015) Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372(23):2243–2257
7. von Minckwitz G, Loibl S, Jackisch C et al (2011) The GISS trial: a phase II prevention trial of screening plus goserelin, ibandronate, versus screening alone in premenopausal women at increased risk of breast cancer. Cancer Epidemiol Biomark Prev 20(10):2141–2149
8. NCCN Clinical Practice Guidelines in Oncology (2019) Genetic/Familial High-risk assessment: breast, ovarian, and pancreatic, Version 1.2020-December 4, 2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed 30 Jun 2020
9. Nelson HD, Pappas M, Zakher B, Mitchell JP, Okinaka-Hu L, Fu R (2014) Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med 160(4):255–266
10. NICE National Institute for Health and Care Excellence (2013) Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). Clinical guideline, Published date: June 2013, Last updated: November 2019. http://www.nice.org.uk/guidance/cg164. Accessed 30 Jun 2020
11. Mavaddat N, Barrowdale D, Andrulis IL et al (2012) Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomark Prev 21:134–147
12. Kurian AW, Munoz DF, Rust P et al (2012) Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 30:497–506
13. Sigal BM, Munoz DF, Kurian AW, Plevritis SK (2012) A simulation model to predict the impact of prophylactic surgery and screening on the life expectancy of BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomark Prev 21:1066–1077
14. Evans DG, Howell A (2012) Are we ready for online tools in decision making for BRCA1/2 mutation carriers? J Clin Oncol 30:471–473
15. Hartmann LC, Lindor NM (2016) The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med 374:454–468

16. Giuliano AE, Boolbol S, Degnim A, Kuerer H, Leitch AM, Morrow M (2007) Society of Surgical Oncology: position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. Ann Surg Oncol 14:2425–2427
17. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J et al, Hereditary Breast Cancer Clinical Study G (2008) International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. Int J Cancer 122:2017–2022
18. Skytte AB, Gerdes AM, Andersen MK et al (2010) Risk-reducing mastectomy and salpingo-oophorectomy in unaffected BRCA mutation carriers: uptake and timing. Clin Genet 77:342–349
19. Semple J, Metcalfe KA, Lynch HT et al (2013) International rates of breast reconstruction after prophylactic mastectomy in BRCA1 and BRCA2 mutation carriers. Ann Surg Oncol 20:3817–3822
20. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB et al (2007) Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. Ann Surg Oncol 14:3335–3344
21. Manning AT, Wood C, Eaton A et al (2015) Nipple-sparing mastectomy in patients with BRCA1/2 mutations and variants of uncertain significance. Br J Surg 102:1354–1359
22. Yao K, Liederbach E, Tang R et al (2015) Nipple-sparing mastectomy in BRCA1/2 mutation carriers: an interim analysis and review of the literature. Ann Surg Oncol 22:370–376
23. Frost MHSD, Sellers TA, Slezak JM et al (2000) Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. JAMA 284:319–324
24. Razdan SN, Patel V, Jewell S, McCarthy CM (2016) Quality of life among patients after bilateral prophylactic mastectomy: a systematic review of patient-reported outcomes. Qual Life Res 25:1409–1421
25. Metcalfe KA, Cil TD, Semple JL et al (2015) Long-term psychosocial functioning in women with bilateral prophylactic mastectomy: does preservation of the nipple-areolar complex make a difference? Ann Surg Oncol 22:3324–3330
26. Rebbeck TR, Kauff ND, Domchek SM (2009) Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 101:80–87
27. Walker JL, Powell CB, Chen LM et al (2015) Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer 121:2108–2120
28. Domchek SM, Friebel TM, Singer CF et al (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967–975
29. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ et al (2015) Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 107:pii. djv033
30. Finch A, Metcalfe KA, Chiang J et al (2013) The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psychooncology 22:212–219
31. Stan DL, Shuster LT, Wick MJ, Swanson CL, Pruthi S, Bakkum-Gamez JN (2013) Challenging and complex decisions in the management of the BRCA mutation carrier. J Womens Health (Larchmt) 22:825–834
32. Kotsopoulos J, Rosen B, Fan I et al (2016) Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. Gynecol Oncol 140:42–47
33. Gangi A, Cass I, Paik D et al (2014) Breast cancer following ovarian cancer in BRCA mutation carriers. JAMA Surg 149:1306–1313
34. McGee J, Giannakeas V, Karlan B et al (2017) Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: is preventive mastectomy warranted? Gynecol Oncol 145:346–351
35. The American Society of Breast Surgeons (2019) Consensus Guideline on Genetic Testing for Hereditary Breast Cancer, February 10, 2019. https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Accessed 30 Jun 2020
36. Chiba A, Hoskin TL, Hallberg EJ et al (2016) Impact that timing of genetic mutation diagnosis has on surgical decision making and outcome for BRCA1/BRCA2 mutation carriers with breast cancer. Ann Surg Oncol 23:3232–3238
37. Mamtani A, Morrow M (2017) Why are there so many mastectomies in the United States? Annu Rev Med 68:229–241
38. Haffty BG, Harrold E, Khan AJ et al (2002) Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. Lancet 359:1471–1477
39. Pierce LJ, Phillips KA, Griffith KA et al (2010) Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat 121:389–398
40. Metcalfe K, Lynch HT, Ghadirian P et al (2011) Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 127:287–296
41. Metcalfe K, Gershman S, Lynch HT et al (2011) Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 104:1384–1392
42. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM et al (2015) Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer 136:668–677
43. Metcalfe K, Gershman S, Ghadirian P et al (2014) Contralateral mastectomy and survival after breast

cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ 348:g226
44. Evans DG, Ingham SL, Baildam A et al (2013) Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat 140:135–142
45. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366:2087–2106
46. Verhoog LC, Brekelmans CT, Seynaeve C, Meijers-Heijboer EJ, Klijn JG (2000) Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer. Br J Cancer 83:384–386
47. Cooper BT, Murphy JO, Sacchini V, Formenti SC (2013) Local approaches to hereditary breast cancer. Ann Oncol 24(Suppl 8):viii54–viii60
48. Krajewski AC, Boughey JC, Degnim AC et al (2015) Expanded indications and improved outcomes for nipple-sparing mastectomy over time. Ann Surg Oncol 22:3317–3323
49. Wei CH, Scott AM, Price AN et al (2016) Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. Breast J 22:10–17
50. De La Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM (2015) Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol 22:3241–3249
51. Dent BL, Cordeiro CN, Small K et al (2015) Nipple-sparing mastectomy via an inframammary fold incision with implant-based reconstruction in patients with prior cosmetic breast surgery. Aesthet Surg J 35:548–557
52. Frederick MJ, Lin AM, Neuman R, Smith BL, Austen WG Jr, Colwell AS (2015) Nipple-sparing mastectomy in patients with previous breast surgery: comparative analysis of 775 immediate breast reconstructions. Plast Reconstr Surg 135:954e–962e
53. Tang R, Coopey SB, Colwell AS et al (2015) Nipple-sparing mastectomy in irradiated breasts: selecting patients to minimize complications. Ann Surg Oncol 22:3331–3337
54. Recht A, Comen EA, Fine RE et al (2017) Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Ann Surg Oncol 24:38–51
55. Cordeiro PG, Albornoz CR, McCormick B et al (2015) What is the optimum timing of postmastectomy radiotherapy in two-stage prosthetic reconstruction: radiation to the tissue expander or permanent implant? Plast Reconstr Surg 135:1509–1517

Psychological Aspects of High Risk of Breast Cancer

19

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Abbreviations

BC	Breast cancer
MRI	Magnetic resonance imaging
OC	Ovarian cancer

19.1 Introduction

A disease or the fear of a disease goes beyond biological and medical issues and imply several psychological aspects. When considering a person, affected or not affected with the disease, candidate, or asking for genetic testing, we should understand who she (or he[1]) is, i.e., we should know her/his personal and family history. In addition, we should evaluate the quality of her/his interaction with the physicians, which is influenced by the personal and family history, aims, and the cultural context, as well as by the capability of both the woman and the physician(s) to establish an effective bidirectional transfer of all relevant information.

The choice of language type, more or less scientific or descriptive; the usage of flyers, books, or online tools; and the type of consent forms and of any other material provided by the counselor to the woman (the counselor) strongly contribute to create the context of the relationship that will be established. The interview planned before the decision to perform a genetic test is absolutely important to define the quality of the relationship, the level of confidence between the woman and the physician(s), as well as the expectations about the future on both sides of the relationship. The multidisciplinary team must be coherent with a communication style to be discussed and updated according to the experiences coming from the real work life of the team. There is evidence [1] that a communication style supporting patient's autonomy positively impacts on the decision quality.

The literature on the specific topic of high-risk women is not so large and is also difficult to interpret due to the interplay of specific variables we partially mentioned previously:

- The history of the woman asking for genetic testing and potentially receiving the result;
- The history of the relationship between the referring physician(s) and the psychologist acting as counselor (expected to be not only experts but also sensitive humans);

[1]In the following text, we will refer to women or female patients, even though high-risk patients can be also men, especially in the case of *BRCA2* mutation carriers.

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- The acute biographic anxieties frequently reported during the psychological counseling (e.g., newly diagnosed breast cancer (BC), recent death of a close relative, current pregnancy) and taking also into account the time needed to obtain the results of the test;
- The evolution of scientific research that accumulates new knowledge and modifies the clinical practice, in particular, in the field of risk prediction and of screening high-risk women, including the use of tests such as breast magnetic resonance imaging (MRI), implying to stay in a tube in prone position for a relatively long examination time, and to be intravenously injected with a contrast material.

The following points should be preliminarily investigated during the first interview and are very useful for planning the future interaction.

1. Is it the first time that the woman is asking for a psychological counseling? If not, consider the request if a *second opinion* may be the result of an anxious search for confirmation or for a different view due to personal/family events or to news from the media or Internet that induced a cancer phobia.
2. Why the woman is also asking for a psychological counseling? Is she a patient newly diagnosed with a BC? Was she affected in the past? Or is she healthy but the family history posed the suspect of the presence of a deleterious mutation?
3. What does the woman already know? Is she already aware of the results of the reconstruction of the genealogic tree? Do we need to explain probabilities using graphical tools?

If these points are clarified during the first interview, the next steps, including the possible decision to perform the genetic test, will be relatively easier. This decision may be taken by the woman immediately or during a subsequent interview. Anyway, *she must have the time to understand the information given to her, showing to be able to repeat the essential knowledge on her condition using her own language*.

Scientific terms are often used by the woman to gratify the consultant psychologist, but we should remember that this does not imply a sufficient understanding of the matters under discussion, with special regard to what can happen after the genetic testing. *Of note, during the pre-test interview, all the probabilities of the possible post-test condition are open*. The result of the test will define new decisional steps, increasing or decreasing probabilities, and related anxieties. Each woman will react with her own mode without linear relation with the change of probabilities. One crucial aspect of communicating scientific evidence is *the use of concepts and words that can be understood by the woman and her family*, something that goes far beyond presenting study results in lay language [2].

It is important to note that on this matter, we do not have international guidelines to be adopted. In this chapter, we try to define some questions and to give some answers. Psychological issues are strongly subjected to variation related to the individual characteristics of human beings, not only of the patients but also of the physicians and of the psychologists. It is difficult to take into account all terms of this variability when writing a book chapter. What we wish to underline here is that, in the context of a breast unit or a family cancer clinic, the psychologist can facilitate the discussion on the modalities to be used for communications to the woman and can also act as a mediator between the women and the physicians, according to their different specialties. In addition, we should consider the possibility that psychotherapy may be necessary under particular conditions.

19.2 Post-test Scenarios for the Pre-test Counseling

Malignant tumors, including BCs, are not inherited. What can be inherited is a higher predisposition to the disease, i.e., a higher probability to have the disease in comparison to the average population. This means that, also when a deleterious mutation such as in *BRCA1* or *BRCA2* genes is found, the information the woman receives is

complex and uncertain, given as probabilities, to be added to personal or reported real-life experiences. In other words, *being informed to be a BRCA mutation carrier is an answer that creates a number of further questions*. For this reason, before taking the decision to do the test, it is necessary to verify that the woman has evaluated not only her probability to be a mutation carrier but also the different scenarios that she can face when the result of the test will be available.

These issues depend on the context. In the case of strong family history of BC or ovarian cancer (OC) and search for underlying mutations, the test can be as follows:

- *Positive*, implying the probability to have a BC (and to transmit the mutation to the offspring) associated with the identified mutation;
- *Inconclusive* or *uncertain*, i.e., the absence of known deleterious mutations, in the presence of a familial high risk of BC, the so-called BRCAX situation.

In the case of an already known presence of a deleterious mutation in the family, due to the very low probability of the coexistence of another deleterious mutation in the same genome, the test can be as follows:

- *Positive*, as in the previous case but knowing in advance what mutation is under consideration, with all its implications;
- *True negative*, the best result, of course the easiest to be explained, meaning that the woman even belonging to a high-risk family is not a mutation carrier and has a risk for the disease similar to that of the general population.

Only having clearly explored these possibilities in advance, the woman can take an informed, aware decision to do or to refuse the test, both options possibly being appropriate for the woman depending upon specific circumstances [3]. A study from Japan [4] reported that of 132 subjects who initially declined genetic testing, 58 (44%) postponed the decision, 30 (23%) needed more time to discuss the issue with family members, 22 (17%) did not want to know if they had a *BRCA1/2* mutation, and 22 (17%) declined the test because of financial problems. However, analyzing refusal of testing according to the time period before and after the implementation of health system coverage for *BRCA1/2* testing, refusal for financial reason decreased from 61 to 10%. Anyway, to avoid any misunderstanding we want to highlight that *test refusal has to be considered as an adaptive choice to be respected and well-accepted by the multidisciplinary team*.

An interesting contribution on this matter came from D. Leblond and coworkers [5]. A literature review was conducted regarding the psychological impact of the uncertain genetic test result, compared to the impact of positive or true negative result, or of test refusal. On the basis of eight selected articles, a less emotional distress and a lower perceived risk of predisposition or to develop cancer was observed for an uncertain genetic result compared to a positive result. Interestingly, an uncertain result did not confer a *false reassurance*, not reducing the intentions to have BC surveillance, while the demand for prophylactic surgery was less frequent. However, inappropriate psychological reactions may be highlighted in the case of pre-test clinical distress, a personal cancer history, or multiple family history of cancer. Thus, a *bad reaction to an uncertain result could be predicted based on the pre-test interview*.

19.3 Understanding What the Woman Thinks and Wants

A frequent case during genetic counseling is the difficulty of the woman in understanding the concept of *gene*. It is not a matter of scientific, biologic, or medical knowledge. It is something very small, being inside our cells, which can be abnormal and potentially resulting in cancer. Suddenly, this small entity becomes the central interest of the woman and of all her family.

The wrong gene becomes a symbol, beyond biology and medicine. It embodies “the error of

my parents, my fault towards my children." The future becomes uncertain, with heavy responsibilities and difficult decisions to be undertaken. As it happens with the eye or skin color as well as the characteristics of a recent ancestor, the subject at high genetic risk is thinking to have inherited part of her/his biologic destiny, including the fragility to disease. "I'm my genes" can be the deterministic perception to be certain to have the cancer in the future and also of a very high risk for the disease in the children, either already existing or not. The woman's sensation may be to be strictly determined by a fatal biologic destiny. Also, the communication of a moderate risk can be misunderstood and overrated leading to unproven therapies to sedate the anxiety.

Counseling is a multiphase process (first approach and individual risk estimate; decision to perform or not to perform the test; in the case of positive decision, communication of the test result) sometimes appearing to be a long process to the physician (e.g., the genetician). This can be due to the real or supposed presence of problems that the woman does not clearly raise. The physician can be influenced by the fear of facing pregnant or very young women as well as subjects recalling episodes of her/his personal or family history with high psychological impact. This is a relevant issue if we consider that psychological understanding implies a deep dynamic introspection into what is changing in one person as an effect of what the person is facing.

In our experience, we observed apparently well-balanced persons who recalled painful experiences incompletely elaborated, thus negatively impacting on the current new condition, while apparently not well-balanced persons had a higher propensity to understand, accept, and share relevant long-term responsibilities. The borders between genetic counseling and psychotherapy can be blurred, even though they are quite different in nature and aims. In the former, the psychologist helps the woman and the physician in understanding each other and the woman in taking an informed decision with potential high impact. In the latter, when needed, the psychologist helps the patient in restructuring episodes of her life.

The crucial point is that the emotional color of any given information is determined by the context of personal and family experiences of the subject. Which personal identity or projects will be negated or changed by the new information? It is important to guide the woman in the imagination of future events and of the effect of the decision (e.g., the result of the test) on them. The question is: *will the information potentially deriving from the current decision to perform the test be integrated in the woman's history and identity or is there a substantial risk that it will disintegrate them?*

19.4 What Should Be Taken Into Account When Communicating the Risk

In the context of risk stratification for cancer, the prediction, namely, the *possibility to predict the future*, becomes the key factor. This is usually considered a positive aspect of modern *predictive medicine* [6]. A high-risk prediction (i.e., being a *BRCA* mutation carrier) impacts on prevention, requiring MRI—including screening protocols starting from 25 years of age and the possibility of prophylactic (so-called risk-reduction) mastectomy. A woman who resulted to be positive for a *BRCA* mutation may see a negatively changed destiny of her body. In the woman's mind, the gene can be given an absolute power to determine the future of the body and, as a consequence, the future of the entire person. A positive genetic test can be felt by the woman as a diagnosis of cancer. A determinist perspective joins the inherited unlucky condition with the lack of methods for healing the wrong gene. To know to have the mutation implies the knowledge of a series of heavy unavoidable consequences. Physicians wait and surveil or discuss the possible benefit of prophylactic mastectomy. Anyway, the woman, the mutation carrier, notwithstanding still healthy in the majority of the cases, will have to live in a new condition. She is thinking: *I'm no longer the same woman I was before the genetic test*.

The positive result of the genetic test is a disrupting event that changes the life. The bad news

may cause an emotional crisis. It is a shock that requires a necessary change that rationalizes an irrational reaction. As we will see below, life projects and relations between generations can be modified, balanced, or unbalanced. Basic aspects of the individual psychological equilibrium are involved: identity and sense of belonging to a family. The history of the disease (i.e., BC) is the history of the family: *I have a disease because of my mother (or my father). My children will have the same disease because of me*. The core of being is called into question. The wrong gene goes beyond the biologic information.

When communicating a genetic diagnosis, the team should take into account the following wide spectrum of worries that may trigger an emotional crisis: concern to become affected with cancer; fear of diagnostic examinations (imaging and biopsies); fear of surgical procedures; fear of the effects of medical therapies; concern to transmit (or to have already transmitted) the mutation to children, felt as the transmission of the disease; responsibility toward the involved partner; and difficulties in projecting her future involving lifestyle, type of work, where living (near great hospitals?), preventive surgical choices, etc.

The psychological consequences of a genetic diagnosis can be dramatically different in different persons. Communicating a high-risk condition can be felt as an anticipation of cancer diagnosis by a subject whose frailty is due to previous dramatic family experiences. Not all the variables of such a context can be under control. Thus, a certain degree of unpredictability must be considered.

The woman's reaction to the communication of the risk level can be different according to a series of factors:

- **The woman personality**, in particular, her attitude toward the disease (tendency to consider herself or others as the cause of negative events; feelings or persecution of hypo- or hyperresponsibility).
- **The woman's age** (older persons present with psychological disorders less frequently than younger persons; young women could benefit from a psychotherapy plan for managing the stress and anxiety due to the information to be a mutation carrier, especially if adolescent or planning to have children).
- **The previous or current experiences** (BC cases in the family frequently cause hyperestimation of the risk; a woman who assisted a relative with BC will be more scared of a genetic mutation; in both cases, the woman may feel herself powerless).
- **The coping style** (a watchful person, always looking for reassurances, frequently overestimates the risk and asks for multiple repeated diagnostic tests).

The emotional mood of any received information is given by the subjective context that affects the anticipation of the events, a crucial mental process for the personal status. A limited list of the possible reactions of a subject to the communication of the risk is the following: **anxiety** (compulsory, with feeling of persecution), **aggressiveness** (toward herself, family members, friends and acquaintances, healthcare givers), **feeling guilty** (feeling not vulnerable but bad), **omnipotence** (underestimating the risk), **negation** (not collecting the test result, performing repeat test at another laboratory), and **communication** (sharing objective data and related emotional reactions with relatives and the members of the medical team).

19.5 Helping the Physicians

Of course, also the physicians' psychological profile has to be taken into account, in particular, that of the genetician or the professionals who interact with the woman for the decision to perform the genetic test and who communicate the result of the test. A psychological support to the woman helps in deciding to do or not to do the test and, if performed, in understanding the result, including the case of positivity for a known mutation, i.e., the associated probability of disease for the woman and her relatives, the options for surveillance, chemoprevention, or prophylactic surgery. A psychological support to physicians should help in managing stress levels which have pecu-

liar temporal behavior. We always should remind that the geneticist remains a key actor in women's decision-making about genetic testing [7]. On the other hand, a study reported that genetic counseling changed the perceived risk of BC only in less than half (46%) of women (decreasing or increasing this perception in 40% and 6%, respectively); however, women overestimating their risk ≥ 4-fold at the baseline failed to improve the risk perception accuracy [8].

Figure 19.1 shows the variations of the stress levels in the case of an interview communicating bad news (generally related to the oncology setting, not specific for genetic testing). One reason for this difference is related to the level of knowledge, higher for the physician (the expert), lower for the woman (the nonexpert person) [9].

To bring someone bad news such as a condition of *BRCA* mutation carrier is not a neutral task even for the most expert and experienced physician or counselor. The physician or counselor should understand that it is necessary to give time not only for speaking (explanations to the woman, questions and answers, etc.) but also for emotional silences and pauses which may have a cathartic role. To listen is at least as important as to speak, especially when an emotional crisis must be managed to reestablish the self-control.

The way the physician interprets probabilities associated to pre-test and post-test risk levels is highly important for the content of counseling. The way the woman interprets the given information influences her willingness to go forward with the same team in the same institution. What the clinicians should do for establishing a good relation with the woman can be summarized as follows:

- Pay attention to both verbal and nonverbal communication.
- Pay attention not only to the woman's lexicon but also to the content (medical/technical terms can be used as interposition tools, to mask distress; they can be used to please the physicians without understanding their meaning).
- Observe carefully behaviors, attitudes, gestures, and facial expressions revealing emotions and feelings.

Of note, also from the physician side, technical terms can be used as interposition barriers, to mask distress due to the need of bad news communication.

An interesting contribution to this topic came from a study by Dilla Saman and coworkers [10]. The authors described the relationship between experience of death of a relative, illness perception, and psychological outcome among 40 *BRCA* mutation carriers in Israel. Using self-administered questionnaires assessing sociodemographic variables, illness perception, and well-being, the authors found that experiencing the death of a relative as a result of BC was significantly

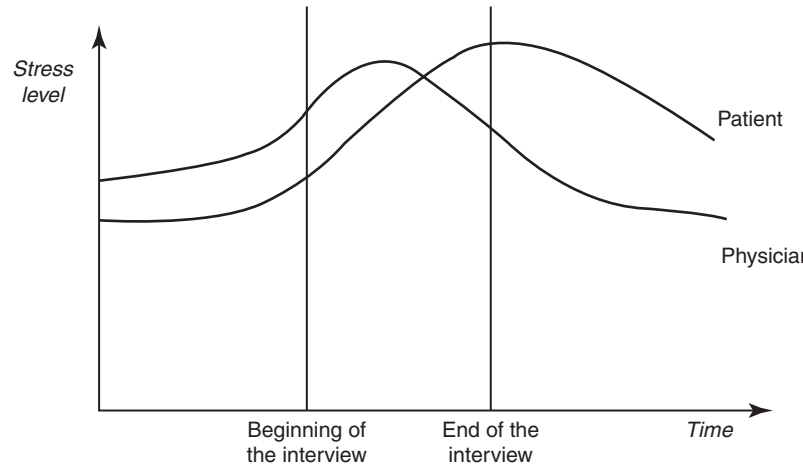

Fig. 19.1 Patient's and physician's stress levels in the case of an interview communicating bad news

correlated with illness perception. Those *BRCA* mutation carriers who experienced the death of a relative perceived BC as correlated with having severe symptoms and dire consequences and as being uncontrollable when compared to carriers who had not experienced the death of a relative. In other words, *the direct experience of death of a relative as a result of BC is a crucial event dramatically influencing the disease perception*. This means that communicating a positive result of a genetic test or of a biopsy to a woman may have a heavier impact if the woman experienced the death of a relative as a result of BC.

19.6 Not to Lose the Relation with the Woman and Her Family

We have already described how previous experiences can influence the relation between the woman and the team. This is a relevant issue also during the time, after the first interviews. Family experiences (also only the fear of them), risk overestimation, reproductive planning, decisions for surveillance, or other preventive acts can change during the time also in relation with new events during the woman's life [11].

Family experiences, including those one who lives firsthand and those told by other family members, contribute to the mirror effect [12]. The woman thinks: *I will experience what had already happened to other women of the family, to my mother, my aunts, my sisters. The same will happen to my daughters, my nephews…* Anxiety is increased by various biographic negative episodes such as friends who are diagnosed with a disease and undergo treatment procedures, prompting the need to do, to know, a condition named *state anxiety* (reactive), especially in women with an anxious baseline personality [13].

To take decisions for daughters and sons undermines one's personality also before the reproductive phase. Physicians' proposals can determine an emotional paralysis, especially when the relationship between the physician and the woman is not fiduciary. One example is the case of a woman who does not collect the results of genetic or diagnostic tests; begins to look for other experts in other hospitals or clinics, other cities, and other countries, when she sends her biological samples to laboratories known by advertising; or immediately asks for definitive surgical ablations to close the problem.

The diagnosis of a genetic mutation touches your essence of human being: your being healthy, your way of life, and your projects for the future [14]. Will this knowledge disintegrate your identity, your perception of reality? And, if the disease history is a family story, it will impact on the whole family ([12] Mendes). How to explain this? An adequate communication should aid the counselor to feel herself completely involved in decision-making.

H. Dijkstra and coworkers [15] showed that during the final visit within BC genetic counseling, more counselor nonverbal encouragements and higher counselor verbal dominance were both significantly related to a higher post-visit anxiety. In addition, counselor verbal dominance was associated with lower perceived needs fulfillment by the counselors. The authors concluded that *more effort could be devoted to involve counselors in the dialog and reduce the counselor's verbal contribution during the consultation*.

After the communication of a positive genetic test, interplaying with the family could be useful and women frequently ask for this. We identify six possible phases for this crucial relation (Table 19.1). The counselor should have a clear interview about this with the woman that first asked for consultation.

The items described in Table 19.1 could be under consideration before performing the test (items 1, 2, and 3) and after the test (items 4, 5, and 6). However, various conditions may influence the pathway: relatives living in distant cities/countries, lack of relevant information from relatives and time need to get it, and relatives who share this experience with the woman from the beginning (before taking the decision to do the test) or only in a late phase (when other relatives are already informed of the test result).

After the test, especially (but not only) if the result is positive, the counselor should pay

Table 19.1 Six phases of communication with the family of a woman who performs genetic testing

1. Investigate about how much the relatives know
• Are they aware that the woman will undergo a genetic test?
• Is the family aware of the potential risk of cancer?
2. Investigate about how much the relatives want to know on the topic
3. Investigate about how much each relative wants to know about her/his personal risk
4. If they, or at least some of them, want to be informed, explain the result of the test, using leaflets/illustrations for supporting the message
• Describe the risk of the woman to develop the disease
• Describe the risk of family members to have the mutation
• Describe the risk of family members to develop the disease
• Describe the possible role of other tests performed by other family members
5. Recognize sentiments
• Be able to understand reactions of relatives to the result of the genetic test
• Propose further help to relatives, when necessary
6. Planning and follow-up
• Give family members leaflets/books or other information supports
• Invite family members to contact a (local) genetic counselor

attention not only to deliver a correct information about the result of the test but also to a right understanding of the message. Emerging woman's distress and possible relationship difficulties between the woman and one or more relatives or between relatives deserve careful attention.

According to the *Health Belief Model* [16], the perception of a familial risk interplays with the individual sensitivity of a woman determining a large spectrum of possible events, as follows:

- Decision to adopt children to avoid inherited mutations that could cause cancer
- Emerging relationship difficulties with the partner related to feelings of responsibility or guilt
- Reemerging previous family dynamics among members sharing the same genetic tree

Emotional crises are also common, as those described by the following list:

- Fear of developing cancer (*The world came crashing down on me. In the evening, I take my sleeping pill so I don't have to think about it*)
- Tiring acceptance of diagnostic tests (*After witnessing numerous cases of cancer within my family, I became convinced and started this diagnostic pathway. I have to accept to take the exams, I want to live again*)
- Fear of transmitting, or having already transmitted, to children the mutation responsible for the disease (*I have a terrible sense of guilt. I cannot afford to become pregnant. Fortunately, I am not married, so I must not transmit anything to anyone*)
- Sense of responsibility toward the partner (*I do not want to sacrifice a man: he never would be a father. So, I broke off the engagement*)
- Difficulties in planning the future (*I'm terrified of the idea of death*)

When these conditions appear, a psychotherapist can play a useful role both for assisting the woman after the communication of the result of genetic testing and for increasing the woman's adherence to the surveillance program.

19.7 The Psychologist's Role

A psychologist can help in planning all the phases of relationship and communication, in drafting explanatory books on the concept of gene, probability, and risk. She/he can examine with the team particular cases and can help in training for specific interviews or listening techniques.

The *CLASS protocol* [17] provides suggestions for conducting the interview, as described in the following paragraphs.

C—Context. Pay attention to the physical context in which the interview takes place, excluding places such as the corridor and the rooms that are easy for other colleagues to pass through.

L—Listening. Listening and interviewing techniques.

- *Open questions*. Those to which the patient can answer in different ways and feel free to tell how she feels at that moment, not only from a medical point of view but also from a psychological and emotional one (*How do you feel today? Is there any other problem you want to talk about?*).
- *Methods for facilitation of listening*. To be silent when the patient speaks, always try to maintain eye contact. When the doctor has expressed a concept or given an information, take a break to give the patient time to reflect and eventually express doubts or questions. When the patient is talking, reinforcement interlayers are also important. They can be either verbal (underlining meaning sentences with an assent such as "Hmm… mm" or "Tell me more about this") or nonverbal (smiling). The repetition of the last sentence said by the woman or of a keyword of her speech or to rephrase the concept she expressed can be useful both to verify if she understood the message and to demonstrate that the team listened carefully to the woman's words. It is a poorly used technique but it is very effective, if applied correctly.
- *Questions for clarification*. It is important to check if you have understood correctly what the woman meant, especially in the case of ambiguous, confusing, or ambivalent information. You can use simple phrases such as "You are telling me that … Let's see if I understand correctly what you told me …."
- *Time and interruption management*. In the case of interruptions due to a colleague entering the practice or to a phone call, it is important to reiterate the woman's priority at that time and quickly manage the interruption by postponing the discussion with the colleague or the phone call. It is also necessary to pay attention to the interview time: it is not necessary to exhaust all the topics in a single meeting. After 45 minutes, it would be advisable to summarize what has been said and possibly postpone other discussions to another meeting.

A—Addressing emotions. During the interview, the recognition of emotions is the most effective way to make you perceived as close to the patient. The reference technique is the empathic answer and consists in identifying the emotion that the patient is expressing, identifying its causes, and demonstrating that you understand the link between emotion and cause (*I realize that what I just told you obviously shocked you a lot*).

S—Strategy. Planning of an intervention strategy after careful verification of the correctness of the information obtained by the woman and her awareness of the disease and prognosis. In fact, incorrect perceptions and beliefs can lead to misunderstandings that hinder communication and undermine the continuity of treatments.

S—Summary. A summary of what has been said and possibly decided during the interview. Scheduling the date for the next interview.

The SPIKES protocol [18] specifically addresses delivering bad news to cancer patients about their illness. The protocol consists of six steps:

S—Setting up the interview

- *Arrange for privacy*. Use an interview room or draw the curtains around the patient's bed.
- *Involve significant others*. The patient may ask for having some family member with her/him. If there are many family representatives, ask the patient to choose one or two of them.
- *Sit down*. It is a sign that you will not rush. Try not to have barriers between you and the patient. If you have recently examined the patient, allow her/him to dress before the interview.
- *Make connection with the patient*. Possible methods are eye contact, touching the patient on the arm, or holding a hand.
- *Manage time constraints and interruptions*. Inform the patient of any time constraints or expected interruptions. Set your mobile phone on silent.

P—Patient's perception. Implement the axiom "before you tell, ask." Use open-ended questions such as *What have you been told about*

your medical situation so far? or *What is your understanding of the reasons we did the CT or the MRI?* These questions also enable you to understand if the patient is engaging in any variation of illness denial [19]. Based on this information, you can correct misinformation and tailor the bad news to what the patient already knows.

I—Invitation from patient to give information. Verify that the patient wants to be informed and try to obtain her/his invitation using simple sentences like this: *How would you like me to give the information about the test results?* To know that the patient wants to be informed decreases the messenger's anxiety [20, 21]. In the case a patient does not want to know details, respect this view and offer to answer any questions she/he may have in the future or talk to a relative or friend.

K—Knowledge to the patient. Warning that bad news is coming may reduce the shock following the disclosure and facilitates the information processing. You may say *Unfortunately I've got some bad news to tell you* or *I'm sorry to tell you that ….*

- *Vocabulary*. Use nontechnical words that can be understood by the patient: *metastases* instead of *spread* and *biopsy* instead of *tissue sampling*.
- *Step by step*. Deliver information in small chunks and check periodically the patient's understanding.
- *Avoid excessive bluntness*. Don't say *You have very bad cancer* or *There is nothing more we can do for you*. In particular, the last sentence is inconsistent with important therapeutic goals such as good pain control and symptom relief [22].

E—Emotions and empathic responses. Patient's reactions may vary from silence to disbelief, crying, denial, or anger. An empathic response is a valid way to give support to the patient [23]. It consists of four steps [24], as described in the following sentences.

- *Observe for any signs of patient's emotion*. Examples are tearfulness, a look of sadness, silence, and shock.
- *Identify the emotion experienced by the patient*. If the patient appears sad but is silent, query the patient as to what she/he is thinking or feeling.
- *Identify the reason for the emotion*. It is usually connected to the bad news, but if you are not sure, ask the patient.
- *Let the patient know that you have connected the emotion with the reason for the emotion*.

S—Strategy and summary. To have a plan for future steps decreases the anxiety. So, to present available surveillance, diagnostic and treatment options and sharing responsibility for decision-making are relevant issues. It is important to check the patient's understanding of the discussion to prevent the patient's tendency to overestimate the efficacy or misunderstand the aims of treatment [25]. Finally, the interview can be closed, summarizing its content.

We remark that the basic axiom of the SPIKES protocol is "before you tell, ask." Many of the steps are similar to those of the CLASS protocol and many other.

The role to be played by the psychologist is to facilitate all these processes and steps. A different issue is the psychotherapist action, with two possible directions: treatment of the physician's psychic overexertion; distressing identification with patients, burnout; and treatment of individual patients or family groups asking for special support or judged to be at risk for not being able to handle anxiety and guilt or loneliness.

19.8 True Stories

We present here six stories we consider meaningful examples of the relation of patients and their family with the information about the presence of genes predisposing to cancer.

A woman who doesn't want to feel like a pain announcer. A woman who underwent mastectomy many years ago and was active in associations of BC patients and consumer movements described her relationship with genetics as follows:

> When I knew that one could find the gene before it causes the disease I thought: well, my dear daughters and grandchildren will not have my experience. So I asked for advice and made the sample for genetic testing. However, when I realized that there were no certainties on what to do next to avoid the disease, I was attacked by doubts about whether or not to involve my family. Finally, on a holiday, I counted around the table seven women from my family, all young. And I said to myself: what right do I have to be the messenger of this news by myself, I who have already brought them the anguish of my illness really. Do I want to repeat to them that through me they can anticipate their future pain? So, I got my testing results and I didn't tell them anything. If it happens that they tell me about it, or something changes, maybe I will change my mind. For now, that's how it is.

Over the years, this woman has consciously taken on many responsibilities for herself and for other women affected with BC. However, she lives the anticipation of risk as an aggressive practice, prompting the perception of the messenger as a bad person. If another woman in her family got sick, she could change her mind and talk about it to the others. However, after a well-informed counseling, she affirmed her right not to feel like an announcer of pain, a bearer of misfortune.

Family involvement. There has been a lot of cancer in the family, both in the breast and the bowel. The patient says:

> When my sister got sick, I had to take care of my little nephews and I preferred not to tell them that their mother would soon die, nor the teenage girl that her mother had the same disease as her grandmother. When my sister died, my nephews felt betrayed by me, they hated me and went away, even though they knew that I had wanted to protect them.

Over the years, this woman helps many family members in sickness, but only when she gets sick, genetic counseling was offered. In this context, she decides to inform various family members of the investigation she began and asks the psychotherapist for help in finding the best way to talk to her various nephews. She is involved in the emotional burden caused by the identification in many family members of various genes at risk, but the family finally overcomes the previous indifference and begins to talk about the past with more unity than in the future, increasing the awareness. The life of all family members is then restructured by the possibility of consciously sharing common information, taking away from our patient the responsibility and attitude of those who do everything by themselves, for themselves, and for others, which had created the previous imbalances.

Maternity. A 20-year-old girl comes in genetic counseling with her older cousin. Their family lives together after their mother and aunt died of BC. She has already announced by phone that she is pregnant. The technical time to get the test result consolidates her already strong decision to have an abortion anyway. The memory of the illness and the death of the mother is devastating. It is reinforced and echoed in the words of both cousins: *I don't want my cousin to suffer what made her mother die*. The young girl says: *My cousin is already so close to me, she also did me as a mother. I cannot let her be the grandmother of an orphan if I get sick*. The counseling, however, reassures the young girl by making it clear that, if she is not herself a mutation carrier, she can think of making a child in the future without this anxiety. This makes the ghosts less worrying and allows her to share a path of decision with people who do not belong to the family and do not enter the game of renewing the pain and fear of memory in the face of all choices.

An 18-year-old girl. She performed the test strongly piloted by her parents, especially her *BRCA1*-positive mother, who fell ill at the age of 25. The test result is positive. This surprises the girl but doesn't let her down. However, she returns repeatedly to the consulting service to discuss decisions already taken: initially she prefers bilateral prophylactic mastectomy and then surveillance with MRI. The repeated request for additional information and clarifications (also by telephone) is in fact requests for sharing the peaks of anxiety with the counseling team. Future choices are also often discussed: the girl claims to want children anyway. When she gets pregnant, there is a strong doubt that it is an acting out, i.e., putting her child's desire forward and realizing it before the age of 25, the age at

which her mother fell ill and her grandmother died, a symbol of misfortune and fear. She says:

> My mother was cured but she fell ill at the age of 25, exactly the age at which my grandmother died. I still have time, but my father has already sent my blood sample to England and they insist that I remove the breasts. I love my boyfriend. We're going to keep the baby.

Given the girl's age and the strong family pressures, she meets the psychotherapist. In this case, serenity is precarious, and anxiety shakes are frequent, both for personal reasons and because of parental influence. Confronting herself with others allows her to feel more free, to organize personal goals, even if different from the wishes of the parents. The same frequency of communication with the team indicates her desire to communicate her anxieties without being an expression of parental fears and decisions, but as an actor of her own future that she will certainly continue to manage with the same medical team.

Time and age. A young woman comes to counseling at the age of 19, shortly after she has reached the majority. The choice could have been made in disagreement with her family. The mother, who has been operated on several times for immunoresponsive tumors, has had serious postoperative consequences and still suffers a great deal. The rest of the family includes both mutation carriers and non-carriers, and she and her younger sister, after they were of age, were given the possibility of independent decision whether or not to perform the test. She decides to perform the test and results to be also a carrier. At first, she seems to react better than the relatives:

> I had the bilateral mastectomy abroad and my family was very close to me but more economically than emotionally. Actually, they do not accept that I still do not feel comfortable and almost do not listen to me.

After surgery and other health experiences, she begins to develop serious forced behaviors, of which we learn by phone from a psychiatrist who is now curing her. She is forced to repeat irrelevant but sedative gestures several times. These testify to a serious pathologic anxiety due to the flow of time, which she wants to deny. Finding herself to be a further cause of pain for the family and to face her own future have resulted in unforeseeably unbearable burdens. She will undergo both psychiatric and psychological therapy. In her case, it is confirmed how an objective result can transform an experience and weaken the subject's personality. The nonrational fact which has perhaps contributed to trigger forced anxiety could be the approach to the period after the operation in which the sister will also be of age.

A man, his wife, and children. A man comes to counseling: his wife is an orphan and sister of a BC patient. After her sister's surgery, she had a bad period of depression and low self-esteem. After the husband has accompanied them to the consultation, both sisters result to be mutation carriers. The wife asks the mutation search to be done also in the 6-year-old daughter: they want another child; they are against abortion and say:

> We are convinced that if the child is as healthy as our nephews, then the chain is broken and even one of our children will not be mutation carrier if the first one is not a carrier.

In this case, in a mystical and superstitious way, it is believed that if misfortune has been interrupted, it will be forever. Although they know and understand that the risk inheritance is individual, these parents say that if one thing went well once, it can go well for two. It will be necessary for them to understand that every decision concerns exclusively their responsibility and their current anxiety, the ability to let their children live with serenity as long as it is necessary for them to have an appropriate program of surveillance. Confidence in the development of science and medicine must be underlined within a relationship of trust that allows them to face the future without feeling orphaned by unborn children or constantly anticipating the worst situations.

A famous actress. This is the well-known story of Angelina Jolie, born in 1975, who became even more famous for her choice of risk-reducing bilateral mastectomy at 38 and salpingo-oophorectomy (removal of ovaries and fallopian tubes) at 39. She was a *BRCA1* mutation carrier as was her mother, who died

of BC in 2007. Also her grandmother and an aunt had died of cancer. She decided to share her decisions with the public opinion, and two letters were published in The New York Times in 2013 and 2015. The resonance of the story was relevant for women all over the world and also scientific societies and professional bodies.

In her second letter, published in 2015 [26], she explained the decision to undergo the second preventative intervention, i.e., risk-reducing oophorectomy. The result of CA-125 blood test was normal, but some inflammatory markers were elevated, a possible sign of early cancer that could be missed by the CA-125 test in 50–75% of cases. She wrote:

> I went to see the surgeon, who had treated my mother. I last saw her the day my mother passed away, and she teared up when she saw me: "You look just like her". I broke down. But we smiled at each other and agreed we were there to deal with any problem, so "let's get on with it".

As we said above, also physicians have emotions … She described the negative results of pelvic physical examination, ultrasound, and positron emission tomography, remembering that the radioactive tracer administered for the last examination meant she could not hug her children for a few days. However, she was aware that there was still a chance of early-stage ovarian cancer, but minor compared with a full-blown tumor. She still had the option of doing a salpingo-oophorectomy. This was her decision. Why? She wrote:

> I did not do this solely because I carry the *BRCA1* gene mutation, and I want other women to hear this. A positive *BRCA* test does not mean a leap to surgery. […] There are other options. Some women take birth control pills or rely on alternative medicines combined with frequent checks. There is more than one way to deal with any health issue. The most important thing is to learn about the options and choose what is right for you personally.

The family history of three women died of cancer in the presence of the *BRCA1* mutation was underlined by doctors who suggested to remove tubes and ovaries as the best option, to be performed *10 years prior* the earliest onset of cancer in my female relatives. The conclusion of her letter is the following:

> My mother's ovarian cancer was diagnosed when she was 49. I'm 39. Last week, I had the procedure: a laparoscopic bilateral salpingo-oophorectomy. There was a small benign tumor on one ovary, but no signs of cancer in any of the tissues. […] It is not possible to remove all risk, and the fact is I remain prone to cancer. I will look for natural ways to strengthen my immune system. I feel feminine, and grounded in the choices I am making for myself and my family. I know my children will never have to say, "Mom died of ovarian cancer".

We want to remark only the following points: she is famous, young, and beautiful, and the breasts are one of the attributes of her femininity; she adopted several children but also has a female daughter whom she procreated, so she chose to have children before making decisions that would determine her infertility; she decided to live by adhering to therapeutic programs that the mother could not resort to; she has all the characteristics of awareness and all the awareness of her power conditioning public opinion since her decision has been worldwide publicized, as mother-woman leaves her daughter a testimony of the need to at least anticipate the destiny.

An observational study of insurance claims data representative of the commercially insured US population [27] measured *BRCA* testing and risk-reducing bilateral mastectomy rates among females ≥18 years before and after the publication in 2013 of the first Jolie's article in The New York Times announcing her decision to undergo risk-reducing bilateral mastectomy. The authors found a highly significant increase in the uptake of genetic testing and in risk-reducing bilateral mastectomy among women without previous diagnosis of BC or OC in the US population and in women who did not undergo testing for *BRCA*.

An online search in the PubMed performed on August 18, 2019 for "Angelina Jolie" found 42 articles. One comment recently published in the *American Medical Association Journal of Ethics* [28] affirms: "… celebrity narratives influence patterns of care … media coverage of cancer can have unforeseen consequences on individual patients exposed to these kinds of stories. For this

reason, clinicians should become familiar with these narratives and comfortable with discussing how celebrity narratives can shape patients' views and decisions."

19.9 Conclusions

The application of psycho-oncology to women and families facing a high risk of breast cancer is a complex matter. Also from the six stories we presented, one may draw the conclusion that each case is an individual, peculiar story. This is certainly true. However, medicine, even when, also in oncology, it is proactive as described by the "P4" formula (predictive, personalized, preventive, participatory) [6], needs protocols and practice rules to be applied. We hope that the content of this chapter may help physicians in meeting, asking, listening to, speaking, and smiling to their patients. *The simple act to touch the arm of the patient during an interview can be more effective than words*. It's true that a fifth "P" should be added to the formula of P4 cancer medicine, that of "psycho-cognitive aspects to be considered in order to empower the patient" [29]. So, "P5 cancer medicine" could be practiced.

On April 8, 2020, Dr. Nadia Crotti Passed Away of an Unexpected Sudden Cardiac Death

She was born in Bergamo, Italy, on October 27, 1956. She graduated in Psychology at the University of Padua in 1979. PhD in medical psychology at the University of Marseille, France. Certified as psychologist and psychotherapist, since 1981 she worked at the Unit of Psychology at the National Institute for Cancer Research in Genoa, Italy, with a great dedication to patients, in particular breast cancer patients, and their relatives and particular interest for hereditary cancers. She attended internships at the units of Pedopsychiatrie (La Timone, Marseille), Oncohematology (Hospital St. Louis, Paris), Psychosomatic Medicine (Clinica Weiszacker, Buenos Aires), and at several departments at the Institut Gustave Roussy, Villejuif. She held courses in psycho-oncology at Master Courses in Senology and Oncology at the Universities of Siena and Genoa. She also significantly contributed to the birth and development of Europa Donna Italia. She authored many books and chapter books on different aspects of psycho-oncology, including the sensitive topic of communication and support to children with parents affected with cancer. During the nineties up to the first 2000s, she answered to letters from patients in the Italian journal *Attualità in Senologia*.

Many young psychologists moved their first steps under her guidance. The content of the chapter she accepted to write for this book is a demonstration of the high level of her expertise.

We asked those colleagues who have had the good fortune to meet her to add their name to the following list.

Ciao Nadia! Thanks for all you did for all the persons, colleagues, patients and relatives, and friends you helped with your words, your thoughts, and your fantastic smile.

Valentina Broglia, Franca Podo, Nadia Fiorenza Rizzolari, Francesco Sardanelli

Ilaria Aggero, Laura Berretta, Massimo Calabrese, Giuseppe Canavese, Valentina Clavarezza, Patrizia Curia, Silvia Di Leo, Elena Duglio, Luigi Cataliotti, Alberto Costa, Emanuele Crocetti, Federica Erca, Alessandra Feltrin, Alfonso Frigerio, Walter Renato Gioffré, Giorgia Gollo, Pierpaolo Lupo, Lorenza Marotti, Laura Martincich, Giuseppe Molinari, Marco Musso, Eugenio Paci, Federica Pediconi, Paola Ponton, Irene Profeti, Paolo Pronzato, Gianni Saguatti, Gloria Selva, Serena Roma, Marco Rosselli Del Turco, Virgilio Sacchini, Giovanni Zaninetta

References

1. Martinez KA, Resnicow K, Williams GC et al (2016) Does physician communication style impact patient report of decision quality for breast cancer treatment? Patient Educ Couns 99:1947–1954
2. Trinidad SB, Ludman EJ, Hopkins S et al (2015) Community dissemination and genetic research: moving beyond results reporting. Am J Med Genet A 167:1542–1550
3. Gil F (1996) Hereditary breast cancer risk: factors associated with the decision to undergo BRCA1 testing. Eur J Cancer Prev 5:488–490
4. Sun Y, Kang E, Baek H et al (2015) Participation of Korean families at high risk for hereditary breast and ovarian cancer in BRCA1/2 genetic testing. Jpn J Clin Oncol 45:527–532
5. Leblond D, Brédart A, Dolbeault S et al (2011) Cognitive, emotional and behavioral impact of an uncertain outcome after study of BRCA1/2: review of the literature. Bull Cancer 98:184–198
6. Hood L, Friend SH (2011) Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol 8:184–187
7. Cypowyj C, Eisinger F, Morin M et al (2003) Information-seeking behavior and psycho-social interactions during the genetic testing process. Community Genet 6:224–234
8. Godino L, Razzaboni E, Bianconi M, Turchetti D (2016) Impact of genetic counseling in women with a family history of breast cancer in Italy. J Genet Counsel 25:405–441
9. Crotti N (2004) Psicologia, comunicazione e gestione del paziente. Quaderni di Oncologia. ArgOn, Medical Communications
10. Samama D, Hasson-Ohayon I, Perry S, Morag O, Goldzweig G (2014) Preliminary report of the relationship between experience of death of a relative, illness perception, and psychological outcome among BRCA carriers. Psychol Health Med 19:698–704
11. Crotti N, Oppenheim D (1996) Personal freedom and genetic overdetermination. Tumori 82:143–146
12. Mendes A, Chiquelho R, Santos TA, Sousa L (2010) Family matters: examining a multi-family group intervention for women with BRCA mutations in the scope of genetic counselling. J Community Genet 1:161–168
13. Crotti N, Broglia V (2007) Genetica e Oncologia, Quaderni di Oncologia: Implicazioni relazionali e di gestione del paziente. ArgOn, Medical Communications
14. Brédart A, Autier P, Audisio RA (1998) Geragthy J. Psycho-social aspects of breast cancer susceptibility testing: a literature review Eur J Cancer 7:174–180
15. Dijkstra H, Albada A, Klöckner Cronauer C, Ausems MG, van Dulmen S (2013) Nonverbal communication and conversational contribution in breast cancer genetic counseling: are counselors' nonverbal communication and conversational contribution associated with counselees' satisfaction, needs fulfillment and state anxiety in breast cancer genetic counseling? Patient Educ Couns 93:216–223
16. Janz NK, Becker MH (1984) The health belief model: a decade later. Health Educ Q 11:1–47
17. Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R (1999) Strategic physician communication and oncology clinical trials. J Clin Oncol 17:3324–3332
18. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP (2000) SPIKES–a six-step protocol for delivering bad news: application to the patient with cancer. Oncologist 5:302–311
19. Lubinsky MS (1999) Bearing bad news: dealing with the mimics of denial. Genet Couns 3:5–12
20. Conlee MC, Tesser A (1973) The effects of recipient desire to hear on news transmission. Sociometry 36:588–599
21. Gattellari M, Butow PN, Tattersall MH et al (1999) Misunderstanding in cancer patients: why shoot the messenger. Ann Oncol 10:39–46
22. Miller SM (1995) Monitoring versus blunting styles of coping with cancer influence the information patients want and need about their disease. Implications for cancer screening and management. Cancer 76:167–177
23. Suchman AL (1997) A model of empathic communication in the medical interview. JAMA 277: 678–682
24. Ptacek JT, Eberhardt TL (1996) Breaking bad news. A review of the literature JAMA 276:496–502
25. Quirt CF, McKillop WJ, Ginsberg AD et al (1997) Do doctors know when their patients don't? A survey of doctor-patient communication in lung cancer. Lung Cancer 18:1–20
26. Angelina Jolie Pitt (2015) Diary of a surgery. The New York Times, 24 March 2015. https://www.nytimes.com/2015/03/24/opinion/angelina-jolie-pitt-diary-of-a-surgery.html. Accessed 30 Jun 2020
27. Liede A, Cai M, Crouter TF, Niepel D, Callaghan F, Evans DG (2018) Risk-reducing mastectomy rates in the US: a closer examination of the Angelina Jolie effect. Breast Cancer Res Treat 171:435–442
28. Yerramilli D, Charrow A, Caplan A (2018) How should clinicians respond when patients are influenced by celebrities' cancer stories? AMA J Ethics 20:E1075–E1081
29. Pravettoni G, Gorini A (2011) A P5 cancer medicine approach: why personalized medicine cannot ignore psychology. J Eval Clin Pract 17:594–596

20 Calculating, Using and Improving Individual Breast Cancer Risk Estimates

Adam R. Brentnall and Stephen W. Duffy

Abbreviations

AIs	Aromatase inhibitors
AUC	Area under the curve
BC	Breast cancer
BCSC	Breast Cancer Surveillance Consortium
BI-RADS	Breast Imaging Reporting and Data System
BMI	Body mass index
BPE	Background parenchymal enhancement
ER	Oestrogen receptor
HER2	Human epidermal growth factor receptor 2
MRI	Magnetic resonance imaging
ROC	Receiver operating characteristic
SERMs	Selective oestrogen receptor modulators
SNP	Single nucleotide polymorphism

20.1 Introduction

Over the past few decades, there has been increasing interest in individual risk assessment for breast cancer (BC) [1–4]. Motivations for this include the identification of individuals at extremely high risk who would be potential candidates for prophylactic surgery or preventive therapy [5]; delineation of populations at moderately enhanced risk who might benefit from enhanced surveillance [6]; and, more recently, identification of populations at sufficiently low risk as not to require surveillance or risk management [7]. Risk-adapted BC screening strategies, including periodical breast magnetic resonance imaging (MRI), have to be placed in this general context.

Breast cancer has a relatively well-established hormonal aetiology, in addition to a growing body of knowledge on genetic risk factors [8–10]. However, development of prevention protocols has been a slow process, and there remain issues of determining appropriate populations to target with specific surveillance or other risk management measures. There are two major issues with which the breast cancer epidemiology and prevention communities have to contend. The first is the fact that *for many BC risk factors, there is a low attributable fraction, due either to modest effects on risk or low risk factor prevalence* [8]. The second is that *while there are identified biological classifications*

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of BCs, such as oestrogen receptor (ER) status, basal/non-basal type and human epidermal growth factor receptor 2 (HER2) expression level, which can categorize the disease by life-threatening potential, *we have few known risk factor profiles for the different categories* [8]. In particular, we have no individual risk models that are calibrated to assess the risk of aggressive ER-negative BCs.

Existing risk models have shown a degree of accuracy in prediction, at least within populations already identified as at enhanced risk, such as women with a family BC history [11, 12]. It is clear that there is room for improvement [12]. In this chapter, we consider how risk models are calculated, their potential clinical use and the targets for research in the future to improve these models, so that they can better inform risk management and surveillance.

20.2 Components and Calculation of Risk Estimates

Here we consider the main approaches used to calculate individual BC risk and the factors included as contributors to risk prediction. We illustrate these with some of the more widely used risk models. We do not here present an exhaustive review of all available risk models. For a comprehensive review, see Jessica A. Cintolo-Gonzalez and coworkers [12].

Broadly speaking, risk models fall into three categories, as described below.

Type 1. Estimation from pedigree data of the probability of carrying one or more high-risk mutations, using segregation analysis,[1] a genetic epidemiology technique based on reversing conditional probabilities of phenotype given *BRCA1/2* and/or other mutations to obtain probabilities of mutations given phenotype. The probability of disease can then be calculated from the probability of mutation status. Examples of this include the Claus, BRCAPRO and BOADICEA models [2, 4, 13].

Type 2. A regression model for cancer risk based on a number of risk factors. The risk is frequently calculated by a combination of the predicted regression model from large analytic studies (such as estimated using logistic or Cox regression) with absolute incidence rates from national cancer registry data. The most prominent example of this is the Gail model [1], and further developments based on this approach [14–17].

Type 3. Combination of types 1 and 2 models. The paradigm for this approach is the Tyrer-Cuzick model [3].

As regards familial and genetic contribution to risk, several points should be borne in mind. Approaches of type 2 models above do include family history. However, this is included as a regression predictor, with no formal genetic model and no attempt to estimate mutation status probabilities. Secondly, approaches of types 1 and 3 usually also include in the pedigrees family history of ovarian cancer as well as BC, as the high-risk *BRCA1* and *BRCA2* mutations predispose to ovarian cancer as well as BC. It is also worth noting that age of the proband and age at diagnosis of the affected relatives are crucial ingredients to the calculation of probabilities of mutation status and therefore of BC risk in the segregation analysis approaches.

Table 20.1 shows the approaches to risk estimation and the factors included as predictors for some of the most commonly used models. Arguably the most comprehensive model is the Tyrer-Cuzick model which incorporates mammographic density and allows the user to include a relative risk calculated from single nucleotide polymorphism (SNP) risk scores [20–23]. The latter reflects the fact that there is no standard polygenic risk score, and the SNPs employed might vary from user to user.

In the following sections, we explore the uses and reliability of BC risk prediction tools.

[1] *Segregation analysis.* The process of fitting formal genetic models to data on expressed disease characteristics (phenotype) in biological family members in order to determine the most likely mode of inheritance for the trait or disease under study (https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/segregation-analysis).

Table 20.1 Methods and components of some commonly used individual risk prediction tools for breast cancer

Broad approach	Model	Factors included
Type 1: segregation analysis	Claus [2]	Age, first- and second-degree female relatives with breast cancer, ages at onset
	BOADICEA [4]	Age; first-, second- and third-degree female relatives with breast cancer, relatives with ovarian cancer and male relatives with breast cancer; ages at onset
	BRCAPRO [13]	Age; first- and second-degree female relatives with breast cancer, relatives with ovarian cancer and male relatives with breast cancer; ages at onset
Type 2: regression modelling	Gail [1]	Age, age at menarche, age at first birth, previous breast biopsies, history of atypical ductal hyperplasia, first-degree relatives with breast cancer
	Gail with polygenic risk added [16]	Gail model plus risk from 7 SNPs
	Gail with breast density added [14]	Gail model plus mammographic density visually assessed in five categories: 0, 1–24, 25–49, 50–74 and 75–100%
	Breast Cancer Surveillance Consortium (BCSC) model [18]	Age, whether affected first-degree relatives (yes/no), benign breast disease, ethnicity, mammographic density (BI-RADS categories)
	BCSC model with SNPs added [19]	BCSC model plus risk from 76 SNPs
	iCARE [17]	Age, age at menarche, age at menopause, age at first birth, alcohol consumption, height, body mass index, hormone therapy, family history of breast cancer, smoking
Type 3: combination of types 1 and 2	Tyrer-Cuzick [3]	Age; first-, second- and some third-degree female relatives with breast cancer, relatives with ovarian cancer and male relatives with breast cancer; ages at onset; whether subject is from Ashkenazi population; genetic testing in family; age at menarche; age at first birth; age at menopause; height; weight; hormone replacement therapy use; history of benign breast disease; previous lobular carcinoma in situ
	Tyrer-Cuzick with density and polygenic risk added [20–23]	Tyrer-Cuzick model plus breast density (either visual percent density, BI-RADS categories or Volpara volumetric percent density), plus relative risk calculated from polygenic status

Numbers in square brackets indicate references
BI-RADS Breast Imaging Reporting and Data System, *SNPs* single nucleotide polymorphisms

20.3 Use of Individual Risk Estimates in Clinical Practice

Perhaps the most important use of risk assessment to date has been to identify women for high-risk family history or genetic clinics. In this section, we first consider how risk assessment has been applied to guide interventions used in high-risk clinics and then how routine risk assessment could improve the effectiveness of genetic clinics, by triaging women at a younger age and through risk-adapted screening.

20.3.1 Eligibility for Genetic Testing and Models Incorporating Genetic Testing

Some risk models may be used to determine a woman's eligibility for *BRCA1/2* mutation testing. Carriers are highly likely to develop BC (penetrance approximately 7 in 10 invasive or ductal carcinoma in situ by age 80 years), but the genes only account for a small proportion of BCs in the population because they are not common (approximately 3 per 1,000 women are carri-

ers in the United Kingdom) [24]. Eligibility for *BRCA1/2* testing is currently usually assessed based on risk of being a *BRCA1/2* mutation carrier, such as determined by the BOADICEA model [4, 25]. Clinical thresholds for testing have changed, and there is evidence to support widening them further because the cost of genetic testing continues to decrease [26].

The search for other BC risk genes has identified a handful of other rare gene mutations that confer between two- and fourfold risks relative to the population, including *CHEK2*, *ATM* and *PALB2* [5]. These genes account for a tiny proportion of the disease in the population. Although the introduction of *BRCA1/2* testing has primed the area to the importance of genetic testing, it is important to note that risk assessment for women who test positive for these genes should also incorporate other risk factors, including family history [27], because they might substantially modify a woman's risk.

20.3.2 Supplemental Screening Eligibility

Mammographic screening has been demonstrated to reduce BC mortality, but with the strongest effect in older postmenopausal women [28]. This is partly because the sensitivity of mammography is related to mammographic density, as described in more detail elsewhere in this book. A woman's breast density declines with age, and it is very common for young, premenopausal women who are with a healthy weight to have dense breasts. Unfortunately, proportionally more cancers diagnosed in younger women have a worse prognosis (such as ER-negative or triple-negative cancer [29]) than at older ages, so that the sensitivity of a screening test is arguably more important in younger women; one would not consider screening them if all the lethal cancers were missed.

Higher-stage interval cancers are also an issue for older women with non-dense breasts; the strong effect of age on the rate of BC means that the risk of a lethal interval cancer may actually be higher for older women than younger women. To improve the sensitivity of screening, many centres around the world offer alternative or additional screening to mammography, including ultrasound or MRI.

For *BRCA1*/2 mutation carriers, MRI is generally recommended annually from age 25 to 30 years (see summary Table 2 in [5]), alone or in combination with mammography and ultrasound depending on the setting. In the United Kingdom, MRI is also recommended for women younger than 50 who are classified as non-carriers because they have not been tested for gene mutations, but are likely to be a *BRCA1/2* mutation carrier (greater than 30% risk) or similarly likely to be a *TP53* carrier [30]. The American Cancer Society criteria for non-carriers are much wider and include that women with a lifetime risk of more than 20% should be offered supplemental MRI screening [31], where the risk assessment is primarily based on family history.

Thresholds for supplemental screening by MRI in the United States and United Kingdom are based on different endpoints. A decision threshold based on the probability of being a gene carrier will be conservative, and many women who could benefit from supplemental screening because they are at risk of the disease due to other factors will not be included. A decision threshold for supplemental screening based on lifetime risk is more equitable, but it also has limitations including that lifetime risk is greater for younger women than older women, but they might be at quite a low absolute risk over the next few years. It is arguable that *a shorter time horizon and different endpoint might be more appropriate than those in current guidelines, such as a 5-year risk of interval cancer based on mammography screening alone*. The reason is that this is closer to the purpose of supplemental MRI screening, which is to avoid a screening failure. Additionally, one would also ideally take into account the chance of a more lethal cancer. We will come back to this in the next section on risk model improvements.

In summary, decision rules based on some form of risk assessment and threshold are used in current guidelines for supplemental screening eligibility, including for breast MRI. *While the thresholds, models and endpoint might change*

with new evidence, decision rules based on risk and thresholds to determine eligibility for supplemental screening are likely to remain.

20.3.3 Preventive Surgery and Therapy Eligibility

Preventive surgery is generally only recommended for a small proportion of women who are at high risk because they are part of a high-risk family, while preventive therapy might be appropriate for a larger number of women. In the United Kingdom, a 10-year risk of approximately 8% or more is the recommended boundary for preventive therapy, and approximately 1% of the screening population fall into this category using classical risk factors [20, 30].

Preventive surgery for BC includes *risk-reducing (prophylactic) mastectomy* and, for *BRCA1/2* mutation carriers, also *risk-reducing (prophylactic) oophorectomy* due to the simultaneous increased risk in ovarian cancer. These are life-changing events, and accurate risk assessment is vital, in order that an informed decision can be made weighing up the potential harms and benefits of the procedures. It has been shown that the family history of disease in *BRCA1/2* mutation carriers helps to refine risk beyond the average lifetime risk of 7 in 10 [24].

Two preventive therapy agents have shown efficacy for the prevention of ER-positive BC. The first are called *selective ER modulators* (SERMs) and include tamoxifen, raloxifene and others [32]. The second are called *aromatase inhibitors* (AIs) and are generally only suitable for postmenopausal women, but they appear to confer greater reductions in the risk of BC [33]. Tamoxifen and anastrozole are off patent and are cost-effective means to prevent BC in women at high risk that are included in health guidelines in the United Kingdom [30]. Recent advances in risk assessment, where polygenic SNP scores and mammographic density are combined with classical factors, are likely to substantially increase the number of women in the population who would meet thresholds for the recommendation of these therapies. However, *the acceptability of the treatments due to serious adverse events, perceived and real side effects, lack of knowledge and logistical difficulties appears to have limited their uptake and adherence for preventive use* [31, 34].

To date, the most likely women to have been offered preventive therapy are those attending genetic clinics. Evidence from the trials suggests that women with high-risk histotypes of benign disease such as atypical hyperplasia or lobular carcinoma in situ may obtain the greatest reductions in risk from preventive therapy agents [35]. Thus, *risk assessment based on benign disease characteristics appears to be particularly important for preventive therapy assessments*. Three models incorporate the pathology of benign disease, the Benign Breast Disease to Breast Cancer (BBD-BC), Breast Cancer Surveillance Consortium (BCSC), and Tyrer-Cuzick models [3, 18, 36].

20.3.4 Population Risk-Adapted Screening Strategies

In a sense, there is nothing new in research proposals for risk-adapted BC screening in the general population, since population screening programmes are based on two of the strongest risk factors for BC: age and gender. Women between a younger age (usually at least 40 years) and an older age (sometimes up to 75 years) are screened every 1, 2 or 3 years depending on the setting [37]. Screening programmes do not generally screen women younger than 40 because their average risk is very low and the sensitivity and specificity of mammography as a screening test does not warrant it: there is evidence that mammography screening for younger premenopausal women confers less mortality benefit than for postmenopausal women. The programmes do not screen women above a certain age because, although they are at a higher BC risk, other diseases have a strong force for mortality so that mortality benefits from screening are less and felt to be outweighed by potential harms. These arguments may be extended to strategies based on risk assessment using additional factors to age.

Routine risk assessment and risk-adapted screening are not commonly undertaken in the general population but have been applied in some settings. In particular, Kaiser Permanente Washington (formerly Group Health Cooperative) has had some form of risk-adapted screening strategy in place for several decades [38]. In 1990 their programme was designed so that a woman was put into one of four screening strategies depending on her age and risk (annual, biannual, triannual or no screening). Routine risk assessment is becoming more common in other centres in the United States partly driven by radiology reporting systems that may automatically run a BC risk assessment, which is then available for the radiologist.

There has been less scope for general risk assessment in population screening programmes, and so some studies have been set up in Europe to assess the feasibility and acceptability of risk assessment in large general population cohorts as well as how it might practically be implemented. In the United Kingdom, the *Predicting Risk of Cancer at Screening* (PROCAS) study recruited from 2009 to 2014; all women completed a risk questionnaire, some donated saliva, and risk feedback was assessed [39]. A similar study in Sweden (KARMA) has finished recruitment [40], and another study is currently recruiting in the Netherlands (PRISMA) [41].

Overall, the evidence appears to support the acceptability of risk assessment for many women, but there are still important questions surrounding risk feedback, including potential harms related to informing healthy women of their risk, and these need further investigation.

20.3.5 Evidence to Support Risk-Based Management

Risk-based screening and prevention is quite a broad topic, and studies to date that provide some evidence on the efficacy of risk-based management have tended to focus on more narrow, well-defined questions. These include a study of annual mammography in women aged 40–49 years who were at an increased risk due to their family history, which showed reduced BC mortality from annual screening [6]. Studies have also generally shown supplemental screening based on MRI and ultrasound to improve the sensitivity of the screening test [42, 43]. As screening with a less sensitive test (mammography) confers BC mortality reductions, supplemental screening is also likely to further improve long-term outcomes for women. But, the increased sensitivity is often offset by decreased specificity and potential overdiagnosis, so it is not a straightforward decision to recommend supplemental screening.

Screening intervals vary between countries, but nowhere has a screening with a longer interval than 3 years been reported [37]. The trials and observational data to evaluate screening performance based on individual screening histories support screening intervals up to 3 years in postmenopausal women, but more regular and more intensive screening in younger women appears needed in order to substantially reduce their mortality and make the test worthwhile. There is very little evidence to support longer screening intervals, and so new trials and studies are needed. For example, shorter screening intervals are expected to reduce mortality (those cancers detected at their screen will be diagnosed earlier than with longer intervals). But it is not clear whether enough women would be diagnosed early enough to reduce mortality to make it effective. There are also questions as to what constitutes a low-risk group. Women are at a much lower risk for cervical cancer than BC, and yet public health strategies are clear that it is worthwhile to screen for cervical cancer. In other words, *the decision to screen or not to screen women should not be solely based on relatively low absolute risks of the disease but also on deaths prevented and other outcomes*.

Some studies are underway or starting that will help to assess risk-based screening. One is the UK age extension trial (ClinicalTrials.gov Identifier: NCT01081288), which will assess the benefits of screening earlier (age 47–49 years) compared with later (70–73 years of age), and the data will indirectly help to inform on the value of additional screening in higher-risk

groups with a higher competing mortality than in lower-risk groups with a lower competing mortality. One trial into the use of supplemental screening for women with dense breasts is being run in the Netherlands (DENSE trial, Breast Cancer Screening with MRI in Women Aged 50–75 Years with Extremely Dense Breast Tissue, ClinicalTrials.gov Identifier: NCT01315015) [44]. Two trials will assess changing the screening interval. These are also the WISDOM trial (Women Informed to Screen Depending on Measures of Risk; ClinicalTrials.gov Identifier: NCT02620852) in the United States, which will compare annual screening with a risk-based BC screening schedule [45], and a European trial that is due to start in 2019 [46].

In summary, there is some evidence to support risk-based management, particularly for increased surveillance of those at higher risk. However, randomized trial evidence is quite limited, and so efforts are ongoing to help fill this gap. *There is also much less evidence to assess the value of reduced surveillance in women at a lower risk of the disease, and a greater understanding of the impact of reduced surveillance appears warranted before the offer of regular screening may be withdrawn from some women in screening programmes.*

20.4 Improvements to Risk Models

Many different risk models have been developed [12]. While this is understandable from a research perspective, from a clinical perspective, it is confusing. For example, if guidelines state that a lifetime risk of 20% is needed for supplemental MRI screening and two 'validated' models assess the risk to be, respectively, 17% and 22%, then what is to be done? Which model is more accurate?

One reason why risk models differ is that they have been developed for different populations. For example, a model such as the Gail model is best suited to the general population and potentially triage to a high-risk genetic clinic [1]. As noted by the developers, it is not at all suited to the assessment of risk in the genetic clinic, because the family history information used is just the number of affected first-degree relatives (mother, sisters, daughters), it doesn't take account of *BRCA1/2* testing and so on. Specialized models based on more extensive family history data are needed.

Another reason why risk models differ is that they use different risk factors. For example, the BCSC model uses some of the same risk factors as the Gail model but also incorporates mammographic density, which is a risk factor with a high population-attributable risk that can substantially alter a woman's risk assessment [15].

A final reason that we consider here is that *the models may have different assumptions on the effect of risk factors*. For example, the Tyrer-Cuzick model is calibrated to BC rates in the United Kingdom and the Gail model to rates in the United States [1, 3]. While these are broadly comparable, they are not identical, so that differences of a few percentage points in terms of absolute risk would be expected depending on the age of a woman.

Risk factors used by some models that are freely available are shown in Table 20.1, and there is a large literature to support them. Theoretically a risk model that combines these factors correctly will provide the greatest accuracy, but a counterbalance is that if not combined correctly, such as having different associated risks for a certain subgroup, a model that combines more of them may provide worse accuracy than another model with just a few of the major risk factors. Validation of risk models in different settings is very important.

The aim of this part of the chapter is to consider how the accuracy of risk models may be assessed and how it might be improved. We also discuss whether new risk models for endpoints other than invasive BC might play a role in risk-adapted screening and prevention strategies.

20.4.1 Validation of Risk Models

It is important to assess whether a risk model is fit for purpose by validating it in external cohorts, i.e. different from those that might have been

used to develop the model. We next discuss some methods used to validate risk models.

A common method is to compare measures of the calibration of absolute risks [47] on criteria for evaluating models, where absolute risk refers to the 'crude' risk after accounting for competing causes of death. For example, suppose a 5-year risk assessment is made for each woman and all women are followed up to 5 years after baseline, so that all BCs that occur within 5 years are known. Then the sum of the predicted risks will provide the expected number of BCs and may be compared with the observed number over the period. Under mild assumptions, the observed number will follow a Poisson distribution, from which a test or confidence interval of the observed to expected ratio may be derived. This is a test of overall calibration, but a model may be well calibrated by the method overall but not in individual risk groups. In this case, the model would be useless for risk-adapted screening strategies based on thresholds and groups of different women, so *it is vital to assess the calibration of a risk model in risk subgroups*.

Validation of absolute risks is important for model validation, but it is difficult in screening settings. The model's absolute risks might be perfectly valid in the wider cohort of women in the population, but they show lack of calibration due to *selection bias*: *the sample cohort does not reflect the wider population*. One reason is that most risk models are calibrated to fit to BC rates in the population, not just those who attend screening. Many of the cohorts available to assess risk will be women attending screening or at least contain more women who attend screening or are willing to participate in scientific studies than the wider population. Thus, overall, one might expect observed rates to be higher than predicted by the risk models: *the women in the cohort have earlier BC detection than the general population*. On the other hand, one often assesses the BC risk in a group of women without BC. If a screening test has been applied at baseline, then the analytic approach of removing cancers detected initially makes the predicted incidence lower than that observed in the population due to the removal of a pool of cancers and the time taken for new cancers to develop (although one might argue that the risk models should take this into account by using information on when the last screen was performed).

Partly due to these and other difficulties in assessing absolute risk, we feel that it is important to also consider the calibration of a model's relative risks. An assessment of the relative risks, after accounting for potentially different background age rates between the model and sample, is particularly informative. A common phenomenon for statistical models is that the highest risk will be a lower risk than anticipated and the lowest risk will be a higher risk than anticipated. The extent of this regression to the mean or shrinkage may be estimated using a regression coefficient, which is an informative performance summary measure for the overall calibration of relative risks [20].

Calibration of relative and absolute risks is important, but it is possible to have a perfectly calibrated model by using the overall risk for everyone. *It is also important for a risk model to have good discrimination.* From a modelling perspective, one might prefer discrimination to calibration, because if the calibration is wrong, then it can usually be fixed. A statistical measure of model discrimination that has often been used is the *concordance index*,[2] which for a binary outcome is also the *area under the curve (AUC) from a receiver operating characteristic* (ROC) *analysis*. However, it is rarely a good idea to focus solely on the concordance index to assess model discrimination [47–49]. A major limitation is that it does not really reflect the clinical utility of a risk model. For example, risk assessment using mammographic density in addition to classical risk factors has been noted to provide very small incremental increases in the concordance index, yet this neglects one intended use of risk models: to identify women at a high risk of BC. *Combining breast density with classical*

[2]The C-statistic (sometimes called the 'concordance' statistic or C-index) for a binary outcome, such as disease or not, gives the probability a randomly selected patient with disease will have a higher risk score than a patient without disease. For a survival outcome, such as time to death, it gives the probability that the person with the higher risk score will live longer [48].

risk factors has been seen to approximately double the number of women in a general screening population at high risk [20], for whom preventive therapy may have the greatest impact on absolute risk reductions. Clearly mammographic density is very informative for this aim, but the increase in concordance index shown is quite small and does not reflect its importance.

In conclusion, many models have been developed, but few have been thoroughly validated, and there is very little direct comparison of the models in (the same) large cohort studies [12]. More research effort in these areas will be valuable.

20.4.2 Risk Factors

In this section, we review how risk assessment might be improved by incorporating more risk factors or refining those currently used.

20.4.2.1 Lifestyle Factors

Figure 20.1 shows a comparison of age-adjusted invasive BC incidence rates in the United Kingdom and Japan. It illustrates a substantial difference in rates for women aged 50–64 years, who are mostly postmenopausal. Further, rates of postmenopausal BC in Japanese women who migrate to western countries tend to converge to the high western rates within a few generations [50, 51] and residual differences when residents in the country are largely explained by the classical 'known' risk factors [52, 53]. It is therefore often posited that environmental factors explain the difference in postmenopausal BC risks by geographical region, including lifestyle factors.

Figure 20.2a compares the obesity rates for women aged 50–64 years in the United Kingdom and Japan, where clearly there are large differences. Figure 20.2b considers a hypothetical age-standardized rate of invasive BC in the United Kingdom over the period, if there was no overweight or obesity, and all women were of a healthy weight. The calculation plugged in the estimated effect of body mass index (BMI) on postmenopausal BC rates (risk increased by 40% for every ten unit increase in BMI [54]) with estimates of overweight and obesity prevalence in women aged 50–64 years over the same period

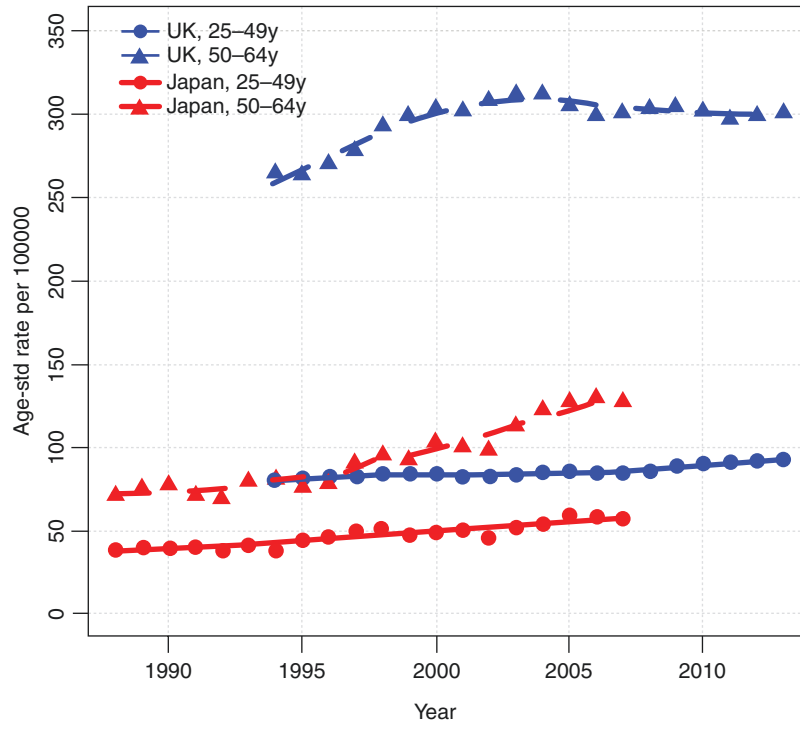

Fig. 20.1 Age-standardized rates of invasive BC in the United Kingdom and Japan, by age group. Data source: United Kingdom, Cancer Research UK (https://www.icr.ac.uk/, accessed September 2020); Japan, IARC (ci5.iarc.fr, accessed September 2020)

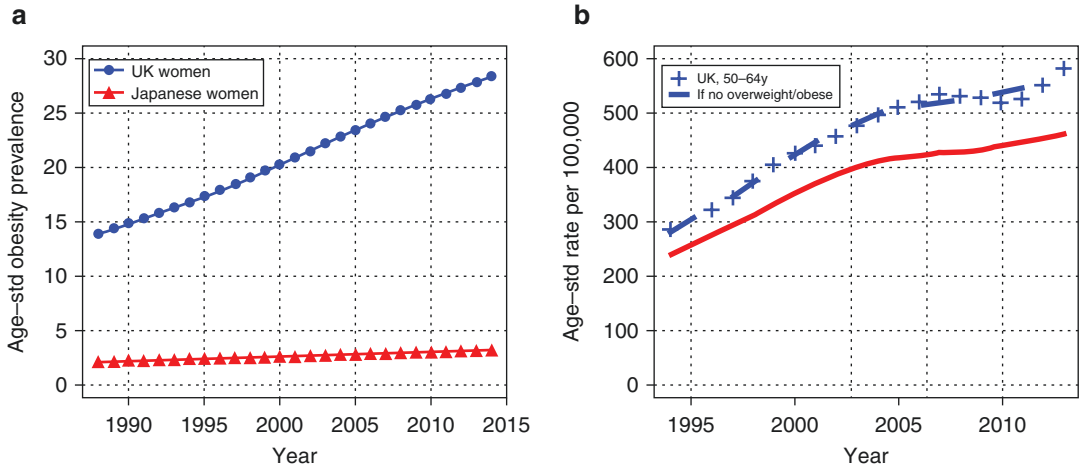

Fig. 20.2 Obesity (**a**) and (**b**) age-standardized rates of invasive BC of women aged 50–64 years in the United Kingdom

(based on Health Survey for England 2015, http://digital.nhs.uk/hse2015trend). It highlights that some of the recent trend towards increased risk for BC is explained by the trends in obesity [55], but not all. Additionally, obesity (at least as measured through BMI) does not explain most of the difference in postmenopausal BC rates between the United Kingdom and Japan, and, although not shown, differences in other moderate risk factors such as height, alcohol and age at first child do not explain the remainder.

This raises two issues. Firstly, there is a question as to whether current risk models are suitable for everyone in the diverse populations that make up screening populations such as in the United Kingdom. Research has arguably been skewed towards risk assessment in white Caucasian populations, and it is not clear whether current models are applicable for, say, migrants from a country with low incidence. More research is needed to assess this issue. Secondly, it is plausible that there is scope to identify better risk factors and measures of differences in lifestyle than done to date. For example, adult weight gain has been associated with BC risk in a number of studies and also with other cancers and disease [56]. Weight gain is associated with BMI because those who have gained the most weight also tend to be obese, so ongoing work is seeking to assess if and how it provides additional information to attained weight.

20.4.3 Genetic Factors

Collaborative research has identified many genetic alterations that are associated with BC risk [19, 57]. Individually these common SNPs have small effects on risk of BC, but when they are combined into a polygenic risk score in combination with other risk factors, they may substantially improve risk stratification [58]. New discoveries are regularly being validated and published [59], and it is likely that the discoveries will continue with statistical methods to develop the most informative polygenic risk scores helping to further improve predictability. To date, it has been estimated that almost half of the genetic variation and clustering due to familial risk may be explained by known genetic factors [27]. However, it is also perhaps likely that the incremental benefits for overall breast cancer from now will be small, but with larger gains in the modelling of disease subtypes, including ER-negative breast cancer. There is a question as to whether and how much the environment might interact with genetic factors, but it appears that

gene-environment interactions with currently known genetic and environmental risk factors are very weak, if present at all [60].

20.4.3.1 Imaging Features

A large literature has developed around mammographic density [61]. In some sense, this confers a level of information similar to that provided by the current SNPs and questionnaire factors beyond age, and it can substantially help to identify high- and lower-risk women [20]. Methods to measure density reliably, accurately and with the strongest risk association is still an ongoing area of research. In addition, many states in the United States now mandate that density is reported by radiologists following a negative screening result; women with dense breasts might consider supplemental screening. Partly for this reason, there is also some ongoing research into methods to measure the masking risk associated with mammographic density.

Mammographic density is the ratio between glandular and fibrous tissue and glandular stroma, but surprisingly little is known about the biological basis through which it confers risk [62]. For example, tamoxifen is well established to reduce mammographic density, but it is not clear what happens at a cellular level when this occurs. It is also perhaps surprising that despite decades of research into measures of mammographic density, very few measures appear superior for risk assessment than a crude BI-RADS categorization that in a general screening population puts the majority of women into two of four categories. There is substantial inter- and intra-reader variation in subjective density assessment, so that the true risk underlying it is likely to be much higher than reported due to attenuation from measurement error.

One area of research that has tried to improve automated density assessment has examined whether other features of a mammogram than just the amount of whiteness are associated with BC risk. The original idea of Wolfe was to use a categorical description that included density in the sense of whiteness but also whether there were prominent ducts or dysplasia [63]. Although percentage density has superseded this description and appears to have a stronger association with risk [64], there is a persistent feeling from experts that there should be additional information in texture to be extracted from mammograms. Despite this, the quantity of research into the area is quite limited. A review paper found just 17 papers that considered textural features for risk, and there was very little consistency between the findings [65]. A key challenge of using textural features of a mammogram is to identify true features rather than statistical artefacts, perhaps due to the study design, and much more remains to be done [66].

Machine learning methods are currently a hot topic, and there are moves to assess methods that use very large data sets to learn appropriate ways to classify them for BC screening problems [67]. Although these methods hold some promise for risk assessment, they are currently largely untested.

While some research has focused on image features from a mammogram, other aspects of the breast become visible when using different imaging techniques. One focus from MRI has been background parenchymal enhancement (BPE), which arises in the breast image after administration of a contrast agent and broadly corresponds to microvessel density. It has been posited that while mammographic density includes both glandular and fibrous tissues, it is only the glandular tissue that is important for breast cancer risk and that BPE is a better measure of glandular tissue than mammographic density. Similar to mammographic density, there is no standard automated method to measure it, and most studies have relied on subjective reader assessment following a four-category scale [68]. As breast MRI is much less common than mammography and only typically applied to women at a high risk of the disease, it is more difficult to assess it as a general risk factor in general populations. However, in high-risk groups, it appears to predict risk and to be as important a risk factor as mammographic density, and it is likely to be an independent risk factor [62, 69].

In summary, breast density is a well-established risk factor with a high population-

attributable risk [70], but better measures of density are needed, and new risk features from different imaging techniques may provide further stratification of risk beyond density.

20.4.4 Risk of Screening Failure

Most risk models focus on the risk of invasive BC in unaffected women, projecting annual rates over the remainder of a woman's lifetime. They have been used to determine the eligibility for supplemental screening, particularly MRI in the United States.

However, it is worth taking a step back to consider whether invasive BC risk is the right endpoint and whether it might be better to focus on the reason for supplemental screening: screening failure or interval cancers. That is, one might determine the screening regimen on the basis of risk (of interval cancer) given the screening rather than underlying risk of cancer in the absence of screening. In the United Kingdom, the cervical screening programme is in the process of changing to human papillomavirus testing but presently offers cytological screening every 3 years for women aged 25–49 years and every 5 years for women aged 50–64 years, not on the basis of underlying risk of cervical cancer in these groups but because the risk of cancer after a negative screen rises more swiftly in the younger age group [71]. Also, it has long been considered likely that mammographic screening in women aged under 50 years should be more frequent than in women aged 50 years or older, despite the lower risk in the former group. The rationale for the shorter interval proposed for the younger group is the more rapid tumour progression on average and the denser breast tissue in that age group.

One might therefore propose a model that includes short-term risk (such as 5-year risk) and imaging features that predict screening failure, particularly mammographic density [72]. Then women with a high risk of interval cancer are offered supplemental screening. This need not be the only approach, and one might also wish to predict the type of cancer and offer supplemental screening to those most likely to have a more lethal interval cancer.

Tailored risk models for supplemental screening are not well developed, and there seems to be scope for model development in this area. However, there are also difficulties that might make decisions based on risk of invasive BC more robust and transferable between settings.

For instance, suppose that one uses a large database to develop a model for lethal interval BCs, then it is validated in a similar setting, and the model is used to undertake formal cost-benefit and other analyses to determine the threshold to use for supplemental screening. This process will take some time and will use historic data. In the meantime, technology will move on, and the model might no longer be applicable. To give an example, film-screen mammography has been replaced by digital mammography, and (in the United States at least) there is now a wide move towards digital breast tomosynthesis. Change in technology will alter the sensitivity of the screening test, perhaps in certain subgroups of women, so that the assumptions in the model may be expected to no longer hold. In addition, there will be differences between good and bad screening centres, and those centres who participate in research projects might be the better centres, with higher sensitivity than those that do not. Thus, while risk of interval cancer is theoretically appealing and seemingly a more sensible index than risk of invasive cancer for decisions about supplemental screening, there are important issues around the data that would be used to build and validate them that make it a challenge.

There is some potential to develop better risk models to determine eligibility for supplemental screening than those with invasive cancer as the endpoint. But current models for the risk of invasive cancer are also not without merit for making decisions about supplemental screening. A model for invasive BC risk that includes mammographic density includes the strongest known predictor of screening failure (density), and the absolute risk of lethal cancer is also highly correlated with the risk of invasive cancer.

20.4.5 Breast Cancer Subtype Models

Most current BC risk models assess the risk of invasive BC. For risk-adapted screening and prevention, it may be more informative to predict the risk of cancer subtypes. In the following, we consider how some risk factors relate to BC subtypes.

Age is an important risk factor for all types of BC. A family history of BC is also a risk factor that is associated with all types of BC, and so is breast density [73, 74].

Reproductive risk factors have tended to be observed to be more associated with hormone receptor-positive than hormone receptor-negative disease [75]. Later age at first child or nulliparity, younger age at menarche and hormone therapy have been associated with hormone receptor-positive disease. On the other hand, there is some evidence that breastfeeding reduces the risk of triple-negative BC [76].

For benign disease, it appears to be important to stratify by pathology. Benign disease with atypical hyperplasia or lobular carcinoma in situ appears to be primarily associated with ER-positive disease [77]. This is consistent with the trials of preventive tamoxifen, which showed a larger preventive effect for women with these types of benign disease [35].

Overweight and obesity are well established to be a postmenopausal risk factor for BC. It has sometimes been observed to show an inverse effect for risk in premenopausal women, but it is not a consistent finding [78], and the relationship of obesity with BC risk appears to be more nuanced than a pre- and postmenopausal change when one considers the type of disease. Obese premenopausal women are likely to have a greater risk of triple-negative BC than women with a healthy weight, and the strength of association for triple-negative BC decreases after the menopause [78].

In terms of genetic risk, women with a deleterious *BRCA1* mutation are more likely to develop triple-negative BC, while most cancers arising in *BRCA2* mutation carriers tend to be ER positive [79]. There is some data suggesting that *CHEK2* mutation carriers are more likely to develop ER-positive cancers [27]. The large majority of SNPs identified with invasive cancer have only been validated for ER-positive disease, but there are also some only for ER-negative disease [59, 80].

Finally, there may be some risk factors associated with BC subtypes missed when studying all invasive cancer together. One example is diet: eating more vegetables has been observed to reduce the risk of ER-negative cancer, but with little effect on the risk of ER-positive cancer [81].

20.4.6 Risk Assessment More Generally

We finally briefly consider where BC risk assessment may fit into a wider picture of a woman's health. To illustrate this issue, we consider an important modifiable risk factor with a high population-attributable risk: overweight and obesity [70].

As noted above, there is some evidence that it is a risk factor for a subtype of BC with the worst survival (triple-negative BC) and obese women are more likely to die of BC than women with a healthy weight [54]. Additionally, overweight and obesity is a risk factor for many other diseases and overall mortality [82]. One concern with risk feedback for BC in healthy women is whether any action may be recommended to modify the risk of BC. Weight reductions might make little discernible difference to a BC risk assessment from an individual woman's perspective, but it is arguably better to frame the impact of behavioural changes on her overall risk of diseases and mortality. Managing a healthy weight will reduce a woman's risk of premenopausal triple-negative BC, her risk of postmenopausal BC and her risk of dying from BC; it will increase life expectancy. A quantification of all these components could be provided, but risk models to help do so do not appear to be developed at present.

20.5 Conclusions

In this chapter, we reviewed some current breast cancer risk assessment models, discussed their use in clinical decision-making and identified some areas for further development. Mammography screening based on age and gender has saved many lives through early detection of breast cancer [83]. Future advances are likely to arise from comprehensive breast cancer risk assessment that combines classical questionnaire factors, mammographic density and genetic testing and use risk-stratified screening and prevention strategies. New trials are indicated to assess the utility of risk-adapted screening strategies compared with current practice.

References

1. Gail MH, Brinton LA, Byar DP et al (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 81:1879–1886
2. Claus EB, Risch N, Thompson WD, Claus EB, Risch N, Thompson WD (1993) The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat 28:115–120
3. Tyrer J, Duffy SW, Cuzick J (2004) A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 23:1111–1130
4. Antoniou AC, Cunningham AP, Peto J et al (2008) The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 98:1457–1466
5. Easton DF, Pharoah PD, Antoniou AC et al (2015) Gene-panel sequencing and the prediction of breast-cancer risk. New Engl J Med 372:2243–2257
6. Teams FC (2010) Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol 11:1127–1134
7. Pashayan N, Duffy SW, Chowdhury S et al (2011) Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. Br J Cancer 104:1656–1663
8. Duffy SW (2003) Screening for breast cancer. In: Evidence-based oncology. BMJ Publishing Group, London, pp 109–117
9. Evans DG, Howell A (2007) Breast cancer risk-assessment models. Breast Cancer Res 9:213
10. Amir E, Freedman OC, Seruga B, Evans DG (2010) Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst 102:680–691
11. Gail MH, Mai PL (2010) Comparing breast cancer risk assessment models. J Natl Cancer Inst 102:665–668
12. Cintolo-Gonzalez JA, Braun D, Blackford A et al (2017) Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. Breast Cancer Res Treat 164:263–284
13. Parmigiani G, Berry DA, Aguilar O (1998) Determining carrier probabilities for breast Cancer-Susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 62:145–158
14. Chen J, Pee D, Ayyagari R et al (2006) Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 98:1215–1226
15. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K (2008) Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med 148:337–347
16. Mealiffe ME, Stokowski RP, Rhees BK, Prentice RL, Pettinger M, Hinds DA (2010) Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. J Natl Cancer Inst 102:1618–1627
17. Maas P, Barrdahl M, Joshi AD et al (2016) Breast cancer risk from modifiable and nonmodifiable risk factors among white women in the United States. JAMA Oncol 2:1295–1302
18. Tice JA, Miglioretti DL, Li CS, Vachon CM, Gard CC, Kerlikowske K (2015) Breast density and benign breast disease: risk assessment to identify women at high risk of breast cancer. J Clin Oncol 33:8869–3143
19. Vachon CM, Pankratz VS, Scott CG et al (2015) The contributions of breast density and common genetic variation to breast cancer risk. J Natl Cancer Inst 107:pii dju397
20. Brentnall AR, Harkness EF, Astley SM et al (2015) Mammographic density adds accuracy to both the Tyrer-Cuzick and gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Res 17:147
21. Cuzick J, Brentnall AR, Segal C et al (2017) Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in High-Risk women: results from two randomized tamoxifen prevention trials. J Clin Oncol 35:743–750
22. Tyrer-Cuzick Model (2017). www.ems-trials.org/riskevaluator. Accessed 1 November 2017
23. van Veen EM, Brentnall AR, Byers H et al (2018) Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. JAMA Oncol 4:476–482
24. Kuchenbaecker KB, Hopper JL, Barnes DR et al (2017) Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317:2402–2416
25. Antoniou AC, Hardy R, Walker L et al (2008) Predicting the likelihood of carrying a BRCA1

or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, myriad and the manchester scoring system using data from UK genetics clinics. J Med Genet 45:425–431
26. Manchanda R, Patel S, Gordeev VS et al (2018) Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. J Natl Cancer Inst 10:714–725
27. Lee AJ, Cunningham AP, Tischkowitz M et al (2016) Incorporating truncating variants in PALB2, CHEK2, and ATM into the BOADICEA breast cancer risk model. Genet Med 18:1190–1198
28. Tabar L, Fagerberg G, Chen HH et al (1995) Efficacy of breast cancer screening by age. new results from the swedish Two-County trial. Cancer 75:2507–2517
29. Nixon AJ, Neuberg D, Hayes DF et al (1994) Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol 12:888–894
30. National Institute for Clinical Excellence (2013) Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. clinical guidelines, CG164. https://www.nice.org.uk/guidance/cg164. Accessed 30 Jun 2020
31. Saslow D, Boetes C, Burke W et al (2007) American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
32. Cuzick J, Sestak I, Bonanni B et al (2013) Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 381:1827–1834
33. Cuzick J, Sestak I, Forbes JF et al (2014) Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383:1041–1048
34. Waters EA, McNeel TS, Stevens WM, Freedman AN (2012) Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat 134:875–880
35. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K (2014) Atypical hyperplasia of the breast – risk assessment and management options. N Engl J Med 372:78–89
36. Pankratz VS, Degnim AC, Frank RD et al (2015) Model for individualized prediction of breast cancer risk after a benign breast biopsy. J Clin Oncol 33:923–929
37. Smith RA (2011) International programs for the detection of breast cancer. Salud Publica Mex 53:394–404
38. Taplin SH, Thompson RS, Schnitzer F, Anderman C, Immanuel V (1990) Revisions in the risk-based breast cancer screening program at group health cooperative. Cancer 66:812–818
39. Evans DG, Warwick J, Astley SM et al (2012) Assessing individual breast cancer risk within the U.K. national health service breast screening program: a new paradigm for cancer prevention. Cancer Prev Res (Phila) 5:943–951
40. Gabrielson M, Eriksson M, Hammarström M et al (2017) Cohort profile: the Karolinska mammography project for risk prediction of breast cancer (KARMA). Int J Epidemiol 46:1740–1741g
41. PRISMA study. https://www.prisma-studie.nl/. Accessed 30 Jun 2020
42. Melnikow J, Fenton JJ, Whitlock EP et al (2016) Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 164:268–278
43. Rebolj M, Assi V, Brentnall A, Parmar D, Duffy SW (2018) Addition of ultrasound to mammography in the case of dense breast tissue: systematic review and meta-analysis. Br J Cancer 118:1559–1570
44. Emaus MJ, Bakker MF, Peeters PH et al (2015) MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. Radiology 277:527–537
45. Esserman LJ; WISDOM Study and Athena Investigators (2017) The WISDOM Study: breaking the deadlock in the breast cancer screening debate. NPJ Breast Cancer 3:34
46. My personalized breast screening (MyPeBS). https://mypebs.eu/it/. Accessed 30 Jun 2020
47. Gail MH, Pfeiffer RM (2005) On criteria for evaluating models of absolute risk. Biostatistics 6:227–239
48. Brentnall AR, Cuzick J (2016) Use of the concordance index for predictors of censored survival data. Stat Methods Med Res 27:2359–2373
49. Brentnall AR, Cuzick J, Field J, Duffy SW (2015) A concordance index for matched case-control studies with applications in cancer risk: a concordance index for matched case-control studies with applications in cancer risk. Stat Med 34:396–405
50. Ziegler RG, Hoover RN, Pike MC et al (1993) Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 85:1819–1827
51. Deapen D, Liu L, Perkins C, Bernstein L, Ross RK (2002) Rapidly rising breast cancer incidence rates among Asian-American women. Int J Cancer 99:747–750
52. Pike MC, Kolonel LN, Henderson BE et al (2002) Breast cancer in a multiethnic cohort in hawaii and Los Angeles: risk factor-adjusted incidence in japanese equals and in hawaiians exceeds that in whites. Cancer Epidemiol Biomark Prev 11:795–800
53. Gathani T, Ali R, Balkwill A et al (2013) Ethnic differences in breast cancer incidence in England are due to differences in known risk factors for the disease: prospective study. Br J Cancer 110:224–229
54. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 335:1134

55. Brentnall AR, Duffy SW, Cuzick J (2017) Breast cancer tumor size and screening effectiveness. N Engl J Med 376:93–95
56. Keum N, Greenwood DC, Lee DH et al (2015) Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst 107:pii djv088
57. Michailidou K, Beesley J, Lindstrom S et al (2015) Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 47:373–380
58. Brentnall AR, Evans DG, Cuzick J (2014) Distribution of breast cancer risk from SNPs and classical risk factors in women of routine screening age in the UK. Br J Cancer 110:827–828
59. Michailidou KS, Lindström J, Dennis J et al (2017) Association analysis identifies 65 new breast cancer risk loci. Nature 551:92–94
60. Rudolph A, Chang-Claude J, Schmidt MK (2016) Gene-environment interaction and risk of breast cancer. Br J Cancer 114:125–133
61. Assi V, Warwick J, Cuzick J, Duffy SW (2011) Clinical and epidemiological issues in mammographic density. Nat Rev Clin Oncol 9:33–40
62. Pike MC, Pearce CL (2013) Mammographic density, MRI background parenchymal enhancement and breast cancer risk. Ann Oncol 24:viii37–viii41
63. Wolfe JN (1976) Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 126:1130–1137
64. McCormack VA, Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomark Prev 15:1159–1169
65. Gastounioti A, Conant EF, Kontos D (2016) Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. Breast Cancer Res 18:91
66. Wang C, Brentnall AR, Cuzick J, Harkness EF, Evans DG, Astley S (2017) A novel and fully automated mammographic texture analysis for risk prediction: results from two case-control studies. Breast Cancer Res 19:114
67. Trister AD, Buist DSM, Lee CI (2017) Will machine learning tip the balance in breast cancer screening? JAMA Oncol 3:1463–1464
68. Sung JS, Corben AD, Brooks JD et al (2018) Histopathologic characteristics of background parenchymal enhancement (BPE) on breast MRI. Breast Cancer Res Treat 172:487–496
69. King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA (2011) Background parenchymal enhancement at breast MR imaging and breast cancer risk. Radiology 260:50–60
70. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K (2017) Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol 3:1228–1236
71. Sasieni P, Adams J, Cuzick J (2003) Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br J Cancer 89:88–93
72. Kerlikowske K, Zhu W, Tosteson ANA et al; Breast Cancer Surveillance Consortium (2015) Identifying women with dense breasts at high risk for interval cancer. Ann Intern Med 162:673–681
73. Mavaddat N, Pharoah PD, Blows F et al (2010) Familial relative risks for breast cancer by pathological subtype: a population-based cohort study. Breast Cancer Res Res 12:R10
74. Antoni S, Sasco A, Santos Silva I, McCormack V (2013) Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. Breast Cancer Res Treat 137:337–347
75. Anderson K, Schwab R, Martinez M (2014) Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat 144:1–10
76. Islami F, Liu Y, Jemal A et al (2015) Breastfeeding and breast cancer risk by receptor status-a systematic review and meta-analysis. Ann Oncol 26:2398–2407
77. Kerlikowske K, Gard CC, Tice JA, Ziv E, Cummings SR, Miglioretti DL (2016) Risk factors that increase risk of estrogen receptor-positive and -negative breast cancer. J Natl Cancer Inst 109:djw276
78. Pierobon M, Frankenfeld C (2013) Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 137:307–314
79. Mavaddat N, Barrowdale D, Andrulis IL et al (2011) Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomark Prev 21:134–147
80. Garcia-Closas M, Couch FJ, Lindstrom S et al (2013) Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 45:392–398
81. Jung S, Spiegelman D, Baglietto L et al (2013) Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst 105:219–236
82. Aune D, Sen A, Prasad M et al (2016) BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ 353:i2156
83. Plevritis SK, Munoz D, Kurian AW et al (2018) Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000–2012. JAMA 319:154–164

21 MRI for Screening Women with a Personal History of Breast Cancer

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Abbreviations

ACR	American College of Radiology
ACS	American Cancer Society
ASCO	American Society of Clinical Oncology
BI-RADS	Breast Imaging Reporting and Data System
CI	Confidence interval
DCIS	Ductal carcinoma in situ
EUSOMA	European Society of Breast Cancer Specialists
IDC	Invasive ductal carcinoma
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PHBC	Personal history of breast cancer
PPV	Positive predictive value
US	Ultrasound

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21.1 Introduction

The combination of early diagnosis and modern treatment protocols, including surgery, radiation therapy, and chemo- and hormonal therapies, has increased survival rates of breast cancer patients, with the relative contribution of screening to this success estimated to be about 46% [1]. In the United States, the average 5-year survival rate for women diagnosed with breast cancer is estimated to be 90% [2]. The 5-year survival rate after breast-conserving surgery and radiation therapy has been recently reported to be 94% in Canada [3] and 97% in Norway [4].

As a result, the number of women with a personal history of breast cancer (PHBC) is increasing across the world. A 2014 population-based study projected that 209,200 women would have been living with breast cancer in Australia in 2017, which is nearly 1% of its total population [5]. There are similar projections in the United States (3.5 million) [6]. In Italy, breast cancer has been estimated to account for about 42% of the total cancer cases in women [7]. Thus, millions of women require post-treatment surveillance, and healthcare systems require planning and development to accommodate this increased demand, including active treatment when necessary.

Women with a PHBC have an increased risk of a second breast cancer if compared with the average female population without a PHBC [8]. This includes (a) ipsilateral locoregional

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recurrences of the first breast cancer (*true* ipsilateral recurrences), (b) distant metastases, (c) new ipsilateral breast cancers, and (d) contralateral breast cancers. After breast-conserving surgery, true ipsilateral recurrences occur during the first 5 years, and in particular the first 2 years, with a subsequent decrease over time [9]. A case of an invasive ductal carcinoma (IDC) detected by screening magnetic resonance imaging (MRI) 4 years after a previous IDC in the ipsilateral breast is shown in Fig. 21.1.

Higher relapse rates occur during the first 5 years, but women with a PHBC remain at risk for recurrences and new (second) primary breast cancers beyond this high-risk period [9, 10]. The overall annual rate of ipsilateral recurrence is approximately 1% for up to 20 years after the initial therapy [11], which contributes to an increase in the cumulative incidence [12, 13]. The onset of new (second) primary breast cancers typically occurs later, after the first 5 years [12, 14, 15]. In a report from the Women's Environmental Cancer and Radiation Epidemiology Study [16], the cumulative 10-year risk of contralateral breast cancer in women with a PHBC diagnosed between ages 25 and 54 and a family history of a first-degree relative with breast cancer was 8.6% (95% confidence interval [CI], 6.1–11.5%) and without a family history was 4.6% (95% CI, 4.0–5.1%). *Given that women with a PHBC remain at risk for recurrences and new cancers, surveillance should continue after the initial high-risk period.* Cases of ipsilateral cancers detected by screening MRI from 8 to more than 15 years after treatment of the previous event are shown in Figs. 21.2 to 21.5. Cases of contralateral cancers detected by screening MRI are shown in Figs. 21.6 and 21.7.

Further stratification of risk among women with a PHBC is important for the planning of surveillance programs. To do so, we may consider a meta-analysis of 17 randomized trials of women treated with breast-conserving surgery and radiation therapy [17], which reported an overall 10-year recurrence rate of 19.3% and a 15-year breast cancer mortality rate of 21.4%. These rates

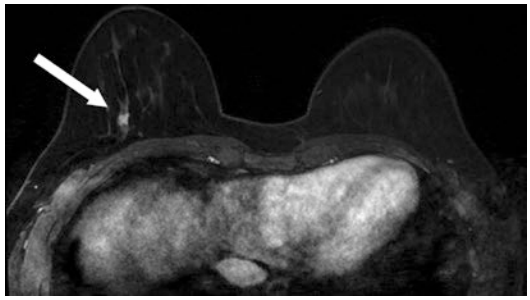


Fig. 21.1 A 49-year-old female with a history of lumpectomy and radiation therapy for an invasive ductal carcinoma of the right breast. Screening MRI performed 4 years after treatment: axial fat-saturated contrast-enhanced scan demonstrates a small enhancing mass with irregular shape and margins in the lower right breast at posterior depth (arrow). Surgical pathology revealed a node-negative invasive ductal carcinoma

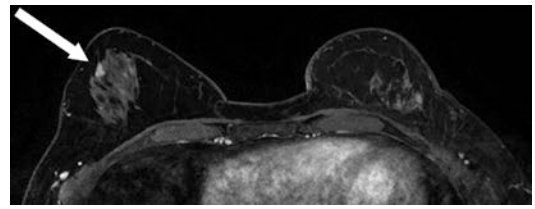


Fig. 21.2 A 60-year-old female with a history of lumpectomy for ductal carcinoma in situ of the right breast and lumpectomy plus radiation therapy for an invasive ductal carcinoma of the left breast. Screening MRI performed 15 years after lumpectomy on the right: axial fat-saturated contrast-enhanced scan demonstrates a small enhancing mass with irregular shape and margins in the lateral right breast (arrow). Surgical pathology revealed a node-negative invasive carcinoma with ductal and lobular features

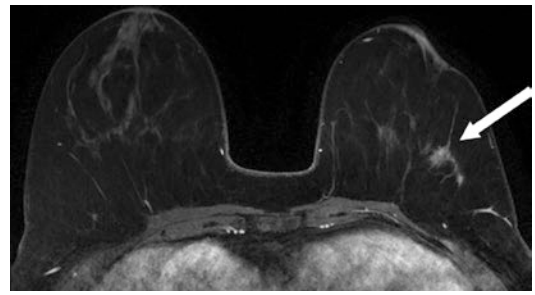


Fig. 21.3 A 40-year-old female with a history of lumpectomy plus radiation therapy for an invasive ductal carcinoma of the left breast. Screening MRI performed 8 years after treatment: axial fat-saturated contrast-enhanced scan demonstrates focal non-mass enhancement adjacent to the surgical site in the left breast (arrow). Surgical pathology revealed a node-negative invasive ductal carcinoma

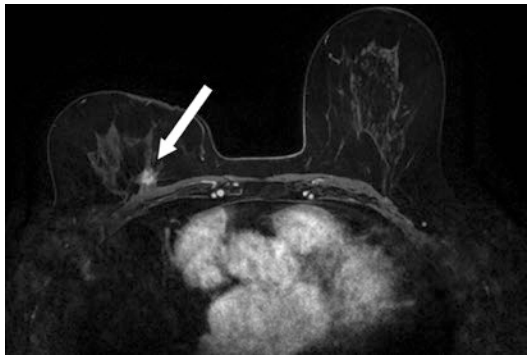


Fig. 21.4 A 72-year-old female with a history of lumpectomy and radiation therapy for an invasive ductal carcinoma of the right breast. Screening MRI performed more than 15 years after treatment: axial fat-saturated contrast-enhanced scan demonstrates an enhancing mass with irregular shape and margins in the central right breast at posterior depth (prepectoral location, arrow), which was biopsied to reveal invasive ductal carcinoma

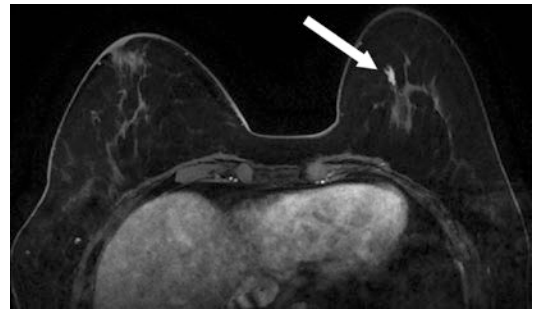


Fig. 21.6 A 69-year-old female with a history of lumpectomy and radiation therapy for an invasive ductal carcinoma of the right breast. Screening MRI performed 6 years after treatment: axial fat-saturated contrast-enhanced scan demonstrates focal non-mass enhancement in the lower inner quadrant of the left breast (arrow). Surgical pathology revealed a node-negative invasive ductal carcinoma

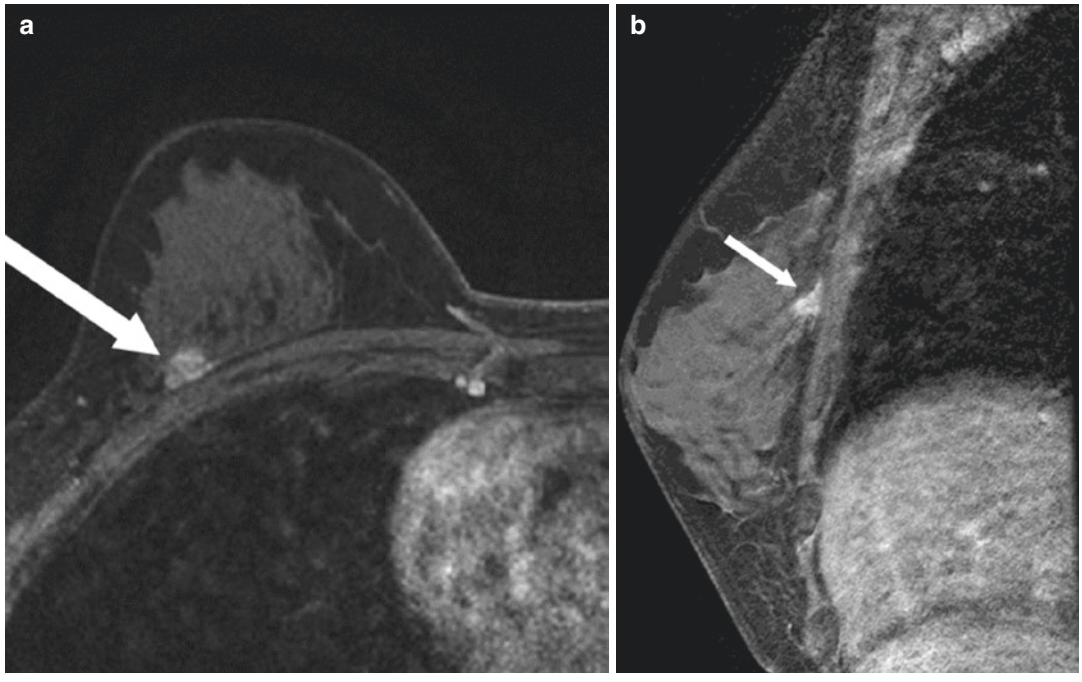


Fig. 21.5 A 57-year-old female with a history of lumpectomy and radiation therapy for an invasive ductal carcinoma of the right breast. Screening MRI performed 12 years after treatment: axial (**a**) and sagittal (**b**) fat-saturated contrast-enhanced scans demonstrate an enhancing mass with irregular shape and margins in the upper outer quadrant of the right breast at posterior depth (prepectoral location, arrows in **a** and **b**), which was biopsied to reveal invasive ductal carcinoma

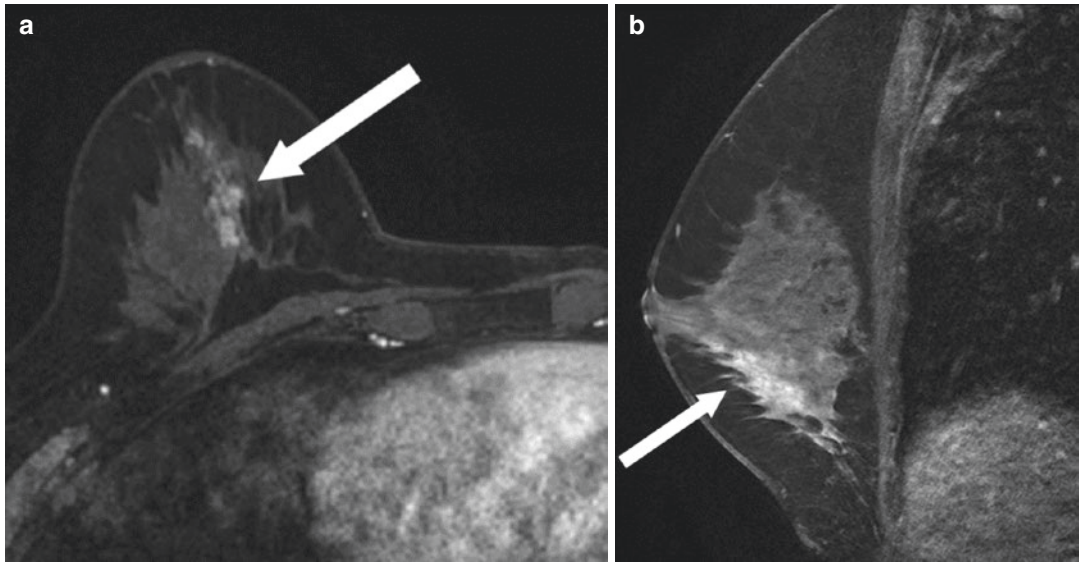


Fig. 21.7 A 59-year-old female with a history of mastectomy for an invasive ductal carcinoma of the left breast. Screening MRI of the contralateral breast performed 12 years after the mastectomy: axial (**a**) and sagittal (**b**) fat-saturated contrast-enhanced scans demonstrate clumped non-mass enhancement in the lower central right breast, which was biopsied to reveal invasive ductal carcinoma

were 42.5% and 42.8%, respectively, in women with nodal disease and 15.6% and 17.2%, respectively, in women with node-negative disease [17]. *The risk of local recurrence has been shown to strongly depend on nodal status, age, tumor size, and grade. Specifically, positive lymph nodes, young age, large tumor size, and high grade are each strongly predictive of locoregional recurrence* [17, 18].

Breast imaging surveillance of women with a PHBC should consider that, as stated above, the overall annual rate of ipsilateral recurrence is approximately 1% for up to 20 years after the initial therapy [11]. Thus, *women with a PHBC represent a subgroup of women with intermediate breast cancer risk, higher than that of women without personal or relevant familial breast cancer history but lower than that of BRCA or p53 mutation carriers* [19]. *Importantly, in women with a PHBC, the detection of a second breast cancer during the asymptomatic phase rather than the symptomatic phase can improve survival by between 27% and 47%* [20].

Surgical and radiation treatment of breast cancer pose difficulties for subsequent surveillance with mammography, since scarring and retractions may obscure or mimic recurrent or new cancers. In a study of 58,870 screening mammograms in 19,078 women with a personal history of ductal carcinoma in situ (DCIS) or stage I/II invasive breast cancer matched to women without a PHBC [8], the cancer detection rate of screening mammography was higher, the sensitivity was lower, and the interval cancer rate was higher in the former group.

This is the context by which to evaluate the potential role of modalities such as breast MRI as an adjunct to standard mammographic surveillance for screening women with a PHBC. In this setting, MRI could be able to not only distinguish true recurrent ipsilateral cancers from post-treatment changes but also to provide early diagnosis of new ipsilateral and contralateral cancers [21–23].

21.2 Available Guidelines for Post-Treatment Screening MRI

Current guidelines by the American Cancer Society (ACS) [24] and the National Comprehensive Cancer Network (NCCN) [25] recommend annual screening MRI as an adjunct

to mammography for women with an increased lifetime risk of breast cancer. Per the ACS [24], screening MRI is recommended only to women at elevated risk for breast cancer because they are more likely to benefit than women at low risk and because of the high false-positive rate of screening MRI. Specifically, MRI is recommended for (1) women with the *BRCA1* or *BRCA2* mutation and their untested first-degree relatives, (2) those with a lifetime risk of approximately 20–25% or greater based on models that are largely dependent on family history, (3) those with a history of radiation to the chest between ages 10 and 30, and (4) those with certain syndromes such as Li-Fraumeni. The ACS [24] and NCCN [25] concluded that there is insufficient evidence to recommend for or against post-treatment screening MRI in women with only a PHBC. More recent guidelines issued by the American College of Radiology (ACR) in 2018 [26] recommend screening MRI in women with a PHBC and dense breast tissue or those diagnosed before age 50. According to the European Society of Breast Cancer Specialists (EUSOMA) working group [27], a previous history of invasive breast cancer or DCIS not associated with other risk factors does not confer an increased risk that justifies the use of routine surveillance MRI. Guidelines by the American Society of Clinical Oncology (ASCO) [28] recommend *against* post-treatment screening MRI for women with a PHBC who are otherwise asymptomatic with no specific findings on clinical examination.

21.3 Review of the Literature on Screening MRI

When the ACS guidelines were issued in 2007 [24], scarce research was available on the use of MRI for surveillance of women with a PHBC. The one study cited in the guidelines was a retrospective review of 367 consecutive women at high risk for developing breast cancer who had negative mammography and their first screening MRI during a 2-year period [29]. Of the 245 women with a PHBC, 33 (13.5%) biopsies were recommended. Thirty biopsies were subsequently performed, ten of which revealed malignancy. Thus, the cancer detection rate by screening MRI was 40.8 per 1,000 examinations (10/245), and the positive predictive value (PPV) of biopsy was 33.3% (10/30). Of note, in women who underwent breast-conserving surgery (rather than mastectomy), the cancer detection rate by screening MRI was 70.2 per 1,000 examinations (8/114), and the PPV of biopsy was 40.0% (8/20). By comparison, in women at high risk based on family history alone, the cancer detection rate by screening MRI was 59.1 per 1,000 examinations (13/220), and the PPV of biopsy was 31.7% (13/41). In women who had both a family history of breast cancer and a PHBC, the cancer detection rate by screening MRI was 75.0 per 1,000 examinations (9/120), and the PPV of biopsy was 50.0% (9/18). The authors concluded that screening MRI is likely to have the highest yield in women with both a family history of breast cancer and a PHBC, particularly those previously treated with breast-conserving surgery.

Since 2007, 15 other studies have been published on the use of MRI for surveillance in women with a PHBC [30–44] (Table 21.1). These studies have included a total of 5,428 patients, the majority of whom had no other known risk factors (such as genetic risk or family history). All studies but two had a retrospective design, with patients referred by physicians for MRI on the basis of their own practice patterns and their own determination of risk status. One of the two prospective studies [32] evaluated the added value of screening ultrasound (US) or screening MRI for breast cancer detection in women at elevated risk (heterogeneously dense or extremely dense breast tissue and at least one other risk factor for breast cancer), and part of the study provided a specific analysis of women with a PHBC. These 15 studies had differing methodologies with varying periods of follow-up after the initial breast cancer surgery and varying numbers of follow-up MRI examinations obtained per patient. In addition, in some studies, women had negative mammography immediately preceding the MRI. Furthermore, the studies differed with regard to the patient population: some studies included only women who had previously undergone curative-intent breast-conserving surgery, while others included women who underwent breast-conserving surgery or mastectomy.

Table 21.1 Summary of studies on screening MRI in women with a PHBC

First author (year) [reference]	Patients	MRI exams	Cancer detection rate by MRI per 1,000 exams	MRI sensitivity	Positive predictive value of biopsy prompted by MRI
Brennan (2010) [30]	144	NR	NR	100.0% (17/17)	27.9% (17/61)
Elmore (2010) [31]	141	202	9.9 (2/202)	NR	33.3% (2/6)
Berg (2012) [32]	275	275	10.9 (3/275)	75.0% (3/4)	18.2% (2/11)
Arazi-Kleinman (2013) [33]	46	46	NR	NR	19.1% (9/47)
Gweon (2014) [34]	607	607	16.5 (10/607)	83.3% (10/12)	43.5% (10/23)
Schacht (2014) [35]	208	NR	NR	NR	NR
Giess (2015) [36]	511	904	7.7 (7/904)	NR	NR
Weinstock (2015) [37]	249	571	19.3 (11/571)	84.6% (11/13)	29.6% (8/27)
Destounis (2016) [38]	52	146	47.9 (7/146)	NR	31.8% (7/22)
Lehman (2016) [39]	915	915	17.5 (16/915)	80.0% (16/20)	25.0% (16/64)
Cho (2017) [40]	754	2,065	7.3 (15/2,065)	88.2% (15/17)	23.5% (12/51)
Kim (2017) [41]	414	422	21.3 (9/422)	81.8% (9/11)	32.1% (9/28)
Strigel (2017) [42]	NR	365	30.1 (11/365)	NR	42.3% (11/26)
Tadros (2017) [43]	68	181	5.5 (1/181)	NR	10.0% (1/10)
Park (2018) [44]	1,044	1,053	2.8 (3/1,053)	75.0% (3/4)	15.8% (3/19)

NR not reported

21.3.1 Cancer Detection Rate

Some studies report the cancer detection rate among *patients* in their study population, whereas others report cancers detected per 1,000 *screening MRI examinations*. For purposes of this review, the cancer detection rate is defined per 1,000 screening examinations and will be used throughout, unless the number of patients was the only available data and the number of examinations was not reported. For studies with only one round of screening, the number of patients and the number of examinations are the same.

One of the largest studies on the use of MRI for screening women with a PHBC compared 915 women with a PHBC but *without* known genetic risk or family history of breast cancer to 606 women with genetic risk or family history of breast cancer [39]. A small number of women (n = 64) in the genetic risk/family history group also had a PHBC. For each woman, the first MRI performed during the 7-year study period was considered for analysis. The authors also collected data on breast cancers that were diagnosed over a 12-month period after the MRI, including interval cancers, but not at the next MRI screen. The cancer detection rate by screening MRI was 17.5 per 1,000 examinations (16/915) in the PHBC group and 18.2 per 1,000 examinations (11/606) in the genetic risk/family history group, with an overall sensitivity of 79.4% (27/34). *The cancer detection rate and sensitivity were not significantly different in the two groups*.

Gweon et al. [34] also found a similarly high cancer detection rate in patients with a PHBC. In their study of screening MRI examinations in 607 Korean women who underwent breast-conserving surgery and had negative mammography and US examinations, single-round screening MRI detected a total of 10 cancers, for a cancer detection rate of 16.5 per 1,000 examinations and an overall sensitivity of 83.3% (10/12). One 1.0-cm IDC was diagnosed on a 6-month follow-up MRI after the initial MRI was given a final assessment category of Breast Imaging Reporting and Data System (BI-RADS) 3, and one additional 0.8-cm IDC was detected on a 6-month follow-up mammogram.

In a prospective study of the diagnostic performance of early (1 year or less) screening MRI examinations [41], a total of 11 breast cancers were diagnosed among 414 women, 6 of which were seen on MRI only. The cancer detection rate of MRI was 21.3 per 1,000 examinations (9/422). Of the two false-negative cases (both of which were DCIS), one cancer had presented as calcifications on mammography without enhance-

ment on MRI, and the other cancer was detected on PET/CT but had a negative MRI because of marked background parenchymal enhancement. In a study of women under 65 years of age with a PHBC and at least one follow-up MRI examination performed along with a mammogram done within 6 months of the MRI [37], 11 women were diagnosed with malignancy, for a cancer detection rate of 19.3 per 1,000 examinations (11/571).

In a study by Giess et al. [36], 7 malignancies were detected by MRI in 511 women with a PHBC and no other risk factors over the 3-year study period, for a cancer detection rate of 7.7 per 1,000 examinations (7/904). By comparison, 5 malignancies were detected by MRI in 172 women with a PHBC plus a family history of breast cancer in a first-degree relative, for a cancer detection rate of 17.8 per 1,000 examinations (5/281).

Elmore and Margenthaler [31] studied 141 women who underwent 202 surveillance breast MRI examinations following curative-intent treatment for breast cancer: 2 were found to have invasive breast cancers, for a cancer detection rate of 9.9 per 1,000 examinations. In the multicenter prospective study reported by Berg et al. [32], single-round screening MRI identified 10.9 additional cancers per 1,000 women (3/275) with a PHBC even immediately after the third round of negative mammography and US examinations.

Schacht et al. [35] compared screening MRI in 208 women with a PHBC to 345 women with family history as the sole risk factor. An additional 97 women had both risk factors. The rate of breast cancer detected on MRI was 2.9% (6/208) in women with a PHBC, 2.0% (7/345) in women with a family history of breast cancer, and 6.2% (6/97) in women with both risk factors. The relative risk for detection of breast cancer given a personal history was 1.42 (95% CI, 0.48–4.17) compared to a family history alone. In addition to the cancers detected by MRI, six cases were detected via physical examination or other breast imaging modality (mammography or US) in the PHBC group, further supporting the concept of a high incidence of cancer in women with a PHBC.

In a multicenter, prospective, nonrandomized study of 754 women with a PHBC diagnosed at age 50 or younger who underwent breast conservation therapy [40], the authors compared the performance of a combination of imaging techniques for screening: mammography and MRI or US versus mammography alone. The addition of MRI to mammography led to the detection of 3.8 more cancers per 1,000 examinations compared with mammography alone. Of the 17 total cancers diagnosed, 2 cancers detected by mammography alone presented with suspicious calcifications and did not demonstrate suspicious enhancement on MRI.

Tadros et al. [43] compared screening MRI in 68 women with a PHBC to 118 women with a family history of breast cancer and/or personal history of a gene mutation conferring increased risk of breast cancer. Nine patients developed a new primary or local recurrence, only one of whom had a PHBC. The cancer detection rate was therefore 5.5 per 1,000 examinations (1/181) among women with a PHBC.

Park et al. [44] reported that screening MRI in women with a PHBC had an intramammary cancer detection rate of 2.8 per 1,000 examinations (3/1,053) and sensitivity of 75.0% (3/4). An additional three extramammary cancers were detected by MRI. The authors suggested that the relatively low intramammary cancer detection rate could be due to the following reasons: nearly 40% (396/1,044) of patients had undergone mastectomy rather than breast-conserving surgery and nearly 90% (930/1,044) had undergone preoperative breast MR imaging. The cancer detection rate of screening MRI performed more than 3 years after surgery was significantly higher than that for screening MRI performed within 3 years, which may provide a basis for establishing guidelines regarding timing of surveillance MRI following surgery.

Three studies reported higher cancer detection rates in women with a PHBC. In 52 women with a PHBC but without family history who underwent 146 screening MRI examinations [38], a total of 7 malignancies were detected, for a cancer detection rate of 47.9 per 1,000 examinations. By comparison, in 79 women with a PHBC plus family history who underwent 235 MRI examinations, a total of 8 malignancies

were detected, for a cancer detection rate of 34.0 per 1,000 examinations. A possible explanation for these high rates is that all women had a history of *premenopausal* breast cancer and 3.1% (4/131) of them tested positive for a genetic mutation. The authors concluded that *women with a personal history of premenopausal breast cancer only are at a similar risk level as those with additional family history for the development of subsequent breast cancer*.

Brennan et al. [30] also found a higher cancer yield compared to other studies. Of 144 women with a PHBC but without family history who underwent screening MRI, biopsies revealed malignancies in 17 (11.8%), 10 of which were detected by MRI only. By comparison, in women with both a PHBC and family history of breast cancer, MRI detected malignancies in 14.7% (20/136). The higher cancer yield in this study may be explained, in part, by the inclusion of multiple years and examinations.

In a single-institution study on screening MRI outcomes in routine clinical practice [42], the cancer detection rate was 30.1 per 1,000 examinations (11/365) in women with a PHBC, compared to 16.3 per 1,000 examinations (6/367) in women with a family history of breast cancer. The authors concluded that the performance of screening MRI in women with a PHBC is promising and suggested that MRI may be an important tool for supplemental screening in this population.

21.3.2 Tumor Characteristics

In one of the largest studies mentioned above [39], the mean size of invasive cancers in the group of 915 MRI-screened women with a PHBC but without genetic risk or family history was 9 mm (range 1–18 mm), and all were node negative. These results, which demonstrate that screening MRI can identify cases that would benefit from earlier detection, are comparable to those of other studies in women with a PHBC. In the study by Gweon et al. [34], all ten cancers detected by screening MRI in women with a PHBC were node-negative T1 invasive cancers (mean tumor size of 8 mm, range 4–14 mm) or DCIS. In a review of 47 MRI-guided biopsies in 46 women with a PHBC (and no additional risk factors) [33], more than half of cancers detected by MRI were DCIS (55.6%, 5/9). In the study by Brennan et al. [30], 10 of 17 cancers (58.8%) detected by MRI were minimal cancers (DCIS or node-negative invasive breast cancers less than 1 cm in size). The ten cancers detected by MRI only (versus seven later found to have correlates on mammography and/or US) were more likely to be minimal breast cancers.

In the aforementioned studies, the vast majority of cancers were DCIS or node-negative T1 invasive cancers. However, Destounis et al. [38] reported that two of seven MRI-detected malignancies in women with a PHBC had axillary metastases. In women with a PHBC and family history of breast cancer, one of eight malignancies had axillary metastases. As mentioned above, a possible explanation for the higher rate of nodal disease in this study may be patient selection, in that all women had a history of *premenopausal* breast cancer and 3.1% (4/131) of them tested positive for a genetic mutation.

21.3.3 Potential Harms Associated with Screening MRI

The high sensitivity of breast MRI makes it suitable to be used as an adjunct screening test in women with a PHBC. However, false positives are not negligible and could prompt a large number of benign biopsies with their associated costs in time, anxiety, and patient morbidity, in addition to their economic burden. (Other issues related to the potential harms from contrast material administration are discussed in Chap. 7.) However, *in one of the largest studies on the use of MRI for screening women with a PHBC* [39], *false positives were significantly lower in the group of women with a PHBC than in the group of women with genetic risk or family history of breast cancer* (113/915 [12.3%] versus 131/606 [21.6%], $p < 0.001$), accompanied by a significantly higher specificity (841/895 [94.0%] versus 509/592 [86.0%], $p < 0.001$). One possible explanation could be that women in the PHBC group were more likely to have a comparison MRI examination; however, the lower false-positive

rate was maintained when considering only those patients without a prior MRI examination [39]. The authors also suggested that *the effects of treatment could lead to easier MRI interpretation in patients with a PHBC*. For example, radiation treatment and hormonal treatment decrease the background parenchymal enhancement, which could lead to less uncertainty regarding suspicious areas of enhancement versus normal physiological background parenchymal enhancement.

In the study by Gweon et al. [34] including 607 women who underwent breast-conserving surgery, had negative mammography and US examinations, and underwent single-round screening MRI, 94 (15.5%) MRI examinations were given a final assessment category of BI-RADS 3, 23 (3.8%) BI-RADS 4, and 0 (0%) BI-RADS 5. The overall PPV of biopsy was 43.5% (10/23). Nearly 92% (557/607) of patients in this study had undergone preoperative MRI, which may have improved the positive biopsy rate.

In a retrospective review of 130 MRI-guided biopsies in 46 women with a PHBC (and no additional risk factors) versus 81 women with familial risk only [33], there was a non-significant higher malignancy risk in the PHBC group (9/47 lesions, 19.1%) than the familial risk group (11/83 lesions, 13.3%). Thus, the pathology results of the MRI-guided biopsies were benign in 80.9% (38/47) of the PHBC group and 86.7% (72/83) of the familial risk group. Given that no significant difference was found between the two groups, the authors called into question the assumption that screening women at lower risk might result in an increased frequency of false-positive biopsy results. Similarly, in the study by Destounis et al. [38], 22 percutaneous and surgical biopsies were performed in women with a personal history of premenopausal breast cancer, 7 of which demonstrated malignancy (7/22, 31.8%). By comparison, 33 biopsies were performed in women with a personal history of premenopausal breast cancer plus family history, 8 of which revealed malignancy (8/33, 24.2%).

In the study by Elmore and Margenthaler [31] including 141 women who underwent 202 surveillance breast MRI examinations following curative-intent treatment for breast cancer, 6 biopsies were performed, 2 of which revealed invasive breast cancers (for a PPV of biopsy of 33.3%). Brennan et al. [30] reported that 30.6% (44/144) of their previously treated cancer patients who underwent screening MRI had findings prompting biopsy, with a range of one to five biopsies performed per patient and 27.9% (17/61) of total biopsies with malignant pathology. In addition, 40.3% (58/144) of their patients underwent short-term follow-up studies.

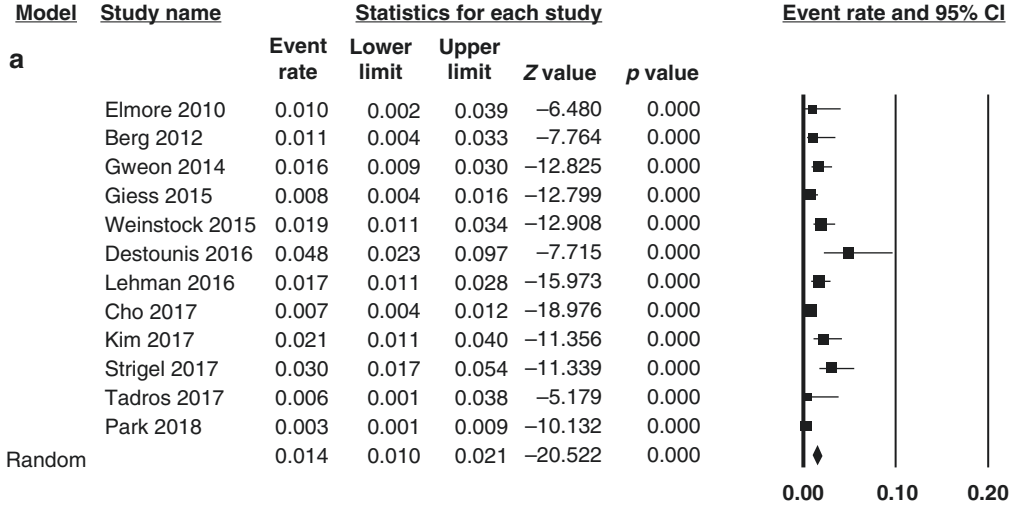
In a study from the Breast Cancer Surveillance Consortium on breast biopsy intensity and findings following screening mammography and screening MRI in women with and without a PHBC [45], the authors reported that women with and without a PHBC who undergo screening MRI experience higher biopsy rates and lower cancer yield from biopsy, compared with screening mammography alone. The higher biopsy rates and lower cancer yield following MRI were not explained by age or 5-year breast cancer risk. The authors concluded that further work is needed to identify women who would benefit from screening MRI in order to ensure an acceptable benefit-to-harm ratio.

21.3.4 Summary of the Evidence on Screening MRI in Women with a PHBC

Table 21.1 summarizes the main characteristics of the above cited articles, with a sample size ranging from 46 [33] to 1,044 [44] women and 46 [33] to 2,065 [40] examinations, for a total of 5,428 women and 7,752 examinations.

The studies have been pooled together using meta-analytic methods; one study [35] was excluded, as the relevant performance metrics were not reported. For each of the three indices of diagnostic performance discussed (cancer detection rate, sensitivity, and PPV of biopsy prompted by MRI), we report below (1) a forest plot, showing the among-study heterogeneity (I^2 statistics, considered as substantial when larger than 50%) together with the pooled estimation obtained with either the fixed-effect or the random-effect models, and (2) a funnel plot, providing a visual inspection of the risk of publication bias together with the Egger test for significance.

Cancer detection rate. The cancer detection rate was provided by 12 of the 14 studies [31, 32, 34, 36–44]. It showed substantial heterogeneity (I^2 = 71%) among studies, ranging from 3 per 1,000 examinations [44] to 48 per 1,000 examinations [38]. The forest plot is shown in Fig. 21.8a, reporting a pooled estimation of 14 per 1,000 examinations (95% CI, 10 per 1,000 to 21 per 1,000) obtained using the random-effect model. At visual inspection, the funnel plot (Fig. 21.8b) does not show any risk of publication bias, as confirmed by the Egger test (p = 0.398). For comparison, based on a review article about the role of MRI in breast cancer screening, the



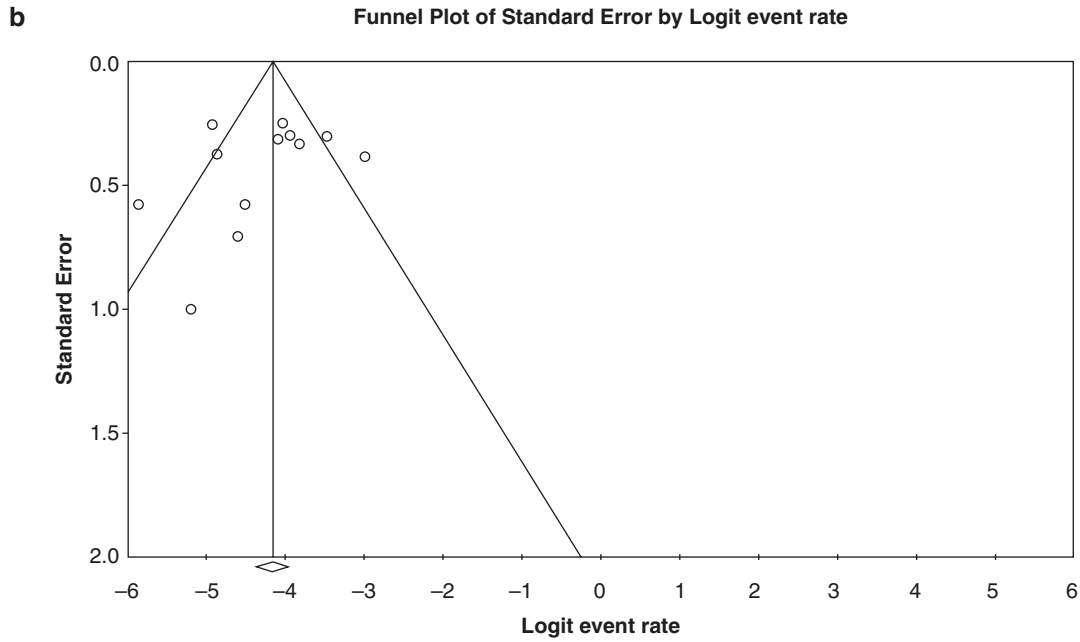


Fig. 21.8 (**a**) Forest plot of 12 studies on the cancer detection rate by screening MRI in women with a PHBC. Data are substantially heterogeneous (I^2 = 71%). Using the random-effect model, the pooled estimation is 14 per 1,000 examinations (95% CI, 10 per 1,000 to 21 per 1,000). (**b**) Funnel plot of 12 studies on the cancer detection rate by screening MRI in women with a PHBC. It shows low risk of publication bias, as confirmed by the Egger test (p = 0.398)

cancer yield from MRI alone in women at high risk for breast cancer according to ACS and NCCN guidelines averaged 22 cancers per every 1,000 women screened [46].

Sensitivity. Sensitivity of MRI in this setting was reported in 8 of 14 studies [30, 32, 34, 37, 39–41, 44]. It showed no heterogeneity ($I^2 = 0\%$) among studies, ranging from 75% [32, 44] to 100% [30]. The forest plot is shown in Fig. 21.9a, reporting a pooled estimation of 84% (95% CI, 74–90%) obtained using the fixed-effect model. At visual inspection, the funnel plot (Fig. 21.9b) does not show any risk of publication bias, as confirmed by the Egger test ($p = 0.362$). For comparison, based on a review article about the role of MRI in breast cancer screening, the sen-

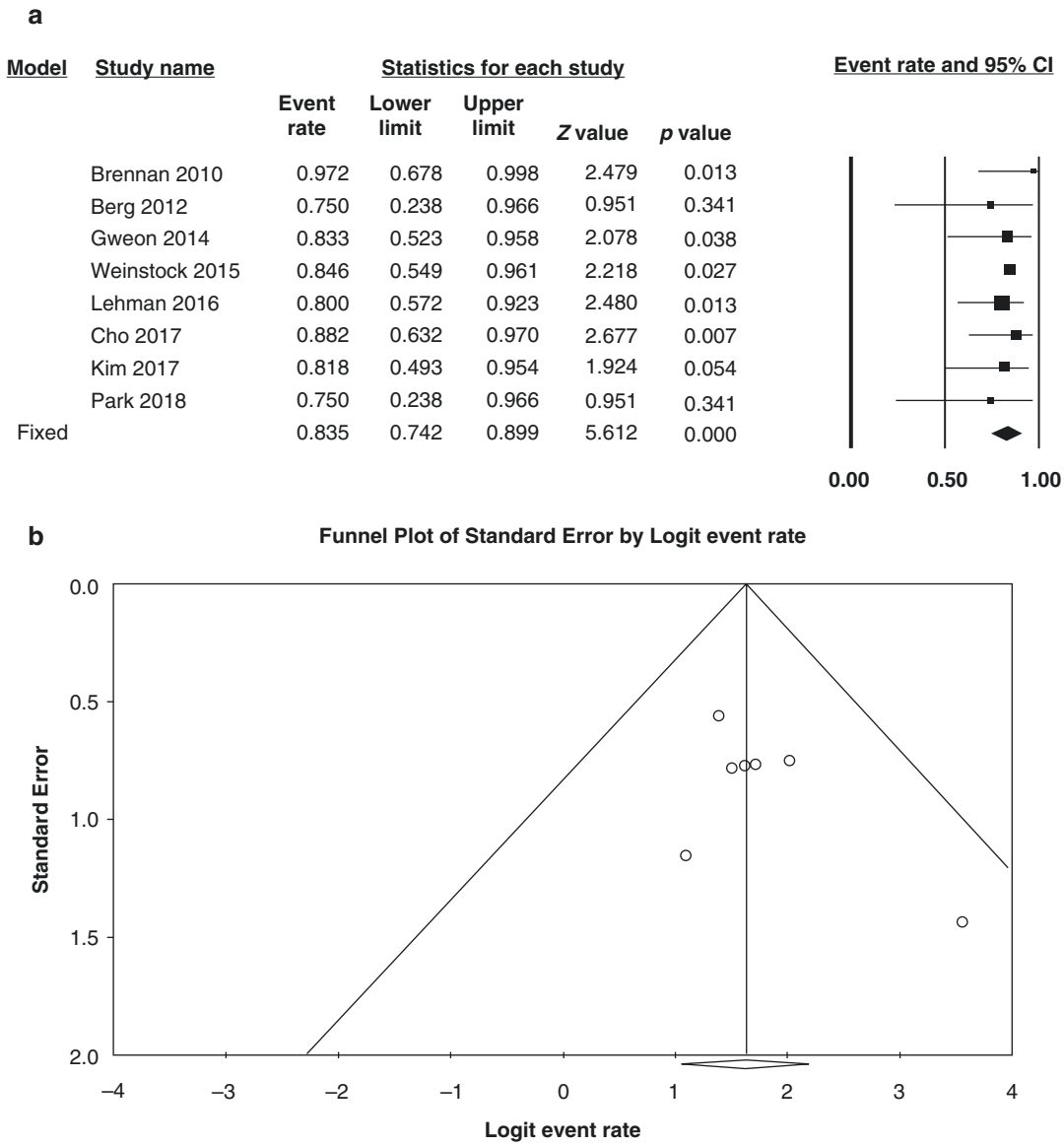


Fig. 21.9 (**a**) Forest plot of eight studies on the sensitivity of screening MRI in women with a PHBC. Data show no heterogeneity ($I^2 = 0\%$). Using the fixed-effect model, the pooled estimation is 84% (95% CI, 74–90%). (**b**) Funnel plot of eight studies on the sensitivity of screening MRI in women with a PHBC. It shows low risk of publication bias, as confirmed by the Egger test ($p = 0.362$)

sitivity of screening MRI in women at high risk for breast cancer according to ACS and NCCN guidelines ranges from 71% to 100% [46]. The suggested sensitivity benchmark for screening MRI in the fifth edition of the *BI-RADS Atlas* is greater than 80% [47].

Positive predictive value of biopsy prompted by MRI. The PPV of biopsy prompted by MRI in this setting was reported in 13 of 14 studies [30–34, 37–44]. It showed no heterogeneity (I^2 = 0%) among studies, ranging from 10% [43] to 44% [34]. The forest plot is shown in Fig. 21.10a,

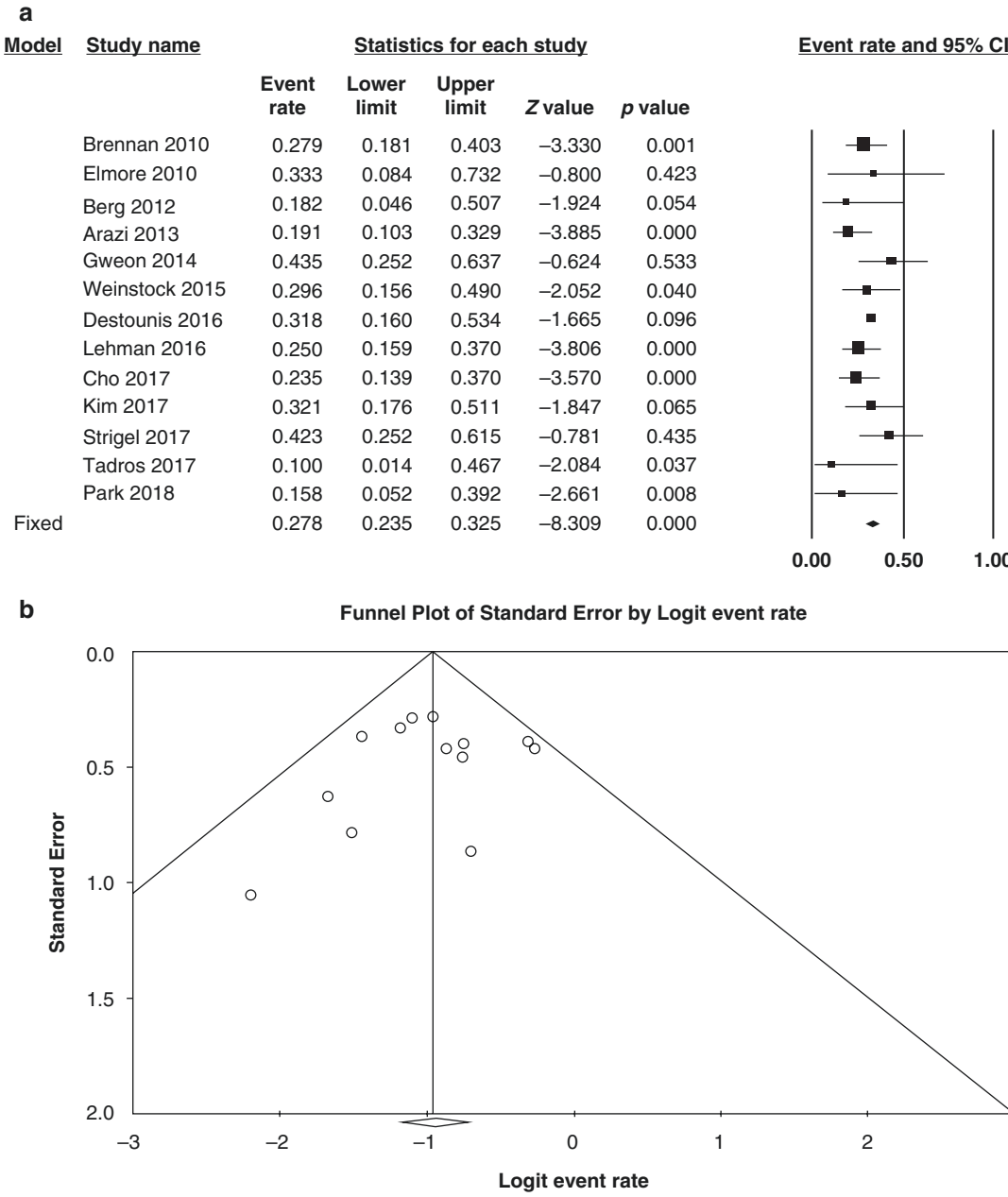


Fig. 21.10 (**a**) Forest plot of 13 studies on the positive predictive value of biopsy prompted by MRI in women with a PHBC. Data show no heterogeneity (I^2 = 0%). Using the fixed-effect model, the pooled estimation is 28% (95% CI, 24–33%). (**b**) Funnel plot of 13 studies on the positive predictive value of biopsy prompted by MRI in women with a PHBC. It shows low risk of publication bias, as confirmed by the Egger test (p = 0.541)

reporting a pooled estimation of 28% (95% CI, 24–33%) obtained using the fixed-effect model. At visual inspection, the funnel plot (Fig. 21.10b) does not show any risk of publication bias, as confirmed by the Egger test ($p = 0.541$). For comparison, the PPV in women at high risk for breast cancer according to ACS and NCCN guidelines ranges from 17% to 89% [46]. The suggested PPV benchmark for screening MRI in the fifth edition of the *BI-RADS Atlas* is 20% to 50% [47].

21.4 Future Research on Specific Subgroups of Women

Preliminary research suggests that certain subgroups of women with a PHBC would most benefit from MRI surveillance, and surveillance regimens could thus be tailored to a woman's individual second breast cancer risk [48]. In the study by Gweon et al. (with women who were treated with breast-conserving surgery, had negative mammography and US examinations, and underwent subsequent screening MRI) [34], independent factors associated with MRI-detected cancers at multivariate logistic regression analysis were *age younger than 50 at first diagnosis and interval between initial surgery and screening MRI longer than 24 months*. An analytic model also suggested that all women treated with breast-conserving surgery and with a first diagnosis at or before age 50 would meet the 20% threshold of lifetime risk prompting surveillance MRI [49].

In a retrospective review of women with a PHBC, personal history of a high-risk lesion, and/or dense breasts who did not qualify for the provincial high-risk screening program [50], annual screening MRI detected 15 cancers, all but 1 of which was mammographically occult, for a cancer detection rate of 56.4 per 1,000 examinations (15/266). The authors suggested that screening MRI should be considered in women with a combination of these risk factors, particularly if they have a family history of breast cancer and are not on anti-estrogen therapy [50].

In a study from the Breast Cancer Surveillance Consortium [51], the risk of interval invasive second breast cancers was highest in women younger than 40 years of age at first breast cancer diagnosis, those with extremely dense breasts, those with a first-degree family history of breast cancer, and those treated with lumpectomy without radiation. Lee et al. [52], also from the Breast Cancer Surveillance Consortium, found that independent predictors of interval invasive second breast cancers included grade II primary breast cancer, treatment with lumpectomy without radiation, interval primary breast cancer presentation, and heterogeneously dense breasts on mammography. The authors suggested that selective application of supplemental screening, such as with MRI, in patients with the aforementioned risk factors could reduce interval invasive second breast cancers [52].

In a study among non-mutation carriers with a PHBC, the risk of developing contralateral breast cancer was associated with a family history of breast cancer, particularly for women less than 45 years of age with first-degree relatives affected at young ages or with first-degree relatives with bilateral disease [16]. A statistical model for contralateral breast cancer risk in women with a PHBC, developed using information from the Breast Cancer Surveillance Consortium and Surveillance, Epidemiology, and End Results databases, found that factors such as age at first breast cancer diagnosis, family history of breast cancer, and breast density were significantly associated with contralateral breast cancer [53]. Tumor receptor status of a patient's first breast cancer has also been correlated with the risk of new or recurrent breast cancer [54, 55].

Further research is needed to define populations most likely to benefit from screening MRI. At this time, practices vary widely, with some centers basing surveillance decisions on young age, increased breast density, and/or mammographically occult primary cancer, and others emphasizing future risk of breast cancer events [56]. In addition, while studies have found MRI to be cost-effective in patients with *BRCA* mutations and in other high-risk women [57, 58], the cost-effectiveness of MRI surveillance in patients with a PHBC, in the absence of *BRCA* mutations or other high-risk characteristics, has not been similarly described.

21.5 Challenges of Access to and Health System Coverage of Screening MRI

There is wide variation by practices with regard to which women are recommended to undergo MRI surveillance. In addition, there is overall low engagement in screening MRI among all women at increased risk for breast cancer. Data collected from five national Breast Cancer Surveillance Consortium registries showed that, over a 5-year period, less than 5% of women with greater than 20% lifetime breast cancer risk underwent screening MRI [59]. In a prospective cohort of 64,659 women presenting for mammographic screening at a single high-volume clinic, less than 15% of women with a lifetime risk of or greater than 20% underwent screening MRI within 1 year, despite a written recommendation by the radiologist [60]. *Reasons for refusal include claustrophobia, time and financial concerns, a physician that would not provide referral or did not believe MRI was indicated, and lack of patient interest* [61]. An additional reason could be lack of availability of MRI facilities outside of urban areas [59]. Moreover, not all insurers reimburse for breast MRI, even when it is recommended by the ACS (such as for women with a lifetime breast cancer risk of approximately 20–25% or greater). In a multi-site clinical trial in the United States studying women at intermediate or high risk for breast cancer, participating centers received no payment or only a partial payment (up to $500) for 48% of MRI examinations that were initially billed to insurance [61]. Women without insurance could be billed more than $2,000 for an examination, and additional costs could arise from follow-up MRI examinations or MRI-guided biopsies. Although costs are lower in Europe, coverage varies across countries, and access to screening MRI remains a global challenge [62].

21.6 Conclusions

Women with a PHBC are at increased risk for future breast cancer events, and the early detection of recurrence significantly improves long-term survival, thus warranting surveillance in this patient population. Current guidelines by the ACS and NCCN recommend neither for or against screening MRI in women with a PHBC due to insufficient evidence regarding the risk-to-benefit ratio. However, since those guidelines were issued, several studies have demonstrated that women with a PHBC may be appropriate candidates for MRI surveillance in view of the high detection rate for small node-negative invasive cancers and the acceptable PPV of biopsy. Breast cancer patients face challenging decisions related not only to treatment but also to methods for post-treatment surveillance, and evidence about the benefits and harms of screening MRI can inform decision-making regarding effective options for surveillance.

Further research on the role of screening MRI in women with a PHBC will require creative strategies for study design, data collection, and data sharing. Given the potential advantage of adding MRI to mammography in high-risk groups, traditional study designs with randomization may be problematic (see Chap. 15). Study design strategies that make use of surrogate markers and historic controls may be more practical and feasible. Multicenter studies could allow for more efficient data accumulation in this specific population. An international cooperation is also desirable for meta-analyses that could bring a higher level of evidence to the breast cancer specialist community.

References

1. Berry DA, Cronin KA, Plevritis SK et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators (2005) N Engl J Med 353:1784–1792
2. Cancer.Net. https://www.cancer.net/cancer-types/breast-cancer/statistics. Accessed 30 Jun 2020
3. Fisher S, Gao H, Yasui Y, Dabbs K, Winget M (2015) Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system. Ann Oncol 26:1161–1169
4. Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Nygård JF (2015) Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: a registry-based follow-up study of

Norwegian women primary operated between 1998 and 2008. Ann Surg Oncol 22:3836–3845
5. Yu XQ, De Angelis R, Luo Q, Kahn C, Houssami N, O'Connell DL (2014) A population-based study of breast cancer prevalence in Australia: predicting the future health care needs of women living with breast cancer. BMC Cancer 14:936
6. Breast Cancer Research Foundation. https://www.bcrf.org/breast-cancer-statistics. Accessed 30 Jun 2020
7. AIRTUM Working Group (2014) Italian cancer figures, report 2014: prevalence and cure of cancer in Italy. Epidemiol Prev 38(Suppl 1):1–122
8. Houssami N, Abraham LA, Miglioretti DL et al (2011) Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. JAMA 305:790–709
9. Elder EE, Kennedy CW, Gluch L et al (2006) Patterns of breast cancer relapse. Eur J Surg Oncol 32:922–927
10. Saphner T, Tormey DC, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738–2746
11. Kreike B, Hart AA, van de Velde T et al (2008) Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. Int J Radiat Oncol Biol Phys 71:1014–1021
12. Freedman GM, Anderson PR, Hanlon AL, Eisenberg DF, Nicolaou N (2005) Pattern of local recurrence after conservative surgery and whole-breast irradiation. Int J Radiat Oncol Biol Phys 61:1328–1336
13. Montgomery DA, Krupa K, Jack WJ et al (2007) Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. Br J Cancer 96:1802–1807
14. Smith TE, Lee D, Turner BC, Carter D, Haffty BG (2000) True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Radiat Oncol Biol Phys 48:1281–1289
15. Montgomery DA, Krupa K, Cooke TG (2009) Locoregional relapse after breast cancer: most relapses occur late and are not clinically detected. Breast J 15:163–167
16. Reiner AS, John EM, Brooks JD et al (2013) Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol 31:433–439
17. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C et al (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707–1716
18. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
19. Bucchi L, Belli P, Benelli E et al (2016) Recommendations for breast imaging follow-up of women with a previous history of breast cancer: position paper from the Italian Group for Mammography Screening (GISMa) and the Italian College of Breast Radiologists (ICBR) by SIRM. Radiol Med 121:891–896
20. Houssami N, Ciatto S, Martinelli F, Bonardi R, Duffy SW (2009) Early detection of second breast cancers improves prognosis in breast cancer survivors. Ann Oncol 20:1505–1510
21. Dao TH, Rahmouni A, Campana F, Laurent M, Asselain B, Fourquet A (1993) Tumor recurrence versus fibrosis in the irradiated breast: differentiation with dynamic gadolinium-enhanced MR imaging. Radiology 187:751–755
22. Heywang-Köbrunner SH, Schlegel A, Beck R et al (1993) Contrast-enhanced MRI of the breast after limited surgery and radiation therapy. J Comput Assist Tomogr 17:891–900
23. Viehweg P, Heinig A, Lampe D, Buchmann J, Heywang-Köbrunner SH (1998) Retrospective analysis for evaluation of the value of contrast-enhanced MRI in patients treated with breast conservative therapy. MAGMA 7:141–152
24. Saslow D, Boetes C, Burke W et al (2007) American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75–89
25. Bevers TB, Anderson BO, Bonaccio E et al; National Comprehensive Cancer Network (2009) NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. J Natl Compr Cancer Netw 7:1060–1096
26. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA (2018) Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol 15(3 Pt A):408–414
27. Sardanelli F, Boetes C, Borisch B et al (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 46:1296–1316
28. Khatcheressian JL, Hurley P, Bantug E et al (2013) Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 31:961–965
29. Morris EA, Liberman L, Ballon DJ et al (2003) MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol 181:619–626
30. Brennan S, Liberman L, Dershaw DD, Morris E (2010) Breast MRI screening of women with a personal history of breast cancer. AJR Am J Roentgenol 195:510–516
31. Elmore L, Margenthaler JA (2010) Breast MRI surveillance in women with prior curative-intent therapy for breast cancer. J Surg Res 163:58–62

32. Berg WA, Zhang Z, Lehrer D et al (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
33. Arazi-Kleinman T, Skair-Levy M, Slonimsky E et al (2013) Journal Club: Is screening MRI indicated for women with a personal history of breast cancer? Analysis based on biopsy results. AJR Am J Roentgenol 201:919–927
34. Gweon HM, Cho N, Han W et al (2014) Breast MR imaging screening in women with a history of breast conservation therapy. Radiology 272:366–373
35. Schacht DV, Yamaguchi K, Lai J, Kulkarni K, Sennett CA, Abe H (2014) Importance of a personal history of breast cancer as a risk factor for the development of subsequent breast cancer: results from screening breast MRI. AJR Am J Roentgenol 202:289–292
36. Giess CS, Poole PS, Chikarmane SA, Sippo DA, Birdwell RL (2015) Screening breast MRI in patients previously treated for breast cancer: diagnostic yield for cancer and abnormal interpretation rate. Acad Radiol 22:1331–1337
37. Weinstock C, Campassi C, Goloubeva O et al (2015) Breast magnetic resonance imaging (MRI) surveillance in breast cancer survivors. Springerplus 4:459
38. Destounis S, Arieno A, Morgan R (2016) Personal history of premenopausal breast cancer as a risk factor for referral to screening breast MRI. Acad Radiol 23:353–357
39. Lehman CD, Lee JM, DeMartini WB et al (2016) Screening MRI in women with a personal history of breast cancer. J Natl Cancer Inst 108. pii: djv349
40. Cho N, Han W, Han BK et al (2017) Breast cancer screening with mammography plus ultrasonography or magnetic resonance imaging in women 50 years or younger at diagnosis and treated with breast conservation therapy. JAMA Oncol 3:1495–1502
41. Kim EJ, Kang BJ, Kim SH, Youn IK, Baek JE, Lee HS (2017) Diagnostic performance of and breast tissue changes at early breast MR imaging surveillance in women after breast conservation therapy. Radiology 284:656–666
42. Strigel RM, Rollenhagen J, Burnside ES et al (2017) Screening breast MRI outcomes in routine clinical practice: comparison to BI-RADS benchmarks. Acad Radiol 24:411–417
43. Tadros A, Arditi B, Weltz C, Port E, Margolies LR, Schmidt H (2017) Utility of surveillance MRI in women with a personal history of breast cancer. Clin Imaging 46:33–36
44. Park VY, Kim EK, Kim MJ, Moon HJ, Yoon JH (2018) Breast magnetic resonance imaging for surveillance of women with a personal history of breast cancer: outcomes stratified by interval between definitive surgery and surveillance MR imaging. BMC Cancer 18:91
45. Buist DSM, Abraham L, Lee CI et al (2018) Breast biopsy intensity and findings following breast cancer screening in women with and without a personal history of breast cancer. JAMA Intern Med 178:458–468
46. Lehman CD, Smith RA (2009) The role of MRI in breast cancer screening. J Natl Compr Cancer Netw 7:1109–1115
47. Sickles EA, D'Orsi CJ (2013) ACR BI-RADS® follow-up and outcome monitoring. In: American College of Radiology (2013) Breast Imaging Reporting and Data System® (BI-RADS®). 5th edition. American College of Radiology, Reston, VA, USA, pp 1–73
48. Lam DL, Houssami N, Lee JM (2017) Imaging surveillance after primary breast cancer treatment. AJR Am J Roentgenol 208:676–686
49. Punglia RS, Hassett MJ (2010) Using lifetime risk estimates to recommend magnetic resonance imaging screening for breast cancer survivors. J Clin Oncol 28:4108–4110
50. Nadler M, Al-Attar H, Warner E et al (2017) MRI surveillance for women with dense breasts and a previous breast cancer and/or high risk lesion. Breast 34:77–82
51. Houssami N, Abraham LA, Kerlikowske K et al (2013) Risk factors for second screen-detected or interval breast cancers in women with a personal history of breast cancer participating in mammography screening. Cancer Epidemiol Biomark Prev 22:946–961
52. Lee JM, Buist DS, Houssami N et al (2015) Five-year risk of interval-invasive second breast cancer. J Natl Cancer Inst 107. pii:djv109
53. Chowdhury M, Euhus D, Onega T, Biswas S, Choudhary PK (2017) A model for individualized risk prediction of contralateral breast cancer. Breast Cancer Res Treat 161:153–160
54. Kurian AW, McClure LA, John EM, Horn-Ross PL, Ford JM, Clarke CA (2009) Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst 101:1058–1065
55. Saltzman BS, Malone KE, McDougall JA, Daling JR, Li CI (2012) Estrogen receptor, progesterone receptor, and HER2-neu expression in first primary breast cancers and risk of second primary contralateral breast cancer. Breast Cancer Res Treat 135:849–855
56. Hegde JV, Wang X, Attai DJ et al (2017) Predictors associated with MRI surveillance screening in women with a personal history of unilateral breast cancer but without a genetic predisposition for future contralateral breast cancer. Breast Cancer Res Treat 166:145–156
57. Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J (2009) Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol 6:171–179
58. Cott Chubiz JE, Lee JM, Gilmore ME et al (2013) Cost-effectiveness of alternating magnetic resonance

imaging and digital mammography screening in BRCA1 and BRCA2 gene mutation carriers. Cancer 119:1266–1276
59. Wernli KJ, DeMartini WB, Ichikawa L et al (2014) Patterns of breast magnetic resonance imaging use in community practice. JAMA Intern Med 174:125–132
60. Brinton JT, Barke LD, Freivogel ME, Jackson S, O'Donnell CI, Glueck DH (2012) Breast cancer risk assessment in 64,659 women at a single high-volume mammography clinic. Acad Radiol 19:95–99
61. Berg WA, Blume JD, Adams AM et al (2010) Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666. Radiology 254:79–87
62. Mann RM, Balleyguier C, Baltzer PA et al; European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition (2015) Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 25:3669–3678

22 Breast MRI Screening for the Intermediate Risk: An Open Issue

Sylvia H. Heywang-Köbrunner and Astrid Hacker

Abbreviations

ACS	American Cancer Society
ADH	Atypical ductal hyperplasia
ALH	Atypical lobular hyperplasia
DCIS	Ductal carcinoma in situ
EUSOBI	European Society of Breast Imaging
IARC	International Agency for Research on Cancer
LCIS	Lobular carcinoma in situ
LN	Lobular neoplasia
MRI	Magnetic resonance imaging
US	Ultrasound, ultrasonography

22.1 Introduction

Contrast-enhanced magnetic resonance imaging (MRI) has proven to be the most sensitive imaging modality for detecting breast cancer in women at high risk. First evidence is emerging, which indicates that in women with *BRCA1* or *BRCA2* mutation, survival may be improved by intensified screening with MRI and mammography [1]. While, even for women at high risk, conclusive data on mortality reduction are lacking so far, the much higher sensitivity of intensified screening compared to mammography alone or to mammography and ultrasonography (US) has been the reason for scientific societies and guideline development groups, such as the International Agency for Research on Cancer (IARC) of the World Health Organization, the American Cancer Society (ACS), or the European Society of Breast Imaging (EUSOBI), to recommend the use of contrast-enhanced breast MRI for surveillance of high-risk women [2–5]. For women at intermediate risk, data is even more limited, and the above-mentioned international committees so far do not support this indication for MRI screening [2–5].

Thus, to date, mammography screening (sometimes supplemented by US) remains the only method with a proven effect on mortality reduction and the only recommended method. Limitations of mammography screening are, however, known. They become apparent from those cancers which in regular participants of mammography screening are detected at late stages and/or during the interval. It is also known that the percentage of late stages among a screened population inversely correlates with the mortality reduction that can be achieved [6]. The main factors which may influence both stage distribution at detection and interval cancer rate include length of the interval [7], tissue density [8], and the screening method itself.

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In this context, testing MRI screening in women at intermediate risk is a research topic of great interest, since MRI is known to be the most sensitive screening modality and thus promises to optimally complement present imperfect screening schemes. This chapter will give an overview of definitions, existing results, as well as pros and cons of MRI screening in this subset of women, according to the present knowledge.

22.2 Definition of Risk and Intermediate Risk and the Role of Mammographic Density

Intermediate risk of breast cancer is defined as a risk exceeding a 15% lifetime risk of being affected by breast cancer. For comparison, consider that the average lifetime risk of women in industrialized countries to date ranges around 12%, which is approximately equal to one affected woman out of eight.

As expected, the upper limit of the intermediate risk corresponds to the lower limit of "high risk." However, the threshold for transition from intermediate to high risk differs between countries. Most European countries and programs consider a lifetime risk of 30% as the upper limit of "intermediate risk." In the United States, usually a much lower threshold of 20% is used (see Chap. 16 on guidelines). Thus, depending on the definition, 15–25% of the female population might belong to the intermediate-risk subset.

The definition of risk is not trivial. Reasons include significant discrepancies between the existing models for risk calculation and limited population data, on which models can be built. Thus, to date, the predictive capability of all existing models is quite moderate.

The best risk prediction is achieved for predicting whether a woman carries a *BRCA1* or a *BRCA2* deleterious mutation. This risk is, however, not useful for assessing intermediate risk. Many publications are based on the so-called Gail model [9], which today is mostly considered to yield limited accuracy of risk classification. More accurate models like the Tyrer-Cuzick [10], however, require additional data such as body mass index, family history, individual history of breast cancer, and previously biopsy-proven atypical ductal hyperplasia (ADH) or lobular carcinoma in situ (LCIS), which information often is not available. Additional information on mammographic density has been shown to further slightly increase the accuracy of these models [10]. However, for most women at low to intermediate risk, the area under the curve at receiver operating characteristic analysis of these risk models only ranges around 0.5 to 0.6 [9]. Summarizing, risk prediction of all models is so far unreliable. Different risks may be calculated for the same woman when different models are used, and the different models select different groups of women. Thus, optimization of existing models still is a subject of research. Improvements are expected from texture analysis and so-called deep learning from direct analysis of raw data [11].

Overall, the group of women at intermediate risk is quite heterogeneous. It mainly comprises women with:

(a) Personal history of breast cancer or invasive or ductal carcinoma in situ (DCIS)
(b) Biopsy-proven ADH, LCIS, atypical lobular hyperplasia (ALH), or other so-called "risk lesions," which confer an increased risk for breast cancer
(c) Family risk of breast cancer (based on the number of first-, second-, or third-degree relatives affected by breast or ovarian cancer, the age at detection, and the number of unaffected family members) lower than that defined as high risk

Studies concerning the use of MRI in the first group of women were treated in the previous Chap. 21 and will not be considered in this chapter.

Mammographic breast density has also been proposed as one further independent factor of breast cancer risk. Its role as a risk indicator, however, is mostly overestimated. The reason is that many scientists falsely refer to a factor that is calculated from the fraction of risk of women

belonging to the highest breast density class[1] (class 4 or *d*) to that of women at age 40 belonging to the lowest one (class 1 or *a*), which according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) is a rare condition.

Overall both density class 1 (or *a*) and density class 4 (or *d*) occur in only 5–10% of women aged 40–69 years. Considering that 80–85% women have a breast density class 2 or 3 (*b* or *c*), the risk of an average breast should correctly be considered as the reference value, not the rare condition of a 40-year-old woman with little glandular tissue. Compared to the "normal" condition (tissue density class 2 or 3 or *b* or *c*), however, the risk associated with density class 4 (or *d*) only increases by a factor between 1.2 and 1.4. Taking this into account and the large inter- and intra-observer variations of visual density assessment [8], particularly in the normal population with density class 2 or 3 (*b* or *c*), it becomes understandable why mammographic breast density has not proven to be a "strong" indicator of risk in most multivariate statistical analyses.

However, density is an acknowledged factor that indicates the risk of masking. Masking describes the fact that cancers which do not contain microcalcifications (approximately 50–70% of breast cancers) might partly be hidden by surrounding tissue depending on the distribution of the surrounding tissue and its overall volume, the location, size and the morphology of the lesion itself. The risk of masking correlates with the risk of experiencing an interval cancer, which increases with increasing mammographic density [12, 13].

22.3 MRI Screening Studies in Women at Intermediate Risk

Published data on MRI screening at intermediate risk largely include patients examined by state-of-the-art contrast-enhanced MRI. Examinations were performed at 1.5 T, using three-dimensional dynamic fast gradient-echo sequences, which are applied before and several times after intravenous injection of a gadolinium-based contrast agent. Each sequence takes about 1–2 min, and a time period of 6–10 min after injection is usually covered. Of note, data before 2006 may have included slower pulse sequences that, combined with less developed algorithms for image interpretation, may have led to a somewhat lower specificity in the early studies (the reader can find an extended discussion about specificity of MRI in Chap. 3).

The comparisons of the existing studies usually imply a comparison between MRI plus conventional imaging (MRI group) and conventional imaging alone (non-MRI group).

We will discuss the topic for the following risk groups:

1. Women with biopsy-proven ADH, LCIS, ALH, or other so-called risk lesions
2. Women with an intermediate family risk of breast cancer
3. Women with dense tissue at elevated risk

22.3.1 MRI for Screening Women with a Previous Diagnosis of ADH or Other Risk Lesions

These lesions belong to a group of pathological entities classified as "benign but of unknown malignant potential."

ADH is histologically a borderline breast lesion that shows cellular changes similar to low-grade DCIS but concerns a very small volume of tissue. LCIS and ALH, are often considered together using the term lobular neoplasia (LN). They represent lobular proliferations with absence of e-cadherin staining. Both entities are often multifocal (60–85%) or bilateral (30–67%). They are non-obligate precursors of breast cancer. Both ADH and LCIS (LN) are associated with an increased risk of developing breast cancer also in the other quadrants of the same breast or in the contralateral breast, a risk that is more pronounced for ADH than for LCIS, but always lower than that conferred by a previous diagnosis of DCIS. However,

[1]Most data are based on ACR classifications 1–4. The modified ACR classifications a–d was issued in 2013 by the American College of Radiology (acr.org).

among the lesions with unknown biological potential, ADH and LCIS carry a higher risk than that conferred by the other entities. Cancer rates associated with an ADH or LCIS diagnosis are reported to be increased by a factor of 2–5 compared to the normal population [14–16]. Thus, *depending on other risk factors, women with ADH or LCIS may have an intermediate to high risk of being affected by breast cancer*.

On mammography, ADH is mostly associated with microcalcifications but may occur in soft tissue densities and coexist with other benign or borderline changes. On MRI, ADH is mostly an incidental finding in biopsies performed for enhancing benign lesions such as adenosis, fibroadenomas, papillomas, etc. An example of incidental ADH is shown in Fig. 22.1. The percentage of non-enhancing ADH is unknown.

According to Mara H. Rendi and coworkers [17], most cases of LN are detected by mammography, since they are incidentally detected histopathologically close to microcalcifications (even though LN as pathological finding associated with microcalcifications is less frequent than ADH). If microcalcifications are associated, this mostly indicates a higher histopathological grade and increased risk of breast cancer. On MRI, LN is, like ADH, mostly associated with non-mass or mass enhancement. Neither for ADH nor for LN, any specific enhancement dynamics have been described. An example of an incidental MRI-detected LCIS is shown in Fig. 22.2. Overall, the frequency of ADH or LN in MRI-guided biopsies performed for enhancing changes is comparable to their frequency among lesions undergoing mammography-guided biopsies for microcalcifications [18].

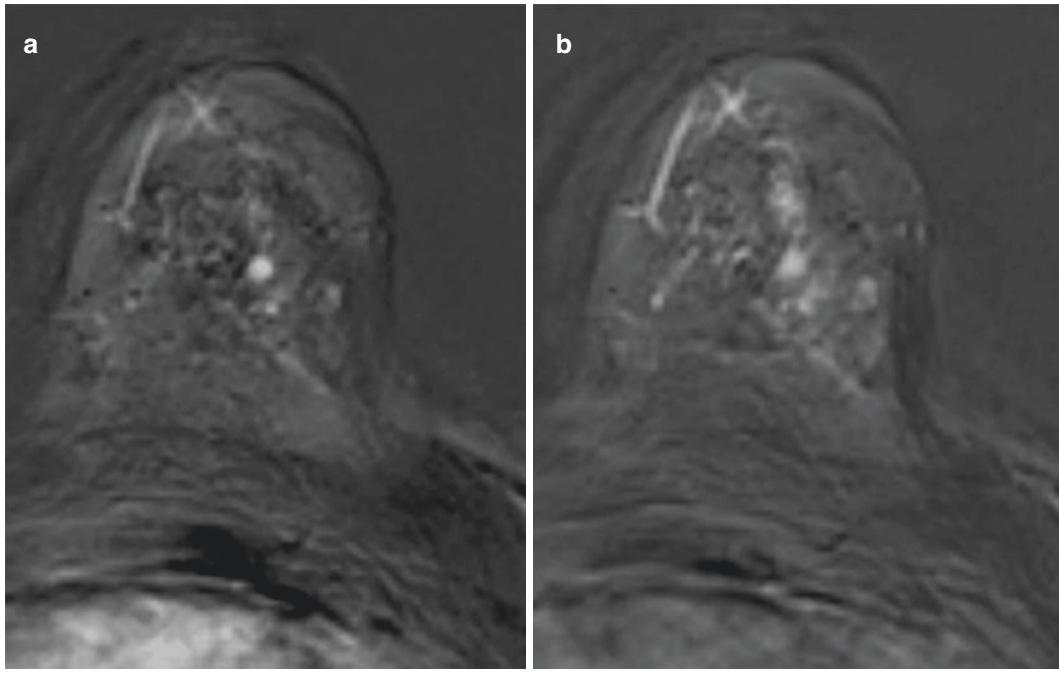

Fig. 22.1 A round 5-mm enhancing lesion was detected in a 58-year-old lady at 6 o'clock. The lady underwent preoperative MRI, since a breast cancer (without microcalcifications) had been confirmed within the very dense tissue in the same breast at 2 o'clock. Her mother had probably been affected by an ovarian or a stomach cancer at age 40. An early subtraction image obtained 1 min after injection of a Gd chelate (**a**) and a later subtraction image (**b**) obtained 4 min after injection show the plateau-type enhancement of this focal round lesion. Since no sonographic or mammographic correlate existed, MRI-guided vacuum-assisted breast biopsy was performed and proved to be focal ADH (surrounded by benign changes with progressive enhancement). The patient eventually underwent mastectomy and reconstruction, since further foci in other quadrants proved to be DCIS. Based on the imaging characteristics, this focus of ADH could not be distinguished from a small malignancy or from other benign focal lesions such as papillomas or fibroadenomas

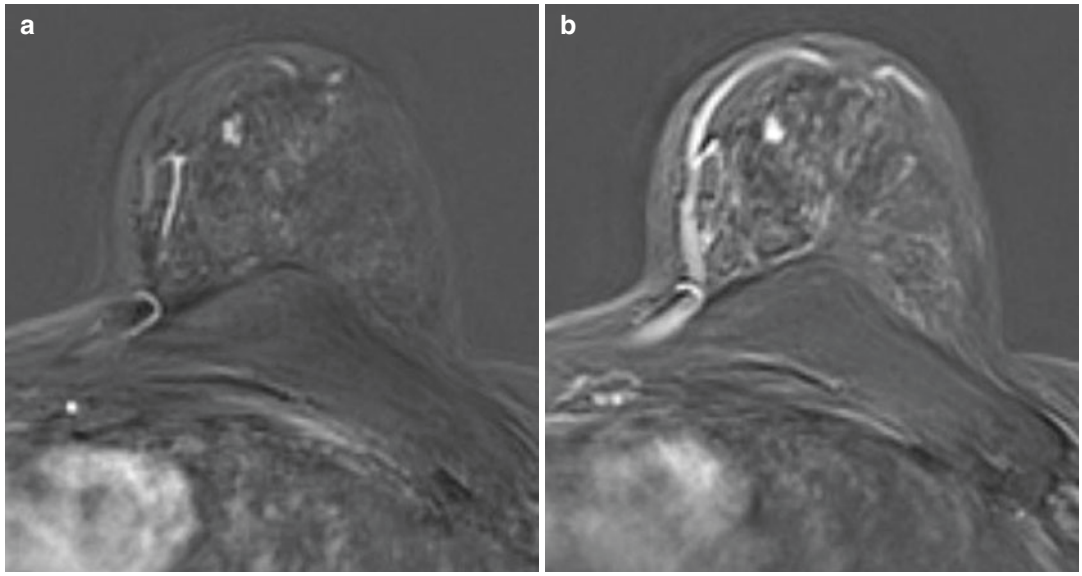

Fig. 22.2 This 49-year-old lady with a family history of one premenopausal breast cancer (aunt) underwent MRI to assess a questionable abnormality within very dense breast tissue, which had been noted mammographically in a different quadrant of the same breast. This index lesion eventually turned out benign. Incidentally, however, the here shown small lobulated 7-mm lesion was detected in the patient's left upper inner quadrant. Comparing the early subtraction image at minute 1 (a) and a late subtraction image at minute 4 (b), it exhibits a delayed enhancement. Due to its morphology and absence of any mammographic or US correlating lesion, MRI-guided vacuum-biopsy was performed to assess this delayed enhancing focal lesion. Histology proved a focal area of classical LCIS. Excision proved further very small areas of LCIS in the surroundings, which were occult by all imaging modalities. Further MRI surveillance for over 3 years has not shown any further significant change or sign of malignancy

So far five studies have been published concerning MRI screening in women with biopsy-proven LCIS or ADH [19–23]. All these studies are retrospective evaluations.

The first published study on this subject by Elisa Rush Port and coworkers [19] is a retrospective evaluation of surveillance in women with a previous diagnosis of LCIS or atypical hyperplasia. The authors report the results of MRI surveillance (in addition to mammography) with 478 examinations in 182 women from April 1999 to July 2005 and compare them with the results in 196 women who underwent usual surveillance with yearly mammography and clinical breast examination (no US) as a control group. Notably, those who had MRI were significantly younger with a significantly stronger family history of breast cancer. For the MRI group, they report 6 MRI-detected malignancies (corresponding to a detection rate of 1.2% cancers in 478 examinations). They mention that none of the six cancers was visible on a "recent" mammogram. However, the time span between the MRI and the recent mammogram is not exactly indicated. Furthermore, they report two interval cancers (stages I and II) in the MRI group. In the control group of 196 women only examined by mammography and clinical breast examination, 8 screen-detected cancers and no interval cancers were reported. Thus the detection rates between these two groups did not differ significantly. Two DCIS were seen only in the MRI group. For the invasive cancers, no significant difference existed concerning stage at detection. Screening MRI was associated with a high biopsy rate of 11.5%, and in 9.6% of the women, biopsies were initiated by MRI only. After 5 years, on average, 25% of the women undergoing MR screening had received a recommendation for biopsy, and 48% of the women had once received a recommendation for short-term follow-up.

Lauren C. Friedlander and coworkers [20] reported on 133 women with LCIS, who had undergone 307 MRI studies from 1996 to 2009 and whose data were evaluated retrospectively. They detected 5 cancers in 307 examinations (1.7%). In these women, 27 biopsies (8.8% of the examinations) were recommended immediately plus another 2 biopsies after short-term follow-up, resulting in 29 biopsies in 307 examinations (9.4%). Short-term follow-up was recommended in another 8.8% of women. This retrospective study had no control group and includes no comparison with conventional imaging.

Janice S. Sung and coworkers [21] reported retrospective results of 670 MRI screening examinations in 220 women with a previous diagnosis of LCIS. No control group was available. In these women, MRI and mammography were mostly performed in a somewhat interleaved scheme, and the intervals before MRI and those before mammography were not provided. Thus, the superior cancer yield of MRI (12 cancers detected in 670 examinations, 1.8%) compared to that of mammography (5 in 670, respectively, 0.7%) is somehow difficult to interpret. Biopsy was immediately recommended after MRI in 60/670 (8.9%) of the examinations and in an additional 8 cases (1.2%) at follow-up. Furthermore 6-month follow-up was recommended after MRI at least once in 108 studies (16%). The overall number of follow-up MRI studies amounted to 170 (25.4%) examinations. The biopsy rate reported for mammography was only 3.9% (26/670).

Theresa Schwartz and coworkers [22] retrospectively evaluated 62 screening MRI studies in 48 women with a previous diagnosis of LCIS and 180 screening MRI studies in 131 women with a previous diagnosis of atypia. No control group was available for evaluation. Also, no information is given on additional imaging in these patients. The authors report a cancer yield of 1/62 (1.6%) for the LCIS group and of 2/180 (1.1%) for the atypia group. In the LCIS group, the biopsy rate was 5/62 (8.1%); in the atypia group, the biopsy rate was 14/180 (7.8%). The positive predictive value of biopsy was 20% in the LCIS group and 14% in the atypia group. No information is given on recommendations of short-term follow-up.

Tari A. King and coworkers [23] retrospectively analyzed the results of 455 patients with histology-proven LCIS, who had undergone MRI screening (in addition to conventional imaging), as compared to 321 patients monitored by conventional imaging alone. After a median follow-up of 58 months, they report a comparable cancer detection in the MRI group (61/455 = 13.4%) as compared to the non-MRI group (43/321 = 13.4%). The number of the examinations is not indicated. During the follow-up time, they report a much higher number of biopsies in the MRI group (293 biopsies in 455 women with 157 biopsies only MRI-initiated) as compared to the non-MRI group (47 biopsies in 321 women with 41 biopsies initiated by mammography). Differences between the two groups were identified and concerned age, risk, and density. It is unknown to which degree these differences could influence the results. Overall, the authors point out that no significant difference was noted for the outcome concerning detection rate or stage distribution in both groups; however, side effects (due to the high number of biopsies of benign lesions) were much higher in the MRI group.

22.3.2 MRI Screening of Women with Intermediate Family Risk of Breast Cancer

A positive family history of breast cancer is defined by at least one first- or second-degree family member being affected [24]. Based on data, which demonstrate a more favorable stage distribution among women screened annually [7], annual mammographic screening is mostly recommended in women with an intermediate risk based on family history.

It is worth noting that *in several publications on MRI screening in high-risk women, a variable proportion of women with an intermediate risk*

have been included. While MRI has proven to be very sensitive in women at high risk and particularly valuable in women with proven *BRCA* gene mutation, we are not aware of any publication that evaluates performance of MRI versus conventional imaging or mammography in any prospectively selected group of women at intermediate risk.

22.3.3 MRI Screening of Women with Dense Tissue at Elevated Risk

Wendie A. Berg and coworkers [25] reported a large prospective study (ACRIN 6666) on 612 women with a single additional MRI scan. The group consisted of 22.9% women at high risk (lifetime risk > 25% or mutation carrier or status after chest wall radiation), 44.6% women with a personal history of breast cancer, 29.9% women at intermediate risk (based on Claus or Gail risk calculation) with dense or very dense tissue, and 2.6% women with previous diagnosis of ADH or LCIS.

In this mixed group of 612 women, 16 cancers were detected (during screening and 1-year follow-up). In this (still limited) number of women, MRI proved to be much more sensitive (100%, 95% confidence interval [CI] 79–100%) than the combination of mammography and US (44%, 95% CI 20–70%), and the median size of invasive cancers detected by MRI only (8.5 mm) was smaller than the overall median size (12 mm) recorded in the large main study. This higher sensitivity of MRI plus mammography plus US was, however, associated with a much lower specificity (65.4%), as compared to mammography plus US (84.4%). Also MRI plus mammography plus US was associated with a much higher biopsy rate (13.2%) and a much higher rate of short-term follow-up recommendations (19.6%) as compared to mammography plus US, for which a biopsy rate of 6.2% and a short-term follow-up rate of 4.6% were reported.

22.4 Conclusions and Outlook

To date, the database for MRI screening at intermediate risk is quite limited. Most studies examine mixed populations, which also include women at high risk. From these data, it is impossible to separate the results for women at intermediate risk.

One large prospective study [25], which included 32.5% women at intermediate risk and another 44.6% women with a personal history of breast cancer and which provides ample detailed information, demonstrates a significantly improved sensitivity and detection rate with the addition of MRI for their mixed population. On average invasive tumors appear to be detected at smaller sizes (median size 8.5 versus 12 mm). The observed significant gain of sensitivity was, however, associated with a significant loss of specificity, when comparing MRI plus mammography plus US with mammography plus US. Of note, even though this study is large, these results are only based on 16 cancers. Considering the limited number of cancers and the fact that 22.9% women at high risk (> 25% lifetime risk) and another 44.6% women with a personal history of breast cancer are included in this excellent study with many reported details, effects and side effects cannot be exactly assigned to any of the above subgroups, such as intermediate risk. The study does, however, demonstrate that results for women with a personal history of breast cancer might differ significantly from women without it. Possibly due to the effects of irradiation and anti-hormonal treatment, specificity of MRI proved much better for MRI in patients with a personal history of breast cancer. However, a possibly life-saving effect of MRI (if demonstrable in the future) may eventually be lower in women with a personal history, since survival may strongly be influenced by the stage of detection of the first cancer, its prognosis, and success of therapy.

Thus, so far for women at intermediate risk based on family history and/or breast density, still insufficient information is available. Data

on selected indications like LCIS and ADH have so far been reported in five retrospective studies [19–23].

We should note that retrospective studies are, almost always, associated with many uncertainties, since they are prone to selection and self-selection bias. Patients at increased risk and patients with uncharacteristic symptoms may select to participate in the study group. Due to lacking prospective documentation and due to difficult assessment of the exact effect even of proven bias on the result, retrospective evaluations should be considered to provide low-level evidence. Documented or possible bias concerning MRI versus non-MRI groups includes different risk due to different age range, different risk assessment (based on family history or individual history), and different breast density distribution (which is usually associated with different accuracy of the test method). Additional diagnostic problems or even undocumented symptoms might have led to the decision for MRI. Inclusion of any symptomatic patients could, in fact, most heavily distort the results of any screening study due to the very different pre-test probabilities among symptomatic and asymptomatic women.

Altogether three of the five retrospective studies (two without control group) appear to achieve similar results [20–22] and agree with the results published in the Berg's prospective study: they indicate that additional tumors may be detected by the addition of a screening MRI and report the detection of small tumors by MRI. Another large study with a control group [23], which includes parts of a former study [19], reports no significant size difference between cancers detected in the MRI and the non-MRI group. Also, detection rates were equal in both groups. All five studies report high biopsy rates and (where available) high rates of short-term follow-up recommendations.

In summary, the database for MRI screening at intermediate risk is very limited, and the achieved level of evidence for MR screening at intermediate risk is low. Considering the high rates of false-positive calls and of short-term follow-up reported, the available results for MRI screening of women at intermediate risk do not provide evidence in favor of this indication.

Figures 22.3 and 22.4 show cases in which screening MRI prompted MRI-guided procedures of eventually benign changes or multiple short-term follow-up examinations.

Before a method can be recommended for screening of asymptomatic women (i.e., repeated yearly application), several prerequisites should be fulfilled to assure an acceptable balance of effects and side effects. The main effect expected from a screening modality is proof of mortality reduction. Neither increased detection nor detection at small size warrants improved mortality reduction. Earlier detection could, as well, just result from preponed diagnoses, which might be treated as successfully when detected at a somewhat later stage. In order to distinguish between potential overdiagnosis and a true life-saving effect of early detection, different study types than the yet available studies are needed.

Conversely, immediate effects of MRI screening are unfortunately obvious. They concern high biopsy rates and numerous recommendations for short-term follow-up. The vast majority of these women will have benign changes only. Thus, with MRI screening, many women will have to deal either with a false-positive diagnosis leading to biopsy or with an uncertain diagnosis, which cannot be resolved for many months. Overall, biopsy rates ranging around 10% in the MRI group imply that after ten screening rounds, every woman of the screened population will on average have experienced at least one breast biopsy. For short-term follow-up recommendations, the numbers are even higher. Also, when weighing side effects of the examination itself, it must be considered that side effects of the contrast agent may be not lower than late side effects estimated from the small amount of radiation exposure associated with digital mammography. Unless mortality reduction or improved survival is proven for MRI screening, side effects of the abovementioned range cannot be accepted.

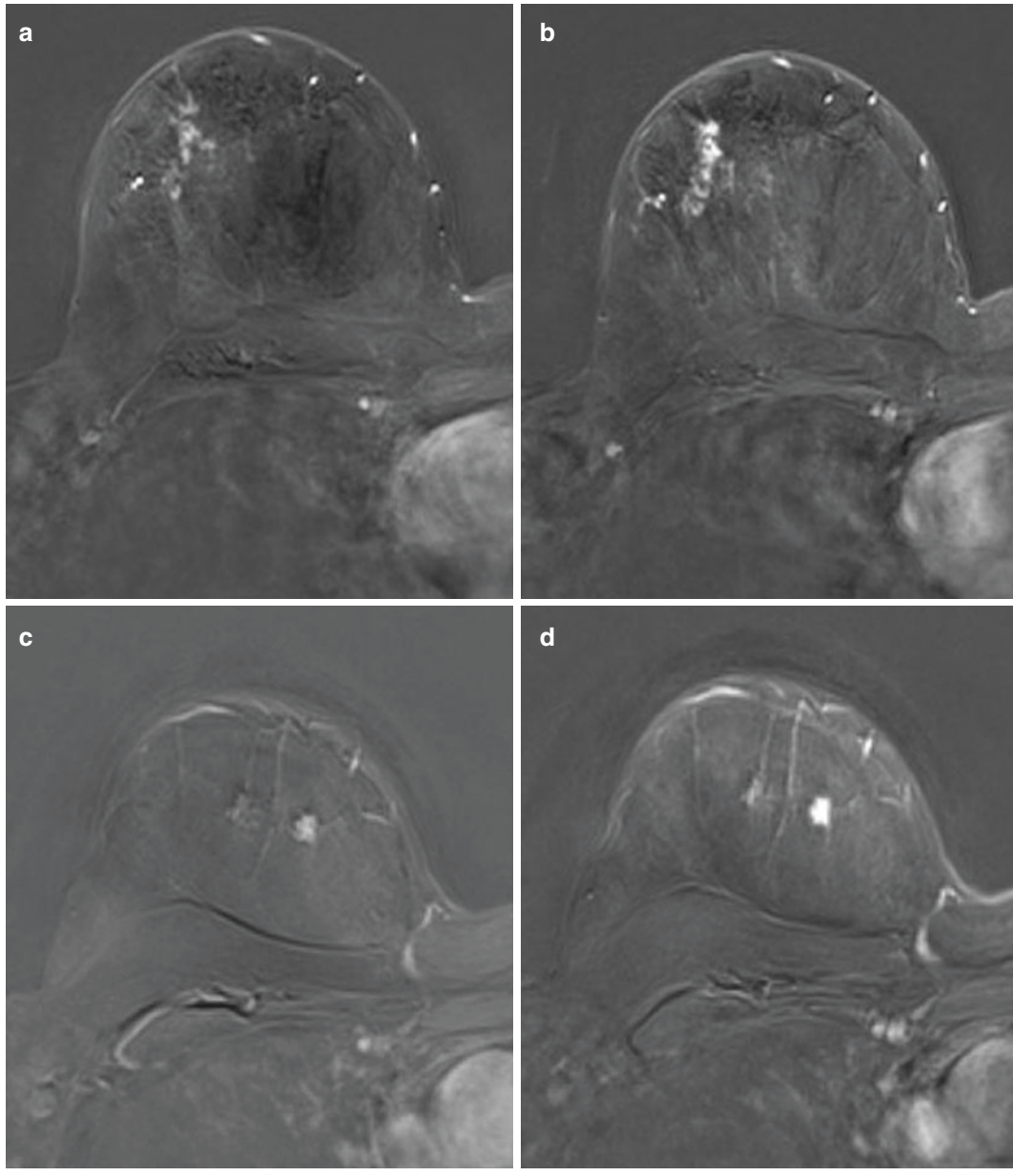

Fig. 22.3 This 40-year-old lady underwent MRI since mammographic and US evaluation was impaired in her large breasts with ample nodular breast tissue, also considering her intermediate risk based on her family history (mother and grandmother affected by breast cancer at age 50 and 55). On MRI, two areas of concern were noted (**a, b**) as segmental enhancement at 10 o'clock, for which no corresponding lesions were found on mammography and US. The lesion, which is demonstrated on representative subtraction images 1 and 3 min after injection of Gd chelate, proved to consist of benign papillomatosis and some chronic inflammatory changes. In addition, (**c, d**) a focal 5-mm ill-circumscribed lesion was found in the upper inner quadrant without any mammographic or US corresponding change. On MRI-guided vacuum-assisted breast biopsy, the lesion proved to be a flat epithelial atypia, which was followed by an additional surgical excision. Considering that the segmental enhancement was judged a benign condition and that flat epithelial atypia indicates some increased risk but eventually is considered a benign condition, too, the patient unfortunately underwent several procedures for benign conditions only

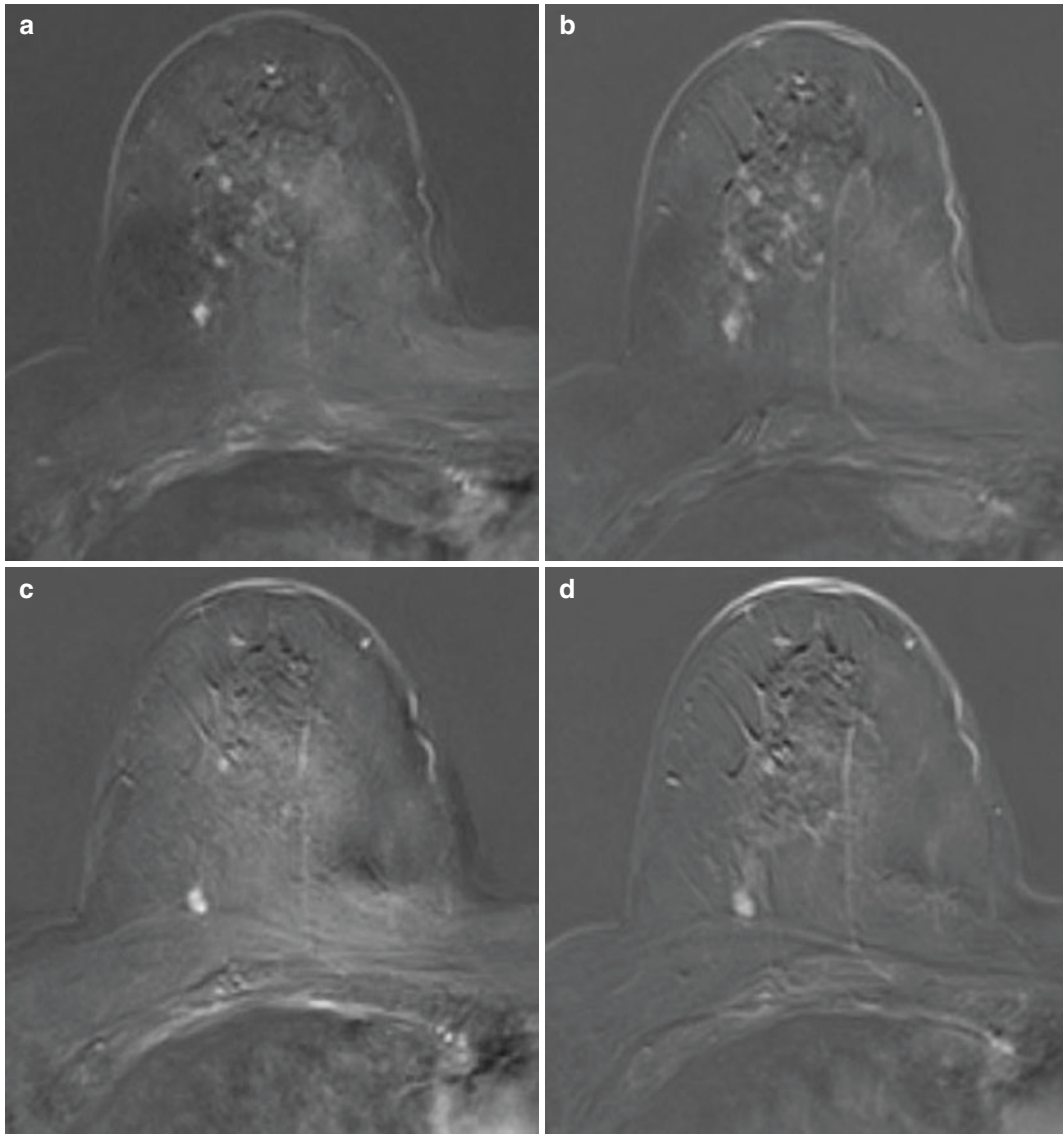

Fig. 22.4 This 62-year-old patient underwent MRI surveillance to monitor the multiple nodules visualized by mammography and/or US within dense breast tissue (BI-RADS class *d*). A first surgery of a nodule increasing in size performed 3 years before had proven to be a papilloma. Six months before her examination in 2014, she had undergone a second surgery of her right breast after an MRI-guided vacuum-assisted breast biopsy had confirmed another papilloma, this time with atypias (not shown). The first post-surgical MRI demonstrates again multiple small nodules (**a** and **b**, subtraction images obtained 1 and 3 min after injection of contrast agent), mostly with plateau-type enhancement, which compared to the previous MRI had not changed in size. A BI-RADS 3 diagnosis was defined and follow-up MRI recommended 6 months later. The follow-up MRI (**b** and **c**, subtraction images 1 and 3 min after injection) shows a slice corresponding to that of the preceding study shown in a and b: part of the nodules seemed to regress. The nodule close to the chest wall appeared slightly more prominent with the suggestion of a slight washout. Considering the patient's recent biopsies, absent change of size, multiplicity of the nodules, and the fact that benign papillomas may exhibit washout curves, another short-term follow-up after 6 months was recommended. The patient returned for the recommended 6-month follow-up study 15 months later. At that time the small nodule had increased to a size of 10 × 6 mm. After intense discussions, it was possible to convince the patient of the necessity of another biopsy. It eventually yielded the diagnosis of a pT1b G3 invasive ductal carcinoma. The case demonstrates the problems determined by MRI surveillance with multiple enhancing lesions and multiple preceding biopsies of eventually benign changes

Different working groups have reviewed the existing scientific evidence of MRI screening of women at intermediate risk [2–5]. So far, only a guideline issued by the American College of Radiologists [26] provides recommendations for screening women with contrast-enhanced MRI below a 20% lifetime risk. This attitude is not commonly shared in Europe or supported by interdisciplinary guideline committees. Based on the available evidence, their judgment has been that present data is insufficient to recommend MRI screening in women at intermediate risk. The IARC, like the National Comprehensive Cancer Network (NCCN) and the Ontario Health Technology Assessment (HTA) Report, point out that there is proof of high false-positive rates, while proof of effect is lacking. Therefore, they explicitly neither recommend for nor against use of MRI at lifetime risk 15–20% and against the use of MRI at lifetime risk < 15% [2, 3, 27, 28]. Whether constantly improving technology, new pulse sequences, or additional information, such as information from diffusion-weighted imaging, will allow the important improvements required for this indication remains to be seen. An important step to adequate testing is the initiation of randomized controlled trials. Such studies have just been started, as reported by two Dutch groups [29, 30] and one Italian group [31].

It may be hoped that future progress associated with appropriate study types, as mentioned above, will help to answer the remaining gaps in this field.

References

1. Passaperuma K, Warner E, Causer PA et al (2012) Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 107:24–30
2. Lauby-Secretan B, Loomis D, Straif K (2015) International Agency for Research on Cancer Handbook Working Group. Breast-Cancer Screening—Viewpoint of the IARC Working Group. N Engl J Med 372:2353–2358
3. International Agency for Research on Cancer (2016) IARC handbooks of cancer prevention. Vol. 15. Breast cancer screening. IARC Press, Lyon, France. http://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Breast-Cancer-Screening-2016. Accessed 30 Jun
4. Oeffinger KC, Fontham ET, Etzioni R et al; American Cancer Society (2015) Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA 314:1599–1614
5. Sardanelli F, Aase HS, Álvarez M et al (2017) Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. Eur Radiol 27:2737–2743
6. Tabár L, Yen AM, Wu WY et al (2015) Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. Breast 21(1):13–20
7. Miglioretti DL, Zhu W, Kerlikowske K et al; Breast Cancer Surveillance Consortium (2015) Breast tumor prognostic characteristics and biennial vs annual mammography, age, and menopausal status. JAMA Oncol 1(8):1069–1077
8. Melnikow J, Fenton JJ, Whitlock EP et al (2016) Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 164:268–278
9. Gail MH, Mai PL (2010) Comparing breast cancer risk assessment models. J Natl Cancer Inst 102:665–668
10. Brentnall AR, Harkness EF, Astley SM et al (2015) Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Res 17:147
11. Gastounioti A, Conant EF, Kontos D (2016) Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. Breast Cancer Res 18:91
12. Mandelson MT, Oestreicher N, Porter PL et al (2000) Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 92:1081–1087
13. Weigel S, Heindel W, Heidrich J, Hense HW, Heidinger O (2017) Digital mammography screening: sensitivity of the programme dependent on breast density. Eur Radiol 27:2744–2751
14. Houssami N, Abraham LA, Onega T et al (2014) Accuracy of screening mammography in women with a history of lobular carcinoma in situ or atypical hyperplasia of the breast. Breast Cancer Res Treat 145:765–773
15. Van de Vijver MJ (2005) Biological variables and prognosis of DCIS. Breast 14:509–519
16. Menes TS, Kerlikowske K, Lange J, Jaffer S, Rosenberg R, Miglioretti DL (2017) Subsequent

breast cancer risk following diagnosis of atypical ductal hyperplasia on needle biopsy. JAMA Oncol 3:36–41
17. Rendi MH, Dintzis SM, Lehman CD, Calhoun KE, Allison KH (2012) Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. Ann Surg Oncol 19:914–921
18. Perlet C, Heywang-Kobrunner SH, Heinig A et al (2006) Magnetic resonance-guided, vacuum-assisted breast biopsy: results from a European multicenter study of 538 lesions. Cancer 106:982–990
19. Port ER, Park A, Borgen PI, Morris E, Montgomery LL (2007) Results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia. Ann Surg Oncol 14:1051–1057
20. Friedlander LC, Roth SO, Gavenonis SC (2011) Results of MRI screening for breast cancer in high risk patients with LCIS. Radiology 261:421–427
21. Sung JS, Malak SF, Bajaj P, Alis R, Dershaw DD, Morris EA (2011) Screening breast MR imaging in women with a history of lobular carcinoma in situ. Radiology 261:414–420
22. Schwartz T, Cyr A, Margenthaler J (2015) Screening breast magnetic resonance imaging in women with atypia or lobular carcinoma in situ. J Surg Res 193:519–522
23. King TA, Muhsen S, Patil S et al (2013) Is there a role for routine screening MRI in women with LCIS? Breast Cancer Res Treat 142:445–453
24. Nelson HD, Zakher B, Cantor A et al (2012) Risk factors for breast cancer for women age 40 to 49: a systemic review and meta-analysis. Ann Intern Med 156(9):635–648
25. Berg WA, Zhang Z, Lehrer D et al (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
26. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA (2018) Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol 15:408–414
27. National Comprehensive Cancer Network (NCCN) (2018) NCCN-Guideline for breast cancer screening and diagnosis. Version 2.2018—May 18. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed 30 Jun 2020
28. Health Quality Ontario (2016) Magnetic resonance imaging as an adjunct to mammography for breast cancer screening in women at less than high risk for breast cancer: a health technology assessment. Ont Health Technol Assess Ser 16(20):1–30. http://www.hqontario.ca/evidence-to-improve-care/journal-ontario-health-technology-assessment-series. Accessed 30 Jun 2020
29. Emaus MJ, Bakker MF, Peeters PH et al (2015) MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. Radiology 277:527–537
30. Saadatmand S, Rutgers EJ, Tollenaar RA et al (2012) Breast density as indicator for the use of mammography or MRI to screen women with familial risk for breast cancer (FaMRIsc): a multicentre randomized controlled trial. BMC Cancer 12:440
31. Panizza P, Viganò S, Bonelli L et al (2012) Screening women at intermediate risk: harm or charm? Eur J Radiol 81(Suppl 1):S116–S117

Hypotheses for the Future

23

Francesco Sardanelli and Franca Podo

Abbreviations

ABUS	Automated breast ultrasound
AI	Artificial intelligence
BC	Breast cancer
BDCT	Breast-dedicated computed tomography
BI-RADS	Breast Imaging Reporting and Data System
CE-MRI	Contrast-enhanced magnetic resonance imaging
CEM	Contrast-enhanced mammography
CI	Confidence interval
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
DWI	Diffusion-weighted imaging
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HHUS	Hand-held ultrasound
MRI	Magnetic resonance imaging
OR	Odds ratio
PPV	Positive predictive value
ROC-AUC	Area under the curve at receiver operating characteristics analysis

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23.1 Introduction

It is very hard to predict, especially the future. This amusing remark is attributed not only to Niels Bohr [1] but also to many others, among them Samuel Goldwyn, Karl K. Steincke, Robert Storm Petersen, Yogi Berra, Mark Twain, and … Nostradamus [2]. In addition, we should also consider the role of serendipity in biomedicine discoveries and innovations [3], including x-rays by Wilhelm C. Roentgen (Table 23.1). Thus, we cannot exclude that currently unpredictable events may dramatically change the scenario of breast cancer (BC) screening in high-risk women and the use of magnetic resonance imaging (MRI) for this aim.

However, limiting the timeframe to the next future (not beyond one or two decades), some hypotheses can be outlined. We will begin with a preliminary basic issue regarding the current practice and will then outline four major trends.

The preliminary issue regards the substantial underutilization of breast MRI for high-risk screening. This failure is related to the

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Table 23.1 Twelve accidental key discoveries/innovations in biomedicine

Year	Discovery/innovation	Scientist(s)
1676	Protozoa and bacteria	Antonie van Leeuwenhoek
1799	Nitrous oxide	Humphry Davy
1796	Vaccination	Edward Jenner
1881	Selective culture of bacteria	Robert Koch
1895	X-rays	Wilhelm C. Roentgen
1928	Penicillin	Alexander Fleming
1889	Pancreas role in diabetes	Oskar Minkowski and Joseph von Mering
1940	Warfarin	Karl P. Link and Mark A. Stahmann
1949	Intraocular lens	Harold Ridley
1959	Benzodiazepines	Leo Sternbach
1963	Percutaneous transluminal angioplasty	Charles Dotter
1982	*Helicobacter pylori* in gastritis and peptic ulcer	Barry Marshall and Robin Warren

Source: Rourke S. 12 Key Accidental Discoveries in Medicine (2017) Medscape. https://www. medscape. com/slideshow/accidental-discoveries- 6008976#13 [3]

organizational context. On one side, we hope that, at least in Europe and in other countries where organized population-based screening programs are activated, MRI screening will be integrated in those programs, as already demonstrated to be feasible in some regions of Canada and in the United Kingdom. This will allow the adoption of the best practices of inviting (high-risk) women on a territorial basis, of quality control, of double reading (if necessary), as well as of all the organizational matters typical of a population-based screening program, under the umbrella of the breast units.

The first trend to consider is the increasing effectiveness of systemic therapies, especially those including both chemotherapeutic drugs and targeted treatments. The question here, not only for women at increased risk but also for those at average (difficult to say "normal") risk, derives from the following obvious statement: in a theoretical model, a break-even point can be hypothesized when the advantages of early diagnosis by screening are nullified by the increasing efficacy of therapies. Can we hypothesize this in the next future, for high-risk women?

Second, we will outline a group of innovative approaches potentially competing with contrast-enhanced MRI (CE-MRI) to screen high-risk women outside the field of medical imaging, including not only the detection of circulating tumor cells, nucleic acids, proteins, etc. (the *liquid biopsy* perspective) but also intriguing technologies such as the *smart bras*. These possibilities would not substitute for breast imaging but would place it as a second step after a first positive test. The second step would be breast imaging, with MRI and contrast-enhanced breast imaging (MRI or dual-energy mammography; see below) as the best candidate for localizing the tumor. Of course, these hypotheses are not limited to high-risk women.

A third trend is the competition coming from non-MRI-based imaging methods such as digital breast tomosynthesis (DBT), automated breast ultrasound (ABUS), contrast-enhanced mammography (CEM), breast-dedicated computed tomography (BDCT), and optical imaging.

Fourth, we will consider new approaches from inside MRI, such as abbreviated contrast-enhanced protocols as well as unenhanced protocols, especially diffusion-weighted imaging (DWI).

Finally, we will draw some conclusive considerations, also evaluating the potential impact of artificial intelligence (AI) on the field of breast imaging.

23.2 Underutilization of High-Risk MRI Screening and Organizational Issues

More than 20 years after the identification of *BRCA* gene mutations and 30 years after the introduction of CE-MRI, evidence has been accumulated in favor of MRI-including screening programs for high-risk women. In some conditions, especially for *BRCA1* mutation carriers, MRI alone can be proposed. Importantly, in the case of previous chest radiation therapy, mammography as an adjunct to MRI is always recommended, as a high incidence of ductal carcinoma in situ (DCIS) with microcalcifications and low neoangiogenesis limits the MRI sensitivity.

Notwithstanding the body of evidence in favor of MRI screening in high-risk women, the access of these women to breast MRI has so far been quite limited. Mary C. White and coworkers [4] reported on factors associated with breast MRI use among women with a family BC history in the United States. A total of 17,894 women participating in the Sister Study cohort, never diagnosed with BC, with at least one sister diagnosed with BC were interviewed. Breast MRI was reported by 16.1% and was more common among younger women and those with higher incomes. Ever use of breast MRI was associated with actual or perceived intermediate or high risk. However, use of breast MRI was reported only by 25% of women with BC risk ≥ 20%, by 33% of women who had a *BRCA1/2* positive test in the family, and by 71% of women who resulted to be *BRCA1/2* mutation carriers. The authors' comment was the following: "To support shared decisions about the use of breast MRI, women could benefit from improved understanding of the chances of getting BC and increased quality of provider communications."

The underutilization of breast MRI screening among high-risk women has been highlighted also by data from 86 Breast Cancer Surveillance Consortium facilities during calendar year 2012 in the United States [5]. Overall, 43.9% (2,403/5,468) of women at high lifetime risk attended a facility with on-site breast MRI screening availability. But only 6.6% of them (158/2,403) obtained breast MRI screening within a 2-year window of their screening mammogram. Patient factors significantly associated with on-site MRI screening use included age below 40 (odds ratio [OR] 2.39), family history (OR 1.72), prior breast biopsy (OR 2.09), and postsecondary education (OR 2.22). The conclusion was that *supplemental breast MRI remains widely underutilized among those who may benefit from earlier cancer detection*.

Still from the Breast Cancer Surveillance Consortium, data from community practice in 5 regional imaging registries [6] showed that out of 348,955 women receiving a screening mammogram, only 1,499 (0.4%) underwent screening MRI. High breast density and previous lobular carcinoma in situ were significantly associated with MRI screening, but 83% of screening MRIs occurred among women with lifetime risk lower than 20% and 36% among women considered at low-to-average BC risk. The authors concluded that *utilization of screening MRI in community settings is not consistent with guidelines and the goal of delivery of high-value care*.

In our opinion, the challenge for public health programs is to integrate these protocols for high-risk women into the general screening organization. This should be part of models for stratification of BC screening protocols on the basis of different risk classes, up to a modulation based on the individual risk estimate, even including a possible reduction of screening invitations to very low-risk women. Studies exploring this hypothesis are ongoing, one of them being the *my personalized breast screening* (MyPeBS) study [7].

The first reported experience of integration of high-risk screening including MRI into a population-based screening program was carried out in Canada. In 2014, Anna M. Chiarelli and coworkers [8] from the Ontario Breast Screening Program reported on 2,207 women with gene mutation predisposing to a high BC risk or untested first-degree relative of a gene mutation carrier, or estimated personal lifetime risk ≥ 25%, or prior radiation therapy to the chest. While the recall rate was significantly higher for abnormal MRI alone (15.1%) than for abnormal mammogram alone (6.4%), out of the 35 BCs detected (16.3‰), none were detected by mammogram alone, and 23 (65.7%) were detected by MRI alone (10.7‰). The authors showed that screening with annual MRI and mammography can be effectively implemented as a dedicated section in the context of an organized breast screening program. The size of this organized program can be assessed from the following figures, reported in 2018 [9]: of 24,811 women who completed genetic assessment, 16,367 (66.0%) had genetic counseling only, 8,444 (34.0%) had counseling and testing, and 8,027 (32.4%) met the high-risk criteria.

Another interesting experience was reported by Terri P. McVeigh and coworkers [10] with an article entitled "Successful repatriation of breast cancer surveillance for high-risk women to the UK National Health Service Breast Screening Programme." In fact, in the United Kingdom,

since 2013, screening centers had to provide services for high-risk women, including those being carriers of highly penetrant single gene mutations (*BRCA1*, *BRCA2*, *TP53*), previously undergoing surveillance at the Royal Marsden Hospital. The authors reported on patient experience of surveillance provided by local services on and 3 years after repatriation. In 2014, 182/346 women (53%) responded to a questionnaire, the same percentage (246/464) in 2016. The percentage of women declaring to have received at least the recommended surveillance was 91% in 2014 and 87% in 2016. At both time points, 17% of women required additional diagnostic investigations, with cancers detected in 2%. The authors concluded that repatriation to screening centers was successfully accomplished.

A single-center study from the University Hospital in Heidelberg [11] investigated counselees' adherence to recommendations for surveillance or prophylactic surgery. They reported a 59% rate of full adherers to the recommendations, with significant predictors for partial or full adherence being having children, younger daughters, a higher awareness of the topic, a higher perceived BC risk, and worries/impairment by it.

Thus, the most important issue is to extend the systematic offer of breast MRI to high-risk women, to increase their awareness about the possibility to have genetic testing and the probability to get a BC, and to give them complete information about advantages and disadvantages of MRI screening. This can be done in an effective way in the context of organized, population-based screening programs under the umbrella of well-identified breast units. This is our hope.

23.3 Do We Still Need High-Risk Screening in the Era of Increasingly Efficient Therapies?

The crucial questions are the following: are we reaching a break-even point where the advantages of an earlier diagnosis by screening can be nullified by the increasing efficacy of systemic therapies? Is this possible, in particular, for high-risk women?

Some considerations regarding mammography screening in the general female population are needed.

Sepideh Saadatmand and coworkers [12] investigated whether tumor stage at diagnosis still influences survival in the Netherlands. Two time cohorts were identified and compared, 80,228 patients diagnosed in 1999–2005 versus 93,569 in 2006–2012, when a wider use of systemic therapy was implemented. In univariate and multivariable analyses, tumor stage and nodal status significantly influenced the overall and relative survival in both cohorts. The relative survival rates ranged from almost 100% in both cohorts for DCIS to 57% and 59% for T4 tumors in the old and recent cohorts, respectively. In multivariable analysis, breast-conserving treatment, more frequent for the 2006–2012 cohort, was associated with a survival benefit compared to mastectomy and lymph node dissection, although less frequent, decreased overall survival. The wider use of chemotherapy in the 2006–2012 cohort conferred a hazard ratio of death of 0.86. These large-scale results clearly demonstrate that while the use of chemotherapy impacts on survival, *tumor size at diagnosis still matters*. Authors conclude that "in the current era of effective systemic therapy, diagnosis of BC at an early tumor stage remains vital."

In 2018, an investigation from the Stanford University, California, USA [13], assessed to what extent digital screening and newer systemic therapies contribute to reduction in overall BC mortality for women aged 30 to 79 years with different molecular BC subtypes from 2000 to 2012. Their results are summarized in Tables 23.2 and 23.3. The overall mortality reduction increased from 37% to 49%. Screening advances contributed on average for 17% of this reduction, reaching 22% for BCs being both estrogen receptor (ER)- and human epidermal growth factor receptor 2 (HER2)-negative. In 2012, the relative contribution of

Table 23.2 Association of screening and treatment with breast cancer mortality in US women from 2000 to 2012

	Mortality reduction (%)			Contribution to the difference in mortality reduction in 2012 versus 2000 (%)			
	In 2000[a]	In 2012[b]	Difference	Screening advances	Chemotherapy advances	Hormone therapy advances	Trastuzumab
Overall	37	49	12	17	38	29	15
$ER^+/HER2^-$	39	51	12	19	39	42	0
$ER^+/HER2^+$	39	58	19	12	22	25	41
$ER^-/HER2^+$	29	45	15	11	32	0	57
$ER^-/HER2^-$	29	37	8	22	78	0	0

Source: Plevritis SK et al. (2018) JAMA 319:154–164 [13]
ER estrogen receptor, *HER2* human epidermal growth factor receptor 2
[a]Relative to the estimated baseline rate of 64 deaths (model range, 56–73) per 100,000 women in 2000
[b]Relative to the estimated baseline rate of 63 deaths (model range, 54–73) per 100,000 women in 2012

Table 23.3 Association of screening and treatment with breast cancer mortality in US women in 2012

	Mortality reduction (%)[a]			Relative contribution (%)	
	Screening alone	Therapy alone	Screening + therapy	Screening	Therapy
Overall	21	35	49	37	63
$ER^+/HER2^-$	21	38	51	36	64
$ER^+/HER2^+$	21	47	58	31	69
$ER^-/HER2^+$	20	30	45	40	60
$ER^-/HER2^-$	20	22	37	48	52

Source: Plevritis SK et al. (2018) JAMA 319:154–164 [13]
ER estrogen receptor, *HER2* human epidermal growth factor receptor 2
[a]Relative to the estimated baseline rate of 63 deaths (model range, 54–73) per 100,000 women in 2012

screening versus therapy in determining mortality reduction was 37% versus 63% overall, 48% versus 52% for BCs being both ER-and HER2-negative.

It is not easy to translate these results to the high-risk population. However, the combination of the definitively higher sensitivity of MRI for small cancers in comparison to mammography and ultrasound shown by many studies [14, 15], the well-known higher growth rates of BCs in high-risk women [16, 17], and the higher rate of triple-negative BCs in *BRCA* mutation carriers when compared to the general population [18], clearly play in favor of a beneficial effect of MRI screening in these women. The effect of the combination of MRI screening and modern therapies of triple-negative BCs has been shown by follow-up data of the HIBCRIT study [18] (see Chap. 13).

23.4 Competition from Outside Imaging

A first option to consider for the future is a series of techniques grouped under the term *liquid biopsy*. They are based on the molecular analysis of biological fluids, typically blood, of nucleic acids, subcellular structures such as extracellular vesicles and exosomes, as well as, in the context of cancer, circulating tumor cells and tumor-educated platelets [19–21]: the so-called tumor circulome (circulating tumor-derived material) [21]. These methods could play a role in the screening/surveillance for BC, including women at high risk.

Major advantages of these innovative, fast-evolving analytical technologies are the minimal invasiveness, the time resolution in longitudinal monitoring, and the potential to change the clinical practice by exploring blood rather than tissue

biopsy as a source of information [21]. The first important milestone in a clinical application of liquid biopsy was reached in 2016, when the Food and Drug Administration approved the first companion diagnostic test for lung cancer based on the circulating deoxyribonucleic acid [22]. The potential clinical impact of these technologies promoted several investigations to assess the value of liquid biopsies to monitor disease response and track the emergence of drug resistance in patients affected by different cancers.

Major present restrictions to the use of these new technologies for cancer screening are the limited amounts of circulating deoxyribonucleic acid and circulating tumor cells, the confounding effects of somatic mutations originated from normal cells, the general need for improvements in accuracy and detection limits, and the present lack of validation. Preliminary data from the ongoing Memorial Sloan Kettering Discovery Study [23] were discussed at the 2018 annual meeting of the American Society of Clinical Oncology on liquid biopsy screening of patients with lesions classified as category 4 according to the Breast Imaging Reporting and Data System (BI-RADS) [24]. These data showed that the mean detection rate for 333 BCs was only 21% (95% confidence interval [CI] 17–26%), with a difference when considering triple-negative cancers (56%), HER2-positive cancers (34%), and hormone receptor-positive HER2-negative cancers (11%), to be compared to higher values reported for other cancers, for instance, 80% (95% CI 44–98%) for 10 ovarian cancers and 63% (95% CI 42–81%) for 27 colorectal cancers. Even though preliminary, these data show that liquid biopsy screening is yet not ready for BC. However, future improvements are expected and could dramatically change this scenario.

Other BC screening perspectives may come from smart technologies. Among wearables, *smart bras* (i.e., BC-detecting bras) remain a possible option. This is a long story. Already in 2008, the literature [25] reported on a 10-year dream of a heat-sensing (thermographic, so in some way still referring to an imaging technology) bra that could detect early signs of BC in premenopausal women. The idea was that wearing the bra for 1 h every day for a month, a woman could learn whether she is at high risk of BC. However up to 2008, no trials were conducted. Technology evolved into systems of microwave antennae, but it was not translated into a usable smart bra. The question remained the following: "What are the statistical strengths of the signals?" [25]. In 2016, a technical proof-of-concept paper [26] reported on a compact and ultra-wideband and flexible material antenna in microwave (20×14 mm^2) designed to be implemented in a bra, operating at frequencies from 4 to 6 GHz. The authors said that the system exhibited an excellent omnidirectional radiation pattern with an average efficiency above 70% and average gain above 1 dBi. A French-Swiss cooperation is now trying to develop a solution based on the measurement of electrical and thermal properties of the mammary tissues. This sensor-equipped intelligent bra is intended to early detect cancers primarily in high-risk women [27]. However, while smart bras represent a very intriguing possibility, no screening results are available up to now.

These new perspectives, when ready for clinical prospective evaluation, could be firstly applied to high-risk women as a high-incidence ground, as it was for MRI.

23.5 The Competition from Non-MRI Modalities and the Potential of CEM

Non-MRI-based imaging methods could represent an alternative to MRI for high-risk screening only if able to provide a similar high sensitivity joined to an acceptable specificity and positive predictive value (PPV). As explained in Chaps. 9 and 11 of this book, neither mammography (screen-film or digital) nor handheld ultrasound (HHUS) can compete with MRI for this task to the point that the "MRI-alone" approach has been demonstrated to be valid by many studies (see Chap. 11). New possibilities are offered by DBT, ABUS, CEM, and various techniques called "optical imaging."

The potential of DBT for high-risk screening was not specifically investigated by means of prospective studies. A useful contribution has

recently come from Roark and coworkers [28]. The authors retrospectively identified 4,418 breast MRI screening examinations. Of them, 2,291 were performed in patients with a negative digital mammogram in the 12 months before MRI (timeframe 2010–2012), while 2,127 were performed in patients with a negative DBT examination in the 12 months before MRI (timeframe 2013–2015). These women were at increased risk for BC, including genetic predisposition, personal history of BC or high-risk lesion, prior chest irradiation, family history, or other risk factors conferring a lifetime risk of greater than 20%. The MRI cancer detection rate was not significantly different for MRI after negative mammography (11‰ examinations) versus MRI after negative DBT group (16‰ examinations; odds ratio 1.4; 95% confidence interval 0.4–1.2; $p = 0.23$). No statistical differences were found also for MRI abnormal interpretation rate (7.4% versus 7.3%), PPV1[1] (15% versus 22%), PPV2[2] (23% versus 33%), and PPV3[3] (28% versus 35%). In both groups, the majority of MRI-detected cancers were invasive, less than 1 cm, and node-negative. Thus, there is some evidence that *DBT, when performed instead of a simple mammogram, does not reduce the diagnostic gain of MRI*.

We can indirectly say that DBT is not an alternative to MRI in high-risk women. If mammography is performed, it can be used generating two-dimensional synthetic images with an x-ray exposure lower than that provided by digital mammography [29], but no substantial diagnostic gain is expected. In other words, as was for the shift from screen-film to digital mammography [30], that to DBT did not solve the intrinsic difficulties of an unenhanced x-ray-based modality in early BC detection in high-risk women: denser breast tissue, falsely benign appearance of malignant lesions, paucity of malignancy with microcalcifications, and fast growth of cancers.

[1]PPV1 is the fraction of true positives related to all positive recalls.

[2]PPV2 is the fraction of true positives related to the number of recommended biopsies.

[3]PPV3 is the fraction of true positives related to number of performed biopsies.

Another potential alternative to screening MRI may be ABUS, with its intrinsic reduction of operator dependency of HHUS. Two studies explored the role of ABUS in high-risk women, one of them with direct comparison to MRI. Kelly and coworkers [31] studied 4,419 women with dense breast and/or at elevated risk of BC with mammography and supplemental ABUS. They doubled the diagnostic yield from 3.6‰ to 7.2‰, with the number of detected invasive cancers 10 mm or less in size tripled from 7 to 21, and a PPV of 39.0% and 38.4%, respectively. Halshtok Neiman and coworkers [32] compared prospectively ABUS and MRI screening, performed 6 months apart or less, in Jewish *BRCA1/2* mutation carriers. Only 68 women, 40 *BRCA1* and 28 *BRCA2* mutation carriers, underwent 79 paired ABUS and MRI examinations. Of 14 discordant cases, there was 1 cancer, revealed by MRI and not by ABUS performed 6 months prior to MRI.

In the absence of large prospective studies, we can say that in high-risk women, ABUS most probably significantly increases the detection rate in comparison to mammography but does not parallel the high sensitivity of MRI. There is some evidence in mixed cohorts (screening and symptomatic women) that the performance of ABUS may be similar to that of HHUS [33, 34]. We note that it does not seem that there is an increase in sensitivity in comparison to HHUS. On the other hand, when HHUS was compared to MRI in a large-scale screening study of women with elevated cancer risk and dense breasts [35], the supplemental cancer yield was 3.7‰ for HHUS and 14.7‰ for MRI. The number of screens needed to detect 1 cancer was 127 for mammography, 234 for HHUS after negative mammography, and 68 for MRI after negative mammography and HHUS results. If ABUS and HHUS have similar sensitivities, ABUS cannot change the scenario of MRI superiority for high-risk screening.

A real potential competitor of MRI is CEM. Its development [36] has been based on the preferential uptake of iodinated contrast agents by breast tumors due to their two-compartment (vascular/interstitial) pharmacokinetics, equal to that of gadolinium chelates used for contrast-enhanced

MRI. After a first phase in which a temporal subtraction (contrast-enhanced minus unenhanced images) was attempted [37], a recombination of low- and high-energy images acquired after intravenous injection of iodinated contrast agents was adopted [38]. Even though technical and procedural standardization is still lacking [39], across the last 15 years, CEM has been introduced in various clinical settings, such as the diagnostic work-up of symptomatic women and screening recalls, problem-solving of equivocal mammographic findings, preoperative local staging, postoperative surveillance, neoadjuvant therapy monitoring, and also screening of women at increased risk or with dense breasts [36, 40]. The diagnostic performance was always increased in comparison to digital mammography, DBT, or ultrasound, frequently reaching performances similar to those of CE-MRI [40]. Of note, CEM low-energy images have been demonstrated to be substantially equivalent to plain digital mammography images [36], which means that a CEM examination practically provides the information of a "standard" mammogram (from the low-energy images) plus that of contrast-enhanced imaging (from the recombined low- and high-energy images). Interestingly, a study [41] found that in screening women at increased risk of BC, a shorter examination time and a less taxing procedure made CEM better tolerated by patients than CE-MRI (even though MRI is a non-breast-compressive approach). Thus, can we consider CEM as a strong competitor of CE-MRI for high-risk screening?

A recent article by Sung and coworkers [42] assessed the diagnostic performance of CEM as a screening tool for women at increased risk of BC. The authors ultimately included 904 baseline CEM examinations, performed from 2012 to 2016 with technical and procedural choices partly shared by other research groups around the world [39]. CEM provided a higher detection rate (15.5‰) than low-energy images alone (8.8‰), with a PPV of 29.4% and 34.8%, respectively. CEM showed a significant higher sensitivity compared to low-energy images (87.5% versus 50.0%) with a significant increase for the negative predictive value too (99.7% versus 99.0%). Specificity was 93.7% for CEM and 97.1% for low-energy images. Of note, CEM specificity and false-positive rate reported by this study is comparable to the ones of CE-MRI applied to the similar category of women at increased risk [43].

An important point is the rate of acute adverse reaction to the iodinated contrast agents, which is, in the radiological experience, on average higher than that of gadolinium-based contrast agents (see Chap. 5). Sung and coworkers [42] reported a total of 15 adverse reactions to iodinated contrast agent in 904 patients (1.7%), over two times the pooled value of 0.82% (95% CI 0.64–1.05%) recently obtained in a meta-analysis of 14,012 patients from 84 studies [39], a rate probably underestimated due to sporadic reporting of the vast number of mild adverse reactions that resolve without any medical intervention, as were 13 out of 15 (87%) adverse reactions reported by Sung et al. [42]. Anyway, also moderate or severe reactions to iodinated contrast agents reported for CEM in this or other publications always resolved without sequelae.

The published clinical experience of CEM is now over 16,000 examinations in different clinical settings, and new papers are published every month. Pooling the data of 50 studies totaling 7,516 and 6,915 lesions, sensitivity was 94.1% (95% CI 92.1−95.6%), specificity 66.6% (95% CI 59.6−72.9%), positive likelihood ratio 2.81 (95% CI 2.28−3.52), and negative likelihood ratio 0.09 (95% CI 0.07−0.11); the summary area under the curve at receiver operating (ROC-AUC) analysis has a value of 0.921[4]. To be practical, CEM has been shown to have a diagnostic performance very close to that of CE-MRI with a general favorable balance in terms of advantages/disadvantages, as summarized in Table 23.4.

Thus, CEM is a possibly preferred technique for many indications such as problem-solving for equivocal findings at first-level examinations, neoadjuvant therapy response monitoring, and identification of occult primary BC. In particular, in the preoperative setting, the high ease of interpretation (by the surgeons) could play a pivotal role. Moreover, the creation and implementation of a CEM-specific BI-RADS lexicon will help to refine lesion characterization. Studies aiming to explore this possibility

[4]Cozzi A, Monti CB, Monaco C et al (2020) Contrast-enhanced mammography (CEM): a systematic review and meta-analysis of diagnostic performance (Abstract accepted as Oral Presentation at the European Congress of Radiology 2020).

Table 23.4 Technical, procedural, and diagnostic characteristics of contrast-enhanced breast magnetic resonance imaging (CE-MRI) and contrast-enhanced mammography. Modified from [44]

Characteristics	CE-MRI	CEM
Type of imaging	Three-dimensional	Two-dimensional
Multiparametric technique	Yes	No
Kinetic analysis	Yes	No
Sensitivity	High	High
Specificity and PPV	Acceptable/good	Acceptable/good
Contraindications	Several	Few
Radiation exposure	No	Yes
Contrast agent health issues	Yes	Yes
Ease of interpretation	Low	High
Breast compression	No	Yes
Patients' preference	Lower	Higher
Cost	Lower	Higher
Accessibility	Low to intermediate	Intermediate to high

PPV positive predictive value

resulted both in improvements of CEM specificity and more appropriate biopsy referral [45].

However, when considering the application of CEM to high-risk screening, radiation exposure associated with CEM has to be taken as a crucial point (see Chap. 12). In fact, repeated low-dose radiation exposure leads to substantial increased risk of radiation-induced BC in women with hereditary predisposition to BC, particularly young carriers of deleterious mutations [46]. In fact, guidelines suggest to avoid or limit the use of mammography in these women, adopting the "CE-MRI-alone" protocol or adding ultrasound instead of mammography, as happens in Australia [47] and some European countries [48, 49]. However, other guidelines (as in the United States [50]) recommend screening high-risk women with both CE-MRI and mammography, performed either concurrently or at a 6-month interval. In the case of mammography 6 months apart from CE-MRI, CEM instead of mammography can be considered as a more effective strategy than standard mammography to avoid interval cancers. In our view, in women with hereditary predisposition to BC, especially those who carry deleterious *BRCA/TP53* mutations, the cautious "CE-MRI-alone" strategy should be preferred even over 40 or 50 years of age.

A different scenario is that of high-risk women who underwent prior chest radiation therapy (typically women who are lymphoma survivors), a topic extensively treated in Chap. 14. These women tend to develop BCs with a relatively higher proportion of ductal carcinoma in situ presenting with microcalcifications and low neoangiogenesis, the latter also as an effect of radiation therapy, which may be missed on CE-MRI [51]. This is the reason for which guidelines suggest to combine CE-MRI and mammography to maximize sensitivity. In that case, CEM is the natural candidate one-shop-stop modality for screening: the low-energy image gives us the unenhanced morphologic information (including the possible presence of microcalcifications), while the recombined low-/high-energy image gives us the functional information about contrast uptake. Prospective, well-designed studies on CEM for screening lymphoma survivors are expected. Of note, the direct parallel visualization of microcalcifications on low-energy images and in the possibly associated contrast enhancement [52] is one peculiar advantage of CEM, solving one well-known limitation of CE-MRI.

Breast-dedicated computed tomography (BDCT) units are already available for clinical use [53]. This technique, which is performed in prone position with unilateral image acquisition, has some advantages such as the real three-dimensional acquisition, the lack of breast compression, and the potential 360° open access to interventional procedures. No studies are available on the application of this new technology to high-risk screening.

A recent study by Nicole Berger and coworkers from the University Hospital Zurich, Switzerland [54], retrospectively reported on 300 consecutive

BDCT examinations performed with the latest CT technology, i.e., *photon counting*. The main reason for preference of BDCT was the lack of breast compression (85%). Four BCs were detected (incidence 1.3%), but 102 possible lesions were detected. Additional ultrasound was performed in 226 women (102 as targeted examinations, 124 due to dense breast tissue), and 3 additional cancers were detected (additional cancer yield 1%). The pectoralis muscle was included in only 58% of the examinations, and complete assessment of breast tissue was only possible in about 24% of examinations. The authors are correctly very cautious in their conclusions suggesting BDCT as an alternative in those patients not otherwise willing to perform mammography because of breast compression. However, here the crucial question is why not MRI?

In addition to these limitations, we must consider the need of double acquisition for bilateral examination and, as the most relevant drawback, radiation exposure, which is surely the crucial point for its application to screening, in particular to high-risk women. Using the well-known cone-beam technology, Johannes Uhlig and coworkers from the University Medical Center Göttingen, Germany [55], reported on the assessment of 31 patients with 57 BI-RADS 4 or 5 lesions identified on mammography and/or ultrasound (30 malignant and 27 benign). Patients underwent enhanced and contrast-enhanced BDCT 2 and 3 min after contrast injection. Malignant showed a significantly higher enhancement than benign lesions at both time points, but the difference was larger at 2 min. However, this CT technology delivers a high x-ray dose: the average glandular dose was 8.8 ± 4.4 mGy for the unenhanced scan only and 26.1 ± 12.0 mGy for the entire examination including also both the 2-min and 3-min scans, unacceptable levels for screening average-risk women, unethical for high-risk women also in a research setting.

Even for photon-counting technology, recent results published by Willi A. Kalender and coworkers [56] from the University of Erlangen-Nürnberg, Germany, reported an average glandular dose per-breast of 5 mGy, a value still remaining in the range of values reported for CEM (ranging from 0.43 to 2.65 per-view, i.e., from 0.86 to 6.30 per-breast [39]). The comparison with the limits suggested by the European guidelines [57] should take into account the thickness of the breast (of the polymethylmethacrylate phantom, for quality check procedures). These limits distinguish between acceptable values and achievable value and range, per-view, from < 1.0 mGy (acceptable) and < 0.6 mGy (achievable) for a 2-cm polymethylmethacrylate thickness to < 6.5 to < 5.1 for a 7-cm polymethylmethacrylate thickness. This means that for a breast with an average thickness (4.5 cm), a 5-mGy radiation exposure from BDCT would be equivalent to the acceptable exposure for a two-view mammogram but about 25% higher than that suggested ("achievable" value). It is highly probable that improvements of photon-counting technology applied to dedicated breast CT will further reduce the radiation exposure (the same being true for digital mammography, DBT, and CEM) but the same radioprotection concerns we raised above for the use of CEM high-risk screening hold for dedicated breast CT.

Finally, optical imaging deserves some comment. Its application to the breast is in an early phase of development. It comprises a spectrum of different technologies including diffuse optical spectroscopy and imaging, fluorescence molecular tomography, photoacoustic imaging, and multiparametric infrared imaging [58]. Interesting results were reported by Roxanna J. Hellgren and coworkers from the Södersjukhuset Hospital, Stockholm, Sweden [59], using infrared imaging to identify women with negative mammography and dense breasts having a higher probability to bear a cancer, and using CE-MRI for side and site detection: of 1,727 women enrolled, 222 (12.9%) were sent to CE-MRI, and in 5 of them (2.3%), malignant lesions were found; this tool was used to select women for CE-MRI examinations. Up to now, no studies are available for specific application of optical imaging to high-risk screening.

23.6 Novelties from Inside MRI

A fourth trend for change comes from inside MRI. Abbreviated contrast-enhanced protocols are already in use for breast MRI screening providing the substantial effect of reducing cost and execution and interpretation time [43, 60–62], as

explained in Chap. 4. The doses of gadolinium chelate can be probably reduced, as shown by Paola Clauser and coworkers from the University of Vienna [63], taking into account that the "standard" dosage (0.1 mmol/kg) has been validated with studies started more than 20 years ago [64], with old hardware (magnets and coil) and software (sequences) allowing for spatial resolutions and contrast-to-noise ratios certainly much lower than those we are able to obtain today.

However, a potential revolution could come from unenhanced MRI protocols, especially including DWI sequences which clearly outperformed proton magnetic resonance spectroscopy in terms of sensitivity and specificity for clinical applications [65]. Especially DWI has some potential for becoming a fast, non-contrast, non-breast-compressing, and radiation-free screening modality. An open issue is the lack of standardization and the variable image quality depending on the echo-planar structure of the sequence [66]. A recent meta-analysis [67] provided pooled data on breast DWI diagnostic performance from 73 eligible studies, 6,791 lesions (3,930 malignant and 2,861 benign): 89% sensitivity, 82% specificity, and 0.92 ROC-AUC. However, this data regards mixed cohorts also including large lesions and not always independent readings, clearly not comparable with screening settings.

Promising results were obtained using blinded unenhanced MRI, basically DWI, double reading in retrospective clinical non-high-risk series. Rubina M. Trimboli and coworkers from the IRCCS Policlinico San Donato, Milan, Italy [68], evaluated a total of 116 breasts of 67 women, with a 32% per-BC prevalence (30 invasive ductal cancers, 2 invasive lobular carcinoma, and 5 DCIS). Per-breast sensitivity was 78% for reader 1, 76% for reader 2, and 78% for double reading; specificity was 90% for both readers and 87% for double reading. Interobserver agreement was almost perfect ($\kappa = 0.873$). More recently, Anna Rotili and coworkers from the European Institute of Oncology, Milan, Italy [69], evaluated 378 women totaling 705 breasts. Per-BC prevalence was 14%. Per-breast sensitivity was 87% for readers and 93% for independent double reading, and per-breast specificity was 93% for reader 1, 88% for reader 2, and 86% for double reading. The interobserver agreement was substantial ($\kappa = 0.736$). Interestingly, per-lesion double reading sensitivity for cancers ≤ 10 mm reached 71%. The authors also reported that the DWI acquisition time varied from 3:00 to 6:22 min; the median interpretation time per patient was 46 s for reader 1 and 51 s for reader 2. So far, no studies evaluated the performance of unenhanced (DWI) MRI protocols in the specific setting of high-risk screening. This is a perspective also deserving well-designed prospective studies.

23.7 Conclusions

The future of screening of women at high BC risk will be a partially unexpected combination of the trends mentioned above[5]. This combination will be mixed with the impact of AI which is the new

[5]A couple of interesting papers have been recently published and have to be mentioned. The first one regards the results of the DENSE study – Bakker MF, de Lange SV, Pijnappel RM et al. (2019) Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med 38:2091–2102 – a multicenter randomized controlled trial. The authors invited 8,061 women to MRI and 32,312 women to mammography (1:4 ratio). The 2-year interval cancer rate was 2.5 per 1,000 in the MRI group versus 5.0 per 1,000 in the mammography group ($p < 0.001$), an important result showing that the high MRI detection rate (16.5 per 1,000) allowed to halve the interval cancer rate. However, for MRI, PPV1 (recall rate) was 17%, PPV3 (biopsy) was 26%, and the false positive rate was 8%, while MRI screening was accepted only by 59% of the invited women. In addition, considering that this was a prevalent screening round, the authors noted "the relatively large number of well-differentiated and hormone-positive cancers among the MRI participants" and that an unknown fraction of MRI-detected cancers may represent overdiagnosis. The second paper – Obdeijn IM, Mann RM, Loo CCE et al. (2020) The supplemental value of mammographic screening over breast MRI alone in *BRCA2* mutation carriers. Breast Cancer Res Treat 181:581–588 – reported an overall screening sensitivity of 95.2% (81/85), with only 4 interval cancers, with a sensitivity of 86% for MRI and 50% for mammography ($p < 0.001$). In women below 40, one 6-mm grade 3 DCIS was detected by mammography, being only retrospectively visible on MRI, while other 7 cancers detected only at mammography were diagnosed in women aged 50 years and older, increasing sensitivity in this subgroup from 80% to 96% ($p < 0.001$). The authors concluded by suggesting to postpone mammographic screening in *BRCA2* mutation carriers to at least age 40.

factor extensively discussed in the literature as potentially changing the world of medical imaging [70], with relevant implication on ethics and regulatory issues [71].

The general impression is that this will be a second profound digital revolution. After the simple change in the physical nature of images (from screen-film to digital), the second revolution comes from the nature of the entire digital process: *images are more than pictures; they are data* [72]. Today this implies the possibility of using machine learning methods that provide results going well beyond what we had from traditional computer-assisted detection/diagnosis systems (see Chap. 7). While MRI is the preferred imaging modality for AI application in research papers [73], a survey among members of the European Society of Radiology [68] showed that breast imaging is perceived as the subspecialty mostly impacted by AI. This is probably due to the known high performance of machine/deep learning software substantially ready to work as one of the two readers of screening mammography. However, the screening reading has similar basic characteristics for whatever imaging and breast MRI; especially abbreviated contrast-enhanced protocols or simplified unenhanced protocols could be perfect candidates for AI systems for BC screening.

A systematic mapping review on AI for breast MRI [74] performed in June 2018 found 69 studies, which addressed breast lesion classification (54%), image processing (21%), prognostic imaging (13%), and response to neoadjuvant therapy (12%). Supervised learning algorithms were primarily used for lesion characterization, with a median ROC-AUC value of 0.87, a performance that does not allow them to be incorporated into clinical practice. A very recent work from the Tianjin Medical University Cancer Institute and Hospital, China [75], reported that a trained predictive model yielded a ROC-AUC value of 0.89 on an independent image set. However, we are only at the beginning of this road, and studies applying AI to MRI BC detection in the screening setting are lacking. But they are expected to arrive soon.

Independent of any AI applications to imaging (or also non-imaging) BC screening modalities, high-risk screening will be surely included into a general strategy to differentiate the age of beginning to screen, the (imaging) modalities, and the interval between screening events, according to the level of overall BC risk (lifetime or in the next 5 or 10 years), of risk of mammographically occult BC, and of risk of biologically aggressive BC. Breast MRI for high-risk screening has only tracked a first step of a long and large way.

At any rate, we should not forget that in hereditary BC predisposition, even a *BRCA1* deleterious mutation does not imply the certainty of BC during the woman's life: penetrance is limited, and up to 30–40% of mutation carriers do not develop the disease. As the Angelina Jolie story has shown, to know our genetic predisposition can guide our choices (see Chap. 19). However, *we are not our genes.* Environment and behavioral factors (epigenetics) play a role. A randomized controlled trial conducted at the University of Pennsylvania in high-risk women [76] showed that a 5-month 150 or 300 min/week aerobic exercise obtained a significant reduction in body mass, fat mass, body fat, and subcutaneous and visceral fat. Interestingly, for each -1 cm^2 reduction in visceral adipose tissue, the background parenchymal enhancement on breast MRI decreased on average by -3.43 cm^2 and explained 9.7% of the variability in background parenchymal enhancement (while changes in the other body composition parameters did not significantly correlate with changes in background parenchymal enhancement). The authors concluded that shifting energetic homeostasis through exercise may alter the risk of developing BC also in high-risk women.

It is good news that breast MRI could support BC research not only on the side of secondary prevention, i.e., early detection, but also on the side of primary prevention, which would be the best aim of social efforts against BC. We sincerely hope that this represents more than a hypothesis for the future.

References

1. Shapiro FR (2006) The Yale book of quotations. Section, Niels Bohr. Yale University Press, New Haven, p 92.
2. https://quoteinvestigator.com/2013/10/20/no-predict/. Accessed 30 Jun 2020.
3. Rourke S (2017) 12 Key Accidental discoveries in medicine. M edscape. https://www.medscape.com/slideshow/accidental-discoveries-6008976#13. Accessed 30 Jun 2020.
4. White MC, Soman A, Weinberg CR et al (2018) Factors associated with breast MRI use among women with a family history of breast cancer. Breast J 24:764–771
5. Miles R, Wan F, Onega TL et al (2018) Underutilization of supplemental magnetic resonance imaging screening among patients at high breast cancer risk. J Women's Health (Larchmt) 27:748–754
6. Hill DA, Haas JS, Wellman R et al (2018) Utilization of breast cancer screening with magnetic resonance imaging in community practice. J Gen Intern Med 33:275–283
7. My Personal Breast Screening (MyPeBS). https://mypebs.eu/. Accessed 30 Jun 2020.
8. Chiarelli AM, Prummel MV, Muradali D et al (2014) Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program. J Clin Oncol 32:2224–2230
9. Eisen A, Blackmore KM, Meschino WS et al (2018) Genetic assessment wait time indicators in the High Risk Ontario Breast Screening Program. Mol Genet Genomic Med 6:213–223
10. McVeigh TP, Wiggins J, Ward S, Kemp Z, George AJ (2018) Successful repatriation of breast cancer surveillance for high-risk women to the UK National Health Service Breast Screening Programme. Clin Breast Cancer 18:282–288
11. Vetter L, Keller M, Bruckner T et al (2016) Adherence to the breast cancer surveillance program for women at risk for familial breast and ovarian cancer versus overscreening: a monocenter study in Germany. Breast Cancer Res Treat 156:289–299
12. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM (2015 Oct 6) Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173,797 patients. BMJ 351:h4901
13. Plevritis SK, Munoz D, Kurian AW et al (2018) Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000–2012. JAMA 319:154–164
14. Kuhl C, Weigel S, Schrading S et al (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 28:1450–1457
15. Sardanelli F, Podo F, Santoro F et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Investig Radiol 46:94–105
16. Tilanus-Linthorst MM, Kriege M, Boetes C et al (2005) Hereditary breast cancer growth rates and its impact on screening policy. Eur J Cancer 41:1610–1617
17. Tilanus-Linthorst MM, Obdeijn IM, Hop WC et al (2007) BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imaging screening trials. Clin Cancer Res 13:7357–7362
18. Podo F, Santoro F, Di Leo G et al (2016) Triple-negative versus non-triple-negative breast cancers in high-risk women: phenotype features and survival from the HIBCRIT-1 MRI-including screening study. Clin Cancer Res 22:895–904
19. Macías M, Alegre E, Díaz-Lagares A et al (2018) Liquid biopsy: from basic research to clinical. Adv Clin Chem 83:73–119
20. Sato Y, Matoba R, Kato K (2019) Recent advances in liquid biopsy in precision oncology research. Biol Pharm Bull 42:337–342
21. De Rubis G, Rajeeev Krishnan S, Bebawi M (2019) Liquid biopsies in cancer diagnosis, monitoring, and prognosis. Trends Pharmacol Sci 40: 172–186
22. Kwapisz D (2017) The first liquid biopsy test approved. Is it a new era of mutation testing for non-small cell lung cancer? Ann Transl Med 5:46
23. Memorial Sloan Kettering discovery study. https://ichgcp.net/clinical-trials-registry/NCT03372902. Accessed 30 Jun 2020
24. 2018 Annual Meeting of the American Society of Clinical Oncology. https://ascopubs.org/jco/meeting?expanded=tvolume-suppl.d2010.y2018. Accessed 30 Jun 2020
25. Savage L (2008) What happened to the cancer-detecting bra? J Natl Cancer Inst 100:13
26. Rahman A, Islam MT, Singh MJ, Kibria S, Akhtaruzzaman M (2016) Electromagnetic performances analysis of an ultra-wideband and flexible material antenna in microwave breast imaging: to implement a wearable medical bra. Sci Rep 6:38906
27. TG (2019) A French-Swiss research team is developing a "smart bra" for detecting breast cancer more accessible than through mammography. European Biotechnology June 28. https://european-biotechnology.c om/up-to-date/latest-news/news/smart-bra-set-to-detect-breast-cancer.html. Accessed 30 Jun 2020
28. Roark AA, Dang PA, Niell BL, Halpern EF, Lehman CD (2019) Performance of screening breast MRI after negative full-field digital mammography versus after negative digital breast tomosynthesis in women at higher than average risk for breast cancer. AJR Am J Roentgenol 212:271–279

29. Choi Y, Woo OH, Shin HS, Cho KR, Seo BK, Choi GY (2019) Quantitative analysis of radiation dosage and image quality between digital breast tomosynthesis (DBT) with two-dimensional synthetic mammography and full-field digital mammography (FFDM). Clin Imaging 55:12–17
30. Sardanelli F, Podo F, Santoro F, et al for the High Breast Cancer Risk Italian 1 (HIBCRIT-1) Study (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Investig Radiol 46:94–105
31. Kelly KM, Dean J, Comulada WS, Lee SJ (2010) Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol 20:734–742
32. Halshtok Neiman O, Erlich Z, Friedman E et al (2016) Automated breast volumetric sonography compared with magnetic resonance imaging in Jewish BRCA 1/2 mutation carriers. Isr Med Assoc J 18:609–612
33. Vourtsis A, Kachulis A (2018) The performance of 3D ABUS versus HHUS in the visualisation and BI-RADS characterisation of breast lesions in a large cohort of 1,886 women. Eur Radiol 28: 592–601
34. Zhang L, Bao LY, Tan YJ et al (2019) Diagnostic performance using automated breast ultrasound system for breast cancer in Chinese women aged 40 years or older: a comparative study. Ultrasound Med Biol 45:3137–3144
35. Berg WA, Zhang Z, Lehrer D et al (2012) Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 307:1394–1404
36. Ghaderi KF, Phillips J, Perry H, Lotfi P, Mehta TS (2019) Contrast-enhanced mammography: current applications and future directions. Radiographics 39:1907–1920
37. Jong RA, Yaffe MJ, Skarpathiotakis M, Shumak RS, Danjoux NM, Gunesekara A, Plewes DB (2003) Contrast-enhanced digital mammography: initial clinical experience. Radiology 228:842–850
38. Lewin JM, Isaacs PK, Vance V, Larke FJ (2003) Dual-energy contrast-enhanced digital subtraction mammography: feasibility. Radiology 229:261–268
39. Zanardo M, Cozzi A, Trimboli RM et al (2019) Technique, protocols and adverse reactions for contrast-enhanced spectral mammography (CESM): a systematic review. Insights Imaging 10:76
40. Dromain C, Vietti-Violi N, Meuwly JY (2019) Angiomammography: a review of current evidences. Diagn Interv Imaging 100:593–605
41. Phillips J, Miller MM, Mehta TS et al (2017) Contrast-enhanced spectral mammography (CESM) versus MRI in the high-risk screening setting: patient preferences and attitudes. Clin Imaging 42:193–197
42. Sung JS, Lebron L, Keating D et al (2019) Performance of dual-energy contrast-enhanced digital mammography for screening women at Increased risk of breast cancer. Radiology 293:81–88
43. Mann RM, Kuhl CK, Moy L (2019) Contrast-enhanced MRI for breast cancer screening. J Magn Reson Imaging 50:377–390
44. Cozzi A, Schiaffino S, Sardanelli F (2019) The emerging role of contrast-enhanced mammography. Quant Imaging Med Surg 9:2012–2018.
45. Knogler T, Homolka P, Hoernig M et al (2017) Application of BI-RADS descriptors in contrast-enhanced dual-energy mammography: comparison with MRI. Breast Care 12:212–216
46. Colin C, Foray N, Di Leo G, Sardanelli F (2017) Radiation-induced breast cancer risk in BRCA mutation carriers from low-dose radiological exposures: a systematic review. Radioprotection 52:231–240
47. MRI for high risk women | Cancer Australia. https://canceraustralia.gov.au/clinical-bestpractice/breast-cancer/screening-and-early-detection/mrihigh-risk-women. Accessed 30 Jun 2020
48. Associazione Italiana di Oncologia Medica (2018) Breast neoplasms guidelines. https://www.aiom.it/wp-content/uploads/2018/11/2018_LG_AIOM_Breast_ENversion.pdf. Accessed 30 Jun 2020
49. Bick U, Engel C, Krug B et al (2019) High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat 175: 217–228
50. National Comprehensive Cancer Network (2019) Genetic/Familial high-risk assessment: Breast and ovarian. https://www.nccn.org. Accessed 30 Jun 2020
51. Mariscotti G, Belli P, Bernardi D et al (2016) Mammography and MRI for screening women who underwent chest radiation therapy (lymphoma survivors): recommendations for surveillance from the Italian College of Breast Radiologists by SIRM. Radiol Med 121:834–837
52. Cheung YC, Tsai HP, Lo YF, Ueng SH, Huang PC, Chen SC (2016) Clinical utility of dual-energy contrast-enhanced spectral mammography for breast microcalcifications without associated mass: a preliminary analysis. Eur Radiol 26:1082–1089
53. Wienbeck S, Lotz J, Fischer U (2017) Review of clinical studies and first clinical experiences with a commercially available cone-beam breast CT in Europe. Clin Imaging 42:50–59
54. Berger N, Marcon M, Frauenfelder T, Boss A (2019) Dedicated spiral breast computed tomography with a single photon-counting detector: initial results of the first 300 women. Invest Radiol 55:68–72
55. Uhlig J, Fischer U, Surov A, Lotz J, Wienbeck S (2018) Contrast-enhanced cone-beam breast-CT: Analysis of optimal acquisition time for discrimination of breast lesion malignancy. Eur J Radiol 99:9–16
56. Kalender WA, Kolditz D, Steiding C, Ruth V, Lück F, Rößler AC, Wenkel E (2017) Technical feasibility

proof for high-resolution low-dose photon-counting CT of the breast. Eur Radiol 27:1081–1086
57. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L (2007) European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol 19:614–622
58. Di Leo G, Trimboli RM, Sella T, Sardanelli F (2017) Optical imaging of the breast: basic principles and clinical applications. AJR Am J Roentgenol 209:230–238
59. Hellgren RJ, Sundbom AE, Czene K, Izhaky D, Hall P, Dickman P (2019) Does three-dimensional functional infrared imaging improve breast cancer detection based on digital mammography in women with dense breasts? Eur Radiol 29:6227–6235
60. Kuhl CK (2019) Abbreviated magnetic resonance imaging (MRI) for breast cancer screening: rationale, concept, and transfer to clinical practice. Annu Rev Med 70:501–519
61. Heller SL, Moy L (2019) MRI breast screening revisited. J Magn Reson Imaging 49:1212–1221
62. Ko ES, Morris EA (2019) Abbreviated magnetic resonance imaging for breast cancer screening: concept, early results, and considerations. Korean J Radiol 20:533–541
63. Clauser P, Helbich TH, Kapetas P et al (2019) Breast lesion detection and characterization with contrast-enhanced magnetic resonance imaging: Prospective randomized intraindividual comparison of gadoterate meglumine (0.15 mmol/kg) and gadobenate dimeglumine (0.075 mmol/kg) at 3T. J Magn Reson Imaging 49:1157–1165
64. Knopp MV, Bourne MW, Sardanelli F et al (2003) Gadobenate dimeglumine-enhanced MRI of the breast: analysis of dose response and comparison with gadopentetate dimeglumine. AJR Am J Roentgenol 181:663–676
65. Sardanelli F, Carbonaro LA, Montemezzi S, Cavedon C, Trimboli RM (2016) Clinical breast MR using MRS or DWI: who is the winner? Front Oncol 6:217
66. Iima M, Honda M, Sigmund EE, et al (2020) Diffusion MRI of the breast: current status and future directions. J Magn Reson Imaging 52:70–90
67. Baxter GC, Graves MJ, Gilbert FJ, Patterson AJ (2019) A meta-analysis of the diagnostic performance of diffusion MRI for breast lesion characterization. Radiology 291:632–641
68. Trimboli RM, Verardi N, Cartia F, Carbonaro LA, Sardanelli F (2014) Breast cancer detection using double reading of unenhanced MRI including T1-weighted, T2-weighted STIR, and diffusion-weighted imaging: a proof of concept study. AJR Am J Roentgenol 203:674–681
69. Rotili A, Trimboli M, Penco S, et al (2020) Double-reading of diffusion-weighted magnetic resonance imaging for breast cancer detection. Breast Cancer Res Treat 180:111–120
70. Pesapane F, Codari M, Sardanelli F (2018) Artificial intelligence in medical imaging: threat or opportunity? Radiologists again at the forefront of innovation in medicine. Eur Radiol Exp 2:35
71. Pesapane F, Volonté C, Codari M, Sardanelli F (2018) Artificial intelligence as a medical device in radiology: ethical and regulatory issues in Europe and the United States. Insights Imaging 9:745–753
72. Gillies RJ, Kinahan PE, Hricak H (2016) Radiomics: images are more than pictures, they are data. Radiology 278:563–577
73. European Society of Radiology (ESR) (2019) Impact of artificial intelligence on radiology: a EuroAIM survey among members of the European Society of Radiology. Insights Imaging 10:105
74. Codari M, Schiaffino S, Sardanelli F, Trimboli RM (2019) Artificial intelligence for breast MRI in 2008–2018: a systematic mapping review. AJR Am J Roentgenol 212:280–292
75. Ji Y, Li H, Edwards AV et al (2019) Independent validation of machine learning in diagnosing breast cancer on magnetic resonance imaging within a single institution. Cancer Imaging 19:64
76. Brown JC, Kontos D, Schnall MD, Wu S, Schmitz KH (2016) The dose-response effects of aerobic exercise on body composition and breast tissue among women at high risk for breast cancer: a randomized trial. Cancer Prev Res (Phila) 9:581–588

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