Radiological Screening of Breast Cancer: Evolution

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Abbreviations

AWBU	Automated whole-breast ultrasound
BC	Breast cancer
CAD	Computer-aided diagnosis
CC	Case-control
CE	MRI Contrast-enhanced magnetic resonance imaging
CI	Confidence interval
CNBSS	Canadian National Breast Screening Study
CRT	Chest radiation therapy
DBT	Digital breast tomosynthesis
HIP	Health Insurance Plan
HR	High risk
IBM	Incidence-based mortality
IT	Information technology
LTR	Lifetime risk
MR	Magnetic resonance
MS	Mammography screening
NBCSP	Norwegian Breast Cancer Screening Programme
NCR	Nordic Cochrane review
NNS	Number needed to screen
OR	Odds ratio
PPV	Positive predictive value
RCT	Randomized controlled trial
RR	Relative risk
STC	Swedish Two County
TNBC	Triple negatibe breast cancer
US	Ultrasound
USPSTF	US Preventive Services Task Force

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17.1 Normal Risk Population

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Abstract Mammography screening is one of the revolutionary advances in the fight against breast cancer, alongside breast-conserving surgery. Few medical interventions have been so extensively evidence-based and yet subjected to persistent critiques. The clear scientific evidence of the efficacy of screening in reducing breast cancer mortality is discussed. Benefits provided by screening are substantial, well above any negative effect. In the age of modern treatment, early detection still contributes to breast cancer mortality reduction.

A full appreciation is advocated for organized screening programs and the added value they provide in terms of high quality, equitable health service, and as the optimal environment where best capitalize on the new advances in treatment. Future evolution might include (a) tailored, risk-based protocols, in the first place extending the age range of offered screening; (b) new imaging tools; and (c) optimization of existing programs, through better monitoring, training, and research—always abiding by the big caveats: evidence of efficacy, incremental cost-effectiveness, and sustainability. Both screening and treatment have merits in achieving mortality reduction. It would be clever to recognize their mutual enhancing power and devote resources to a very appropriate topic for research: how early detection might or should change the treatment of breast cancer.

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17.1.1 Introduction

Breast cancer (BC) has been a curse for women's health since historical records exist, back to the ancient civilizations thousands of years ago. Our generation has had the privilege to witness the first real breakthrough in a long-standing story of sufferance and defeats. It was only the final decades of the twentieth century that brought about decisive innovations, in both diagnosis and treatment of this ominous disease. New medical therapies were introduced, and radiation oncology was developed, both attaining a relevant role in treatment protocols, especially so in their adjuvant capacities.

However, the two major advances came (a) with the introduction of breast-conserving surgery and (b) with the prospective, randomized controlled trials (RCT) that demonstrated for the first time in history the possibility to reduce BC mortality through early diagnosis, by the systematic application of mammography screening (MS).

The therapeutic equivalence of quadrantectomy to mastectomy in the treatment of small cancers, originally suggested and then scientifically demonstrated by Veronesi and others [1, 2], presented women with an amazing chance to avoid the traditional, mutilating, standard treatment of the last century, namely, Halsted's radical mastectomy.

Almost at the same time, population-based radiological (mammographic) screening was proposed and validated as a major health achievement that made it possible to decrease BC mortality by treating the disease when it was still localized in the breast.

Indeed, these two major innovations enhanced each other's benefits, as early mammographic diagnosis provided surgeons with more and more small cancers, which could be a candidate for the new breast-sparing surgery. Early detection allowed also for the adjuvant therapies, both medical and radiation-based, to achieve extraordinary results in disease control. Through this mutual support, early diagnosis in conjunction with more effective treatment opened the way to a new era in the fight against BC.

It is ironic that in recent years, it was just this enhancing, synergic action that offered one of a series of spurious arguments to discount the value of early detection as a powerful measure to control BC mortality, in this epoch of developing new therapeutic regimens. Such argument has given support to a great deal of data misinterpretation and a long sequence of futile controversies.

The present pages shall try to summarize and highlight the clear, overwhelming scientific evidence on the efficacy of MS in reducing BC mortality and the importance of building and keeping up large population-based screening programs as a needful strategy in order to best capitalize all the treatment advances that have been and are being developed.

It will be shown how current estimates of benefits achievable through MS are substantially undervalued, and it will also be suggested that the future evolution of BC management should strive to include an innovative rethinking of some concepts that form the basis of pathological representation, description, and classification of breast diseases, taking into consideration many new pieces of knowledge derived from the screening experience. This new perspective could bring about a change in the fundamental concepts of BC treatment, at least when the tiny, screen-detected cancers are involved. New tailored treatment protocols, based on a full appreciation of different parameters of tumor characterization, should be developed. These in turn would make it negligible the concern that has been raised on the overdiagnosis at screening (and the ensuing overtreatment) of a proportion of indolent cancer cases.

In the near future, alongside some anticipated technology-based modifications of the protocols (the subject of subsequent chapters in this book), the evolution of MS will have to consider many different ways of customizing the screening intervention, according to various risk factors, in order to maximize the cost-effectiveness of the system.

17.1.2 The Evidence

Few medical procedures and interventions have been so extensively studied, proven effective, thoroughly evidence-based as MS, and yet discussed and subjected to persistent critiques and unrelenting, often specious attacks.

Since the pioneering New York Health Insurance Plan (HIP) project [3], a wealth of studies, trials, and service programs formed the basis for hundreds of publications that have been dedicated to MS, so that an exhaustive bibliography is practically impossible to collect and report. It is worthy of note and almost a paradox that the prospective, randomized controlled trials (RCTs) where we base the core of our knowledge have been subjected to far more analyses and meta-analyses than the original number of trials. Therefore, references at the end of this chapter should be considered as a very selective choice of relevant contributions. A comprehensive list of references (up to year 2012), as well as a very knowledgeable analysis of their contents, may be found in the special supplement issue of the *Journal of Medical Screening* edited by Paci and reporting the efforts of the Euroscreen Working Group in providing in-depth, expert discussion of the literature on MS, as well as precious, recent data from many European countries [4]. It is convenient to remark at this point that from the immense database accumulated through the screening experience, the best researchers have been able to draw illuminating concepts on the natural history of BC [5].

It was just this incredible number of publications, combined with the substantially variable quality among them and with the extreme complexity of the subject matter, that in the first place made it possible and then immensely contributed

to the diffusion of a still unending trail of largely futile controversies. However, a portion of the conflicting views on MS may in fact derive from different ways of expressing the same results, rather than from substantial disagreement on the data available.

It is still unfortunate that what has been opportunely defined as "an active anti-screening campaign […] based on erroneous interpretation of data from cancer registries and peer-reviewed articles" [6] has been kept alive over the last two decades to this day, with a disconcerting pattern of following waves. This process may be described as a "provocative sequence" of:

(a1) Main question
(a2) Scientific proof provided
(a3) Evidence questioned on poor or unsubstantiated terms
(a4) Evidence (to some extent) conceded, but then
(b1) New question set forward
(b2) Scientific proof provided - etc, through (d4)

According to this pattern, the subsequent questions and critical waves against MS can be summarized as follows (a discussion of these points and relevant references are given below):

(a) Can MS reduce BC mortality?—**the efficacy issue**: (a1) evidence provided by the big RCTs; (a2) evidence questioned, most pugnaciously by the Nordic Cochrane Centre; (a3) evidence eventually (to some extent) conceded in subsequent articles; and (a4) new issue set forward about effective reproducibility of trial results into public health practice.

(b) Can MS service programs reproduce the results of the RCTs and actually save lives in a sustainable way in the context of the health-care system?—**the effectiveness issue**: (b1) evidence provided by a large number of observational studies; (b2) evidence questioned, mostly on the basis of methodologically poor "ecological" studies, lacking information about actual exposure of women to MS; (b3) evidence eventually conceded in subsequent articles; and (b4) new issue set forward about "harms" of screening surpassing the possible benefits.

(c) Are the benefits provided by MS more substantial than any unwanted effect that it may produce?—**the harm/benefit balance** analysis of MS: (c1) evidence of a favorable balance provided by many researchers and prominently in the Euroscreen Working Group analysis; (c2) evidence questioned, especially on the basis of grossly inflated estimates of overdiagnosis; (c3) evidence conceded, most authoratively by the UK Independent Panel [7], the "Marmot report;" (c4) new issue set forward about any remaining significance of the role of early detection in the new age of effective cancer treatment.

(d) Even after MS was proved valid and effective by RCTs and even conceding that its side effects could be minor in respect to the potential benefits, does early detection through MS still hold its meaning in the new era where very effective new treatments for BC have become available? Is it not the case that most of the BC mortality reduction that has been recently observed should be credited to treatment rather than MS?—**the "expired validity" issue** of MS: (d1) evidence has been provided confirming a substantial net benefit of screening on top of the achievements of treatment and (d2) discussion on this point (d3–d4) will be commented in the following pages.

It might reasonably be argued that the above sequence respects the very basics of scientific debate. This would be certainly true, if such sequence was not undermined, as in this case, by an almost breathtaking, unrelenting introduction of methodologically weak or clearly erroneous arguments.

Then, for all these questions, is there any real room for genuine controversy?

The clear, plain answer has to be no.

It is soundly proved that MS substantially does reduce BC mortality and is effective in actual health-care practice; the benefits produced by MS are large and substantial, well above any negative effect.

MS does still substantially contribute to BC mortality reduction even in the age of modern treatment.

The exception where there is indeed space for further analysis is overdiagnosis which, although well compensated for by the mortality reduction benefit, is an extremely complex topic that deserves a more thorough discussion.

In the above series, one more argument has been purposely skipped that had at one point been raised to fuel the debate, namely, the lack of evidence about MS reducing general (all-cause) mortality in the population. This appears the most specious in a series of largely specious arguments. As clearly stated in the Marmot report, reducing BC deaths by 20% in ages 55–79 years would yield a 1.2% reduction in all-cause deaths. The RCTs were not designed for and "are not of sufficient size to allow such small reductions to be reliably estimated. Hence, a statistically non-significant effect for all-cancer or all-cause deaths in the trials cannot be interpreted as evidence against a reduction in BC deaths" [7].

Rather, two key points deserve to be highlighted already at this point, as central in the debate:

1. The quality evaluation of the studies considered has to be factual and circumstantial, i.e., their internal validity must be convincingly proven.
2. The importance of very long follow-up times. These are imperative as we aim at the precise estimate of the benefits involved with the early detection of a group of diseases like BC, which are characterized by a variable, often very long natural history.

Of the above sequence, **issue (a)** will be discussed at this point.

Issues (b–d) will be the subject of paragraph three (service screening).

17.1.2.1 The Efficacy Issue

MS involves an active intervention on large populations over extended times, i.e., huge numbers of study subjects, observed for very long study and follow-up periods, with many parameters to consider, subjected to a number of possible biases. The rationale for screening is advancing the time of diagnosis in order to improve prognosis through earlier treatment. Thus, the apparent incidence of BC has to increase at the start of the process. Also average time from diagnosis to death will increase, introducing a powerful bias (lead-time bias). This might induce erroneous estimates of benefits and harms of MS, when not judiciously taken into account. However, MS efficacy can be stated with great confidence, thanks to available scientific data of the best quality in order to overcome lead-time bias, as mortality data from RCTs are available to support it.

The wealth of evidence provided by a number of excellent, more recent observational studies will also be considered and highlighted in the next paragraph.

The story itself of MS was in fact born with a randomized study. It originated from a brilliant idea back in the 1950s–1960s, when the new technical tool of mammography was suggested [8] and then put to test in New York City in a prospective, randomized trial of annual invitation to mammography plus physical examination vs. current clinical practice in the HIP project. The statistically significant mortality reduction from BC in the study vs. control group [3, 9] was confirmed by further updates of the HIP data [10], as well as by a number of subsequent RCTs set up in the period 1976–1991.

Up to 14 RCTs [11] could be considered, the total number depending on counting trials with two parts (Malmoe, Swedish Two-County, Canada I and II) as separate studies or not and on exclusion criteria for one or more trials on different motivations, either of design or of their quality. As a consequence, meta-analyses and systematic reviews of RCTs, the most common gold reference for directing decisions on screening policies, may vary in their conclusions mainly due to the quality criteria for selection of trials to be included in the review process. More commonly, eight big RCTs are considered, and seven are actually included [7, 11], since all reviews agree to discard the Edinburgh trial on major unbalances in the randomization process [12].

The seven trials considered are the HIP study, started in 1963; the Malmoe trial I, started in 1976; the Swedish Two-County (STC) study (Kopparberg arm, started in 1977, and Ostergotland arm, started in 1978); the Canada I and II (CNBSS), started in 1980; the Stockholm trial, started in 1981; the Gothenburg trial, started in 1982; and the UK Age trial, started in 1991.

It is remarkable that, beyond all the many differences among the trials in design, technicalities (e.g., number of mammographic views), intervals between screening rounds, age groups involved, duration of follow-up, etc., meta-analyses tend to converge on an estimate of around 15–20% relative risk (RR) reduction in BC mortality for women invited to MS vs. the non-invited.

The Marmot report [7] may rightly be considered as the most balanced among the recent highest profile reviews, with regard to the MS debate, coming from a group of independent experts, selected and nominated by the UK authorities on the basis of their knowledge and on the absence of any personal involvement in the dispute. These authors recognize a 20% mortality reduction from BC associated with invitation to screening. They summarize their findings in a table that we reproduce in a simplified form as in Table 17.1, for ease of reference and discussion.

On the other hand, one might regard the series of meta-analyses from the Cochrane Collaboration, as the most pugnaciously critical of MS. Originated from a commission back in 1999, they were first published in 2001 and revised a number of times to the latest review in 2013, to which we now refer as the Nordic Cochrane review (NCR) [11]. These authors consider that the only three trials with "adequate randomization," i.e., Canada, Malmoe, and UK Age trials, did not show a significant reduction in BC mortality, with a RR of 0.90 (95% CI: 0.79–1.02). They recognize that the other four trials that they considered of "suboptimal randomization" showed a significant RR reduction of 0.75 (95% CI: 0.67–0.83). It must be remarked though that the quality evaluation as proposed by the NCR has been substantially subverted by the more balanced review of the UK Independent Panel [7]. The RR for all seven trials in the NCR was statisti-

Table 17.1 Breast cancer mortality reduction in RCTs of mammography screening

Study, date of start	Age group	RR	95% CI	Weight (%)
New York, 1963*	40–64	0.83	0.70–1.00	16.9
Malmoe I, 1976*	45–69	0.81	0.61–1.07	9.5
Kopparberg, 1977	38–75	0.58	0.45–0.76	10.7
Ostergotland, 1978	38–75	0.76	0.61–0.95	13.0
Canada I, 1980**	40–49	0.97	0.74–1.27	10.2
Canada II, 1980**	50–59	1.02	0.78–1.33	10.2
Stockholm, 1981*	39–65	0.73	0.50–1.06	6.0
Gothenburg, 1982	39–59	0.75	0.58–0.98	10.7
UK age trial, 1991*	39–49	0.83	0.66–1.04	12.8
Overall		0.80	0.73–0.89	

A meta-analyses after 13 years of follow-up, based on the Cochrane [11] and Marmot reviews [7] (modified)

RCT randomized controlled trial, *RR* relative risk, *CI* confidence interval

*Studies falling short of statistical significance and/or RRs between 0.80 and 0.90

**Studies with no statistical significance and RRs beyond 0.90

cally significant at 0.81 (95% CI: 0.74–0.87). The NCR concludes that assuming a 15% reduction in BC mortality with MS, one would need to invite 2000 women throughout 10 years to save one life.

Duffy et al. [13] argue that the number needed to invite is not the proper measure, since it will be heavily influenced by the attendance rate of the population; they recommend the number needed to screen (NNS) to prevent 1 BC death, as a more adequate measure of MS benefit. They work on this and make assumptions about a UK scenario. After correction for the actual participation rate to the UK screening program of 77%, starting from the Cochrane value of 15% mortality reduction in the invited women, they come to an estimate of 257 NNS in 10 years to prevent 1 BC death, as compared to the 2000 needed to invite in the Cochrane estimate. It is opportunely remarked that the very low estimate of absolute benefit in the Cochrane review derives from unduly restricting the benefit analysis to a 10-year period and from their selection of trials dominated by the younger (below 50) age group, which has considerably lower absolute mortality. Applying the same reasoning, corrections and NNS to another major recent review by the US Preventive Services Task Force (USPSTF) [14], Duffy et al. come to a similar result of 193 NNS to prevent 1 BC death. They insist that expressing results relative to the same denominator, with the same follow-up lenght, referring to absolute mortality rates, and applying them to different published reviews - we end up with absolute measures of benefit of the same, relevant order of magnitude. This supports the concept that the so-called controversy on BC screening is to a large extent an artificial one.

The NNS idea refers to the underlying problem of trials reporting benefits of invitation (intention to treat analysis), rather than an actual screening. Higher mortality reductions are expected in women actually attending screening; still it is difficult to say by how much, since different background risks may be involved due to selection bias. Women who attend screening are as such representative of a health-aware portion of the population that might gain extra benefits (beyond those conferred by MS) from the attitude that makes them keen to seek medical support, whenever needed.

One way to tackle this theme would be to consider the RCT evidence as the extremely reliable proof on which to base health policies and screening recommendations. It should be reminded though that the trials tested the impact of invitation to screening on BC mortality. As for the benefit expected for a woman actually attending screening, RRs should be best derived from service screening mortality estimates of attenders vs. nonattenders (see next paragraph).

It is also interesting to consider the USPSTF meta-analysis stratified on different age groups. The USPSTF estimates BC mortality reductions of 15% in the 39–49 age group, of 14% in the 50–59, and of 32% in the 60–69. One might consider that these differences could be determined by the well-known detection limitations of mammography in the denser breasts of younger women. Yet, it is worthy of note that the USPSTF estimates of the two younger age groups very closely resemble the Cochrane analysis of the so-called "adequately randomized" trials, among which only the smaller Malmoe trial includes a portion of women over 59 years old. In fact, it is the relative weight of the Canadian data that do not include the over 60 age group, to introduce a powerful bias.

At this point, some special remarks are warranted on the disgraceful impact of the Canadian National Breast Screening Studies (CNBSS) I and II on the screening debate.

The Canadian Contamination

The CNBSS was set up in 1990 as a thoroughly designed, ambitious project, into which enormous energy, resources, and good will were invested. It ended up as a huge amount of significantly flawed data that should not be considered any more in meta-analyses of screening trials. The fact that these data [15, 16] and one recent update of the same, based on a 25-year follow-up [17], have been widely considered in reviews and referred to contributed extensively to building up and maintaining the artificial controversy on MS. This process may be defined "the Canadian contamination." Instead, it has to be clearly stated that these Canadian results lack methodological value and should not be relied upon for evidence-based conclusions [18]. A quick glance at Table 17.1 suffices to show the CNBSS trials as the flagrant outlayers, showing no hint of benefit, as compared to the other seven studies, whose RRs range from 0.57 to 0.83. It is sadly ironic that the outlayer studies, with a flawed evidence base, should have cast their shadow on a wealth of scientifically sound data from so many other researchers.

It was immediately after their original publication in 1992 that a flourish of critics exploded in the scientific literature. These have obviously been resparkled after the Canadian follow-up article was published in 2014 [17]. In a recent paper by Heywang-Köbrunner et al. [18]—to which we refer the reader for an extremely detailed analysis of the debate and for punctual references—a systematic search on this topic yielded close to 300 articles, 70 of which were deemed of special interest. These articles split in two similar parts of 33 "defending" papers, mostly authored by the original directors of the study vs. 37 "critical" articles by a much wider, representative group of researchers.

The long series of critiques to the Canada trials fall in two main fields:

(a) Technical/clinical quality issues
(b) Methodological/management issues

Both are extensive; however, the methodological/management points are overwhelming.

Group (a) critiques were mainly on the quality of mammography. Quality of images (low contrast resolution, insufficient sharpness, and over- and underexposure) and of positioning was so heavily questioned that many external expert reviewers resigned from their position in the trial on claims of unacceptably poor standards and of their corrective measures not being taken into proper consideration. Also the interpretation of films was criticized as some readers had insufficient training and many obvious cancers were missed. Although quality issues must have played a role in the final results, the core reason why the CNBSS trials should not be considered eligible to be reckoned in meta-analyses of RCTs has to be found in the other group of arguments.

Group (b) issues (the methodological/management problems) are indeed conspicuous. The study design has often been described (most prominently by its authors) as ideal, due to randomization being carried out at the individual level. Conceding that, in principle, individual randomization would be preferable over cluster randomization, what in fact matters is the quality of the process. Most reviewers, among them the UK Independent Panel, recognized that cluster randomization produced significant biases in the Edinburgh trial, and on that basis, they excluded it from meta-analyses, but not in the STC trials, where cluster randomization did not result in relevant unbalances, so that the same reviewers agree to consider this study as soundly evidence based, eligible to be included in reviews.

On the other hand, the randomization process blatantly failed in the Canadian trials, as so apparently shown by the disproportionately large number of participants with late-stage cancer in the mammography arm at the first round [17–19]. Indeed, soon after the first CNBSS publication, the observation of the heavily unbalanced distribution of advanced cancers in young women was supported by a series of reports [20–23] on various contradictions to the initial study design. It was reported that randomization was performed at certain sites after a clinical breast examination, blinding was not consistently warranted, and various easy possibilities of subversion existed and could be done in practice. The motivation for this would have been—in good faith and with no fraudulent intention—to guarantee that significantly symptomatic women would be offered a mammogram. It is a recognized fact that at one time the coordinator of one unit was removed because of suspected subversion of the randomization.

The weak defense of the CNBSS investigators has eventually to face the striking fact that among the first round of younger women, 19 advanced cancers were allocated to the screening arm vs. five in the control arm. Also, eight women in the screening arm vs. one in the control arm had previous history of BC. It is clearly preposterous on the investigators' side to argue that a long list of other variables was perfectly balanced in the two study arms, when the most clinically significant variable, i.e., late-stage BC at first round, was so heavily unbalanced.

The Canadian update itself [17] that has been widely publicized to the scope of discrediting the benefits of MS does in fact supports the contrary view. In that paper, deaths from BC detected at year 1 of the study were double (52 vs. 26) in the mammography arm vs. control arm, a fact that is the obvious consequence of flawed randomization, as shown by the exceedingly unbalanced number of late-stage cancers.

It is telling to quote the authors' own words: "it has been suggested that women with a positive physical examination before randomization were preferentially assigned to the mammography arm. If this were so, the bias would only impact on the results from BC diagnosed during the first round of screening … However, after excluding the prevalent BC from the mortality analysis, the data do not support a benefit for MS (HR = 0.90, CI 0.69–1.16)."

This passage is so important as (1) it implicitly concedes that preferential assignations might indeed have happened within the trial organization and (2) recalculates HRs for only incident rounds of the trial demonstrating a clear drop in HRs. At this point, the authors, rather than expressing this as it should be, i.e., as a shocking 50% difference from the infamous HR value of 1.47 in the prevalent round of the trial (explainable only by subverted allocation) to a promising HR of 0.90 for incident rounds, prefer to highlight the fact that this value still shows a benefit of no statistical significance. The point is that it does suggest a benefit that might have been significant (a) in a high-quality screening service, as compared to the low mammography quality documented in the trial setting, and (b) in a more powerful study design or within a proper meta-analysis that should exclude the biased prevalent round data of CNBSS.

It is beyond the scope of this chapter to further discuss a number of questionable points in the CNBSS studies that contribute to make their results definitely not applicable to quality-assured screening programs. Just in passing, these other objections include the following: the studies included palpable, symptomatic cancers; these were in fact not blindly allocated to the two arms; long-term mortality reduction was calculated from a mixed trial participation of one to five rounds during up to 5 years, thus diluting enormously the benefit that would be possibly demonstrated; and recommended biopsies were not systematically performed.

The crucial point is that using these Canadian data, "evidence in the field of BC screening has systematically been omitted, distorted or inappropriately used over the last decades" [18]. Instead, CNBSS data are not applicable to evidence-based results of modern MS.

The Follow-Up Factor

One should regard BC as a group of many different diseases, with an average long natural history. Even back when MS and modern therapies were not available, median survival times for BC patients used to be several years. This explains the fact that no screening trials can show a mortality benefit in the first 2–3 years after their start and also that most benefit has to be reckoned only after many years of follow-up.

Screening could be then compared to an excellent mix of financial investment products. The investor may cash some short-term dividends, i.e., from lives saved after 3–5 years, due to the timely detection of very aggressive, Grade 3 cancers. Most profits will come in the middle term, these being lives saved 6–10 years after detection of Grade 2 cancers, while some long-term returns should be expected from lives saved 11–20 years after the detection of slowly growing cancers.

This consideration justifies the extra mortality reduction that is still evident in RCTs, after the moment when the control group is offered MS: a fact that puzzled many critics of MS, as in the original Cochrane reviews. This phenomenon is particularly well represented in the 29 years of follow-up publication of the Swedish Two-County trial [24] where most of the prevented BC deaths were those that would have occurred over 10 years after the start of screening, from cancers diagnosed in the first 7–8 years of the study, since after that time the control group was exposed to screening.

This supports the principle that in MS, as is the case with other primary and secondary prevention activities, considerable long-term follow-up is necessary for a full appreciation of the benefits involved. In a RCT setting, most benefit is to be expected more than 10 years after the trial starts, from cancers diagnosed in the first 5–10 years (recruitment period), depending if and when the control group is offered screening after the study recruitment phase.

Failure to fully appreciate this concept has led to many inconsistent or weak analyses and meta-analyses and to a substantial undervaluation of the merits of screening.

The importance of prolonged follow-up times will be shown for the observational studies, in the following paragraph. As to RCTs, implications are also important, e.g., when one considers the latest updates of the UK Age and Gothenburg trials [25, 26], both showing significant benefits from screening after follow-up times extended to 17 years, also in younger women (and provided one restricts the UK analysis to cases diagnosed in the intervention phase).

A similar pattern was demonstrated in an overview of the Swedish RCTs [27] that, restricting the analysis to women randomized when 40–44, demonstrated a 15% reduction in BC mortality at long-term (over 14 years) follow-up. In this overview, benefit increased up to 12 years after randomization and was then maintained.

Conclusive Remarks on the Efficacy Data from RCTs

When all the evidence in favor of MS is considered and duly recognized, screening opponents come up with another argument (issue d—in the above "provocative sequence"), namely, that RCT results are too old to maintain their validity in the modern setting. This is largely objectable, and we shall come back to this in paragraph three. However, this point could be considered more appropriate for trials where the quality of mammography technique was grossly antiquated with respect to modern standards. If this is probably true for the CNBSS studies that are to be excluded anyhow on other more weighty considerations, it is certainly the case with the HIP study conducted in the 1960s, where the quality of mammography (combined for that trial with clinical examination) did succeed in reducing cause-specific mortality mainly staging BCs down from the big lumps that were the usual case pattern of the time (often T3+ cancers), to some relatively "earlier" cases, but still typically in the T2+ TNM size category. These, as well as the average cancer size of close to 20 mm in the CNBSS studies, are not representative of the practice of modern MS, where a great majority of cases are below the 15 mm size threshold and many within the 10 mm limit.

What is difficult to perceive, and is thus totally unappreciated by non-radiologist, is that the amazing results of the Kopparberg arm in the STC trial gained one special contribution from the extremely high quality of mammography that the lead scientist of the trial, Laszlo Tabar, could achieve in the late 1970s. That is attested by the fact that the standard textbook on mammography remains to date the teaching atlas that Tabar published some 30 years ago and that in its latest edition of 2011 is still based on the original mammographic films of the late 1970s [28]. That quality was already representative of the good results that modern MS programs can attain.

To sum up the substantial evidence on MS efficacy as derivable from many sound RCTs, one could start from the table derived from the UK Independent Panel review (Table 17.1) and adapt it based on the above discussion (Table 17.2)—excluding the New York and the Canada trials and substituting the latest publications of the UK Age trial and of the Gothenburg trial [26, 27], since these capitalize on longer follow-up periods, which were not available at the time of the Marmot report.

In this updated Table 17.2, most trials show a consistent BC mortality benefit for women invited to screening, in the very narrow range of 0.70–0.76, the two slight outlayers being Malmoe (RR = 0.81) and Kopparberg at the other end (RR = 0.58). In this updated prospect, studies of borderline significance (marked with asterisk (*)—in Tables 17.1 and 17.2) account for only one quarter of the review material vs. two thirds in the Marmot meta-analysis.

Table 17.2 Breast cancer mortality reduction in RCTs of mammography screening, revised and updated

Study, date of start	Age group	RR	95% CI	Weight (%)
Malmoe I, 1976*	45–69	0.81	0.61–1.07	15.2
Kopparberg, 1977	38–75	0.58	0.45–0.76	17.1
Ostergotland, 1978	38–75	0.76	0.61–0.95	20.7
Stockholm, 1981*	39–65	0.73	0.50–1.06	9.6
Gothenburg, 1982	39–59	0.70	0.53–0.93	17.1
UK age trial, 1991	39–49	0.75§	0.58–0.97	20.4

Data derived from the Cochrane and Marmot reviews [7, 11], applying a restricted selection of trials (see text) and substituting the latest updates of the UK Age trial and of the Gothenburg trial [26, 27]
RCT randomized controlled trial, *RR* relative risk, *CI* confidence interval
*Studies approaching statistical significance and RRs between 0.80 and 0.90
§RR for cancers diagnosed during the recruitment period of trial (see text for discussion)
Weight was recalculated as a proportion from Table 17.1

In conclusion, the evidence from many RCTs supports a significant BC mortality reduction from invitation to MS consistently in the range of 20–30%, for women aged 39–75.

17.1.3 Service Screening

While well-conducted RCTs provide the most reliable information about the efficacy of MS (issue a), being subjected to fewer biases than observational studies, many questions have been and are still raised about a number of other points including the actual effectiveness of MS in real practice, the potential harms of screening, and a diminished role for MS in the age of modern treatment: these points (issues b–d) will be discussed in the present paragraph.

17.1.3.1 The Effectiveness Issue

Almost immediately after the initial publication of the HIP results in 1971 [3], not only other RCTs were launched in different countries, but also service programs were set up, and their number increased exponentially following the subsequent publications of the newer studies' results. This has led to the present situation where, in many countries, large screening programs have been implemented on a population base as a core component of systematic national health policies for cancer prevention. This is the case for many European nations [29]. Also outside Europe, more and more nations, from Canada to Australia, are already managing, while others are in the phase of starting organized MS projects. In many other places, like the USA, screening mammography is extensively employed outside the organized setting, in a form that has been defined "spontaneous" or "opportunistic" screening.

The diffusion of large population-based MS programs provided researchers with the incredible opportunity to produce observational studies that, when thoroughly conducted, i.e., with a special attention to a long series of methodological traps, brought a wealth of new evidence to support the validity of MS in practice. Observational studies are generally more recent than RCTs and can thus reinforce estimates of the effects of screening, offering a robust sense of closer comparability to actual practice, in the present era of continuing developments in diagnostic imaging and clinical care.

If this is certainly the case, one has to be warned that especially the harsher critics of MS suggest to consider observational studies as more relevant than the RCTs. Such assumption allows them to allege biases and problems of interpretation as a polemists' weapon and offers a chance to come up with unfocused analyses of population data, in order to diminish the rigorous efforts of many other researchers. The fine details of methodology are beyond the scope of these pages, and we again refer the reader to the References for comprehensive discussions and especially to the very knowledgeable, large reviews of pertinent literature as may be found in the Euroscreen supplement publication of 2012 [4, 30–32] and in the Marmot report of 2013 [7].

Yet it is crucial to remark that with observational studies, it is fundamental to stick to the polar star that helps to identify the immensely useful, valid publications, namely, the availability of sufficient longitudinal, individual data, i.e., very long follow-ups (ideally beyond 10–15 years) with the possibility to link a woman's screening history to her cause of death. Articles falling short of these requisites should be considered with the utmost caution, if not discarded altogether, even when published in highly regarded scientific journals. A firm warning has to be made about this continuous flow of articles where all the basic methodological prerequisites are not met. Whenever reading observational/ecological/trend publications that lack individual data and/or long-term follow-up, one should be aware that these papers actually use invalid material to fuel the artificial debate on MS [33–36]. Based on conjectures and extrapolations rather than facts, there is obviously not much chance that the benefit of MS can be fully appreciated. In Broeder's words [30]: "Much of the current controversy on breast cancer screening is due to the use of inappropriate methodological approaches that are unable to capture the true effect of mammographic screening."

In brief, we may consider among the observational studies:

1. Trend Studies

This would be the weakest group [7, 31], comparing BC mortality trends with regard to the availability of MS on a population as a whole rather than on an individual basis. Methodological difficulties are overwhelming with these studies. Problems include the impossibility to attribute BC

deaths to cases diagnosed before or after the screening activity started, to the possible relevant contamination from opportunistic screening even prior to the introduction of screening [37]. Some studies attempted to include more detailed analyses, fine corrections for various confounding factors, and extended follow-up [38, 39] and still estimate MS mortality benefits in a relatively wide range. In general, these methods should be considered of limited value for assessment of screening activities and have in fact been considered not reliable by the UK Independent Panel.

2. Case-Control (CC) Studies

This is the best known methodology, apart from RCTs, comparing the history of screening exposure between women dying of BC and live controls. Such a design yields estimates of relative mortality in compliers to screening invitation vs. non-compliers. This produces the main, well-known problem of self-selection bias, since compliers and non-compliers may differ a priori in their risk of dying from BC [7]. Therefore, researchers typically have to introduce a correction for this bias, whose adequacy may be questioned by critics. The Euroscreen review and selection of the best European CC studies, with exclusion of overlapping data, confirm a reduced mortality benefit of 31% in invited women (OR = 0.69; 95% CI 0.57–0.93) and 48% in women screened (OR = 0.52; 95% CI 0.57–0.83), after adjustment for self-selection.

3. Incidence-Based Mortality (IBM) Studies

In IBM studies all BC deaths in a population are considered if the corresponding BC diagnosis occurred in a time window when the woman had the opportunity to be screened, due to eligibility and invitation [7]. These BC deaths are then compared with corresponding BC deaths from women not having the chance to be invited on geographical (region with no screening program) or chronological (historical, pre-screening data) basis. A meticulous selection of the studies with the strongest design [30, 32] and excluding overlapping publications demonstrated a mortality reduction for women invited to screening of 25% (RR = 0.75; 95% CI 0.68–0.91). When women actually attending screening were considered, the benefit estimate was 38% (RR = 0.62; 95% CI 0.56–0.69). The huge amount of valuable data involved should be emphasized, as well as the substantial homogeneity of the results across the studies under review.

The Euroscreen estimates, as derived from the detailed analysis of a wealth of evidence-based data of service screening studies and on the most scrupulous methods [30–32], show a BC mortality reduction of 25–31% for women invited to MS and 38–48% for women actually screened. These figures reaffirm the large benefit demonstrated by the "old" RCTs also in the more recent, real-life situations of service screening.

To further stress the extreme importance of these service screening studies and the powerfully distracting capacity of those studies that do not comply with the basic methodological prerequisites (individual data/long-term follow-up), we shall now analyze a few instances in some more detail.

As a paradigmatic example, let us consider the Norwegian Breast Cancer Screening Programme (NBCSP) that was launched in 1996 and what different studies have published about its impact on BC mortality.

Kalager et al. [34] in 2010 on the basis of aggregated screening data, and a maximum follow-up time of only 8.9 years, with an IBM approach, conclude that in Norway the availability of MS was associated with a 28% reduction in BC mortality in the screening group as compared with the historical preceding 10-year period. Since a similar, although lower, reduction of 18% in BC mortality was observed also in the non-screening group vs. the historical comparison group, they conclude that only a third of the total reduction could be attributed to screening, the remaining benefit being interpreted as a result of improved treatment within an interdisciplinary team. As is commonly the case, the role of the organized MS experience of the 1980s–1990s in building up the concept of the specialized interdisciplinary, collaborative management of BC that has recently led to the institution of the Breast Units system as an international standard of care is not remarked.

In 2013 Olsen et al. [40] still based on aggregated data and an IBM approach, with a maximum follow-up of 13 years, try to improve on some aspects of Kalager's work, in order to correct possible underlying temporal changes in BC mortality. They conclude that the implementation of the Norwegian-organized screening program was associated with a nonsignificant decrease in BC mortality of 11%. There is again a misleading message in this apparently disappointing summary conclusion. In the first place, it should be emphasized that this result does not represent the impact of MS on BC mortality, i.e., this is not a comparison of screening vs. no screening. Rather, it depicts the impact of building an organized MS program on top of existing widespread spontaneous mammography. In Norway, this was estimated by the authors at around 40% prior to the program. Eventually, one might read the conclusions of this study either in an erroneously diminishing fashion as a "nonsignificant effect of MS" or—more opportunely—as a coherent, promising observation of an "extra effect on mortality from organized screening," as compared to a similar, widespread, non-organized mammography coverage of the population, and this extra effect is perceivable even at relatively short follow-up, still in the recent era of modern treatment. This makes altogether a different picture.

Conversely, the first report of the Norwegian program, which was based on the access to individual screening data

[41] with a maximum follow-up of 15 years, shows a significant, conspicuous 43% mortality reduction from BC (RR = 0.57; 95% CI 0.51–0.64) associated with attendance, after adjusting for several factors, most notably for self-selection bias.

After the previous discussion of the serious perturbation of scientific evidence associated with the publicity of the Canadian trials, it seems relevant at this point to emphasize the results of an excellent analysis of BC mortality in a service MS situation published in 2006 by Coldman et al. [42] on data of the Screening Mammography Program of British Columbia (SMPBC) established in 1988 in Canada. The authors show that MS significantly reduced BC mortality at all ages between 40 and 79. Mortality reduction was 40% for all ages combined (RR = 0.60; 95% IC 0.55–0.65). In women entering screening at age 40–49, the reduction was 37%, after exclusion of mortality associated with cancers diagnosed after age 50. Even after correction for self-selection bias, the mortality reduction was 24% for all ages.

In Italy, a series of valuable publications have been produced over the years by the IMPACT study project, a national research task force based on an extensive database linking BC cases in areas covered by cancer registries to individual screening files. In the IMPACT project, all cases are classified by cause of death and detection method (screen detected, interval cases, never respondent, diagnosed before invitation). From this material, a case-control study [43] assessed BC mortality reduction associated with MS exposure at 45% (OR = 0.55; 95% CI 0.36–0.85), over and above the background access to mammography, thus confirming the important impact of service screening in the Italian health situation. The OR associated with invitation was also significant at 0.75 (95% CI: 0.62–0.92).

In 2013, the IMPACT Working Group produced another study of outstanding importance demonstrating a significant decrease of advanced-stage cancers after the introduction of organized screening in Italy [44]. This represents a central issue in the ongoing evaluations of screening programs in practice and is based on an early indicator derived by the data of the STC trial. As back as in 1989–1992, Tabar et al. [45] showed that the incidence of stage II and greater cancers started to decrease 5 years after randomization and this decrease paralleled quite neatly the decreasing mortality curves in the study, with a substantially stable 30% reduction from 8 years onward. This proves that early diagnosis does interrupt the natural history of BC, and this has led to the proposal of the incidence of late-stage BC as one powerful surrogate indicator of a MS program effectiveness.

Many studies have aimed at assessing this parameter, with conflicting results, some confirming the reduction in advanced cancers [46–50], while others showing stable rates over time [51–54]. The IMPACT Working Group study of 2013 [44] adopts a sophisticated approach in order to tackle the subtle methodological traps that are hidden in a service situation, especially from subgroups of the dynamic target population. In this, at any point in time, there are always subgroups of women whose screening exposure is so short as to have no measurable impact, thus causing a dilution of the screening benefit (in part again a consequence of working with insufficient follow-up times). Among the solutions adopted in this study, there was the exclusion from analysis of women aged 50 to 54 because of screening exposure necessarily below 5 years and reference to pathological tumor size (beyond 2 cm) to define advanced cases, rather than the pN data, in consideration of the substantial stage migrations observed in recent years after the introduction of sentinel node biopsy and improvements in the pathological study of lymph nodes. This study, based on a total of 14,447 incident cancers, was able to show a significant and stable decrease in the incidence of late-stage BC from the third year of screening onward. Incidence rate ratio was 0.81 at years 3–4, 0.79 at years 5–6, and 0.71 at years 7–8. This result is consistent with an effect of MS in reducing advanced cases (which anticipates the effect on mortality) around 20% in the first 3–4 years after the screening starts, increasing to some 30% in the medium term (5–8 years), showing a consistent effect in a real-life situation with data of a screening population of 700,000 women, 55–74 years old, from 700 Italian municipalities.

To further stress the importance of extended follow-up times, one cannot leave unmentioned one large Swedish experience of service screening, where an earlier assessment based on mean follow-up of 8 years [55] yielded a nonsignificant impact of MS on BC mortality of younger women (40–49 years old) with a RR of 0.91 (95% CI: 0.72–0.95), while a subsequent publication on the same material [56], but with follow-up extended to 16 years, gave a strong, significant 38% mortality reduction in the same age group (RR = 0.62, 95% CI: 0.42–0.91).

Another study that deserves a special mention was published in 2011 [57] and represents one among many outstanding contributions from a research group based at the Dutch National Reference Centre for Screening in Nijmegen (in this case, as a joint effort with UK experts). This study investigates the impact of screening from the start of the Nijmegen service screening program in 1975 up to 2008. With a case-referent approach [58], BC death rate was 35% lower in the screened women, in the complete period. What is new to this study is the demonstration of a favorable trend of increasingly strong reduction in mortality over time, attributable to MS, from 28% in the period 1975–1991 to 65% in the years 1992–2008 (OR =0.35; 95% CI = 0.19–0.64). The authors consider the probable role of improvements in the quality of service screening in achieving these results, not only from a technical point of view (i.e., availability of more modern technologies) but also from progressions in quality assurance and special training of dedicated

personnel. Also, the multidisciplinary management of BC and a greater combined effect of modern treatment and early detection are highlighted, as possible causes of this progressively increasing benefit.

17.1.3.2 The Overdiagnosis Issue and the Balance Sheet

Given the massive high-quality data in favor of a relevant positive effect of MS on BC mortality, such as to be eventually conceded even by the harsher opponents, the last decade has seen a new outburst of objections, focused on the alleged harms of screening potentially surpassing the possible benefits. In other words, the question is whether the benefits provided by MS are more substantial than any unwanted effect that it may produce.

This debate has often taken the form of a "balance sheet" of screening benefits vs. the potential side effects of the organized intervention. The major potential harms that are taken into account are false-positive recalls and overdiagnosis.

Other negative effects are generally agreed to carry a negligible weight. These would include the risk of X-ray-induced cancer, estimated at 1–10 per 100,000 in a recent review [59], and the false reassurance, which might entail a delay in BC diagnosis after a negative screening result; this is also considered to have minimal effects [60]. When performing the balance sheet exercise, depending on a series of assumptions and on the reference value considered, as apparent from the simple comparison of Tables 17.1 and 17.2, the final picture can be very different. All in all, the Euroscreen publication of 2012 [61] provides the best reference demonstration to date of a well-devised scenario based on a reasonably weighted evidence base.

Overdiagnosis

Central to this field of dispute, the argument of overdiagnosis has been fueled by many in these last years and has in fact been at the basis of the institution of the special panel of experts in the UK that eventually produced the "Marmot report" [7]. To this, the reader is once more referred for an extensive, knowledgeable coverage of this particular argument, and its many methodological implications, although some caveats, will be discussed in this paragraph.

Overdiagnosis is indeed a momentous subject in screening research and evaluation. It refers to the possibility that anticipating the time of diagnosis before clinical symptoms are apparent will result in a number of cancers diagnosed, which would not have provoked harms in the woman's lifetime, if not detected by screening. The two crucial aspects are the quantification of overdiagnosis and the impact on the woman's well-being of an overdiagnosed cancer.

The major methodological difficulty in estimating overdiagnosis lies in the ability of recognizing the excess incidence due to lead time and separates this from that due to overdiagnosis. The excess "lead time" incidence is in fact a requisite of MS, necessary to allow for early diagnosis and effective treatment. In the absence of overdiagnosis, this increase in BC incidence as women enter the screening program would be balanced by a similar decrease in cancers among older women exiting the program at the upper age limit: this phenomenon has been defined as the "compensatory drop" [62]. Again, this requires either a very long follow-up time in order to be fully accounted for or some well-devised statistical adjustment. The UK Independent Panel, recognizing the utter difficulty of the estimate, takes a conservative position, based on data from only a few RCTs (Malmoe plus the Canadian trials), and considers overdiagnosis at about 5–15% from the population perspective and 15–25% from the individual woman's perspective.

The Euroscreen Working Group [61] starting from a focused review of the literature [63–67] concludes on a more substantiated estimate of overdiagnosis in the range from 1 to 10%.

A recent work by Duffy and Parmar [68] reinforces the need for observations up to 10 years beyond the upper age limit for screening (which means up to 30 years of complete follow-up) in order to compensate for lead time and nullify the pseudo-excess of overdiagnosed cases. This represents one further and very strong caveat against all studies that fail to take into account the very long natural history of BC and the related lead time required in order to cash the screening benefit: such studies would produce inconsistent conclusions if based on nonindividual data and/or too short observation times. Also the need for correcting for underlying incidence trends independent of screening requires estimates and extrapolations. This adds to the difficulties and has been taken by some as an excuse to ignore a problematic issue, in fact ending up with even less reliable estimates. Duffy and Parmar convincingly conclude that previous measures of overdiagnosis are likely to be overestimates. They point to further empirical evidence that overdiagnosis is a smaller problem than generally thought, as can be derived from the TCS, where at 29 years the cumulative incidence was identical between study and control groups [69].

However, they also admit that their estimates include only the invasive cancers, while a substantial part of the overdiagnosis debate involves the possibility that MS could detect a vast number of preinvasive lesions that might never evolve into clinically significant cancers. One very recent study [70] shows that this assumption—and the idea that large numbers of invasive BC would never progress in the absence of treatment—might have no actual evidence base. In this paper, an analysis of data from over 5 million women in the UK screening program showed an inverse correlation between invasive interval cancers and DCIS detected at screening. This association suggests that detection and treatment of DCIS at MS effectively prevent invasive disease.

The balance sheet

The Euroscreen Working Group [61] has created a decision-making scenario where the essential components of the harm/benefit balance could be fitted and discussed in a way that could be effectively communicated to the population involved [71]. Such a setting would also allow for the possibility that updated figures could be inserted and worked up as new evidence should be made available. This scenario considers 1000 women entering MS aged 50–51 and screened biennially until 69 and followed until 79 years (a substantial observation time of 30 years). Based on evidence from European service screening programs, results are expressed as a number of women that need to be screened (NNS) in order to achieve any specific outcome. With this framework, estimates are of 125 NNS to save one life (benefit) vs. 250 NNS to have one overdiagnosed BC and 33 NNS to have one invasive assessment (harms). These results represent a brilliant, honest, scientifically sound collection of data that are intended as a tool that will help a woman who is invited to screening to make an informed personal choice about the implications of participating. To such scope, a narrative was also created to help explain a complex situation, like screening actually entails [61]. Two small European cities are described, with 1000 female residents aged 50–51, where only one city invites women to an organized MS. This results in the outcomes outlined in Table 17.3: over 20 years, there will be eight fewer deaths from BC at the cost of four overdiagnosed cases and a considerable number of false-positive assessments. In this narrative, it is stated that "most of the women participating in screening will have only negative mammograms and, therefore, will have no benefits other than a reassurance about their health status, and only short-term harms from service screening (discomfort, anxiety)."

Arguably, this last point may be considered as a diminishing appreciation of the importance of regular, true reassurance about individual women's health status, with regard to such a high incidence disease as BC. At a closer survey, the picture delineated in the Euroscreen narrative shows some weakness in its aiming at a faithful representation of the health-care scenario in the absence of organized MS. Indeed, BC expected in the population with no organized MS should not be considered to come at no cost, be it financial or from side effects. In the absence of an organized program, women still have breast symptoms; besides that, some of them do have tests in a "spontaneous" screening fashion.

Organized MS involves setting up multidisciplinary specialized units, staffed by dedicated personnel, with special training. It also requires regular quality assurance procedures, monitoring, and evaluation of ongoing activities. Screening guidelines and protocols pay close attention to specificity and require that screening cases come to a definite conclusion after each episode, discouraging short-term repeat examinations, as is common practice in many clinical settings.On the other hand, areas not covered by organized screening tend to be served by non-breast dedicated clinicians, resulting in a higher number of unnecessary examinations, inconclusive test, and less straightforward protocols. This is represented in the comparison of the UK organized screening vs. the performance of spontaneous screening mammography in the USA, as detailed in a study by Smith-Bindman et al. in 2005 [72]. This showed that a slightly higher cancer detection rate in the USA was obtained at the expense of more than double recall rates and surgical biopsy rates. These results are fitted in a scenario similar to the one in the Euroscreen balance sheet. A face-to-face comparison (see Table 17.4) immediately shows that it is totally unfair to suggest that the city with organized MS produces 200 false-positive recalls, thus causing more psychological harms than in a neighboring city with no such program.

A possibly more faithful narrative—to accompany and illustrate a revised form (Table 17.5) of the balance sheet—may be the following:

Consider two small towns where an important group of diseases, namely, breast cancers, because of their clinical implications and very high incidence, cause per se a large burden of anxiety in the female population. In one city an organized, controlled, specialized program offers women the continuing reassurance of well-managed periodic tests, significantly cutting back the mortality rate from the disease, at the cost of a limited number of overdiagnosed cases. Participating in such program would also confer these women a reduced burden in terms of false-positive assessments, less psychological harms from too frequently repeated examinations with no conclusive diagnosis, as compared to the neighboring city where such program and all the related skills, organization, protocols, and

Table 17.3 Harm/benefit balance sheet for organized mammography screening of 1000 women[a] from the Euroscreen Working Group 2012 [61], modified and expanded

Outcome	For every 1000 women screened for 20 years	NNS
Number of BC diagnosed	71	14
BC mortality reduction	8	125
Over-diagnosed BC	4	250
False-positive (FP) tests, of which:	200	5
– FP recalls, with non-invasive assessment	170	6
– FP recalls, with invasive assessment (biopsies)	30	33
Reassurance of true negative cases (all rounds)[b]	729	1.4
Equity of access to high quality health care[b]	1000	1

BC breast cancer, *NNS* number needed to screen
[a]Women entering screening at age 50, screened biennially until 69 and followed until 79
Mortality reduction was adjusted for self-selection bias
[b]Original entries

Table 17.4 Harm/benefit balance sheet for mammography screening of 1000 women over 20 years in an organized European setting compared to a US estimate for spontaneous screening, modified and expanded from [61, 72]

Outcome	For every 1000 women screened for 20 years	
	Euroscreen [61]	US [72]
Number of BC diagnosed	71	55
BC mortality reduction	*8*	*8*[a]
Overdiagnosed BC	*4*	*4*[a]
False-positive (FP) tests, of which:	200	694
– FP recalls, with noninvasive assessment	170	553
– FP recalls, with invasive assessment (biopsies)	30	142
Reassurance of true negative cases (all rounds)	729	306
Equity of access to high-quality health care	1000	Not applicable

[a]Mortality reduction and overdiagnosis arbitrarily assumed to be of the same magnitude as in the Euroscreen estimate
BC breast cancer

Table 17.5 Harm/benefit balance sheet for organized mammography screening of 1000 women[a] (current proposal)

Outcome	For every 1000 women screened for 20 years	NNS
Number of BC diagnosed	71	14
BC mortality reduction	8	125
Overdiagnosed BC	4	250
Reassurance of true negative cases (all rounds)	729	1.4
Equity of access to high quality health care	1000	1

[a]Women entering screening at age 50, screened biennially until 69 and followed until 79
BC breast cancer, *NNS* number needed to screen
Mortality reduction adjusted for self-selection bias

quality assurance are not available. The point suggested in the present pages is that the false positives of organized MS should in fact be considered as a protection conferred by screening, being largely inferior in number when compared to a setting of spontaneous, low-specificity clinical and preventive medicine. Hence, balance sheets of harm/benefits of organized screening should not register the false-positive recalls as screening harms. Instead, the true reassurance conferred to the majority of the population, again and again over many years, by an organized program and the equity of access to highly specialized medical care that service screening provide, should stand out among the major benefits of MS alongside the topmost target achievement of reduced BC mortality (Table 17.5). So, the above-quoted statement might be reworded as most of the women participating in screening will have only negative mammograms and, therefore, will have the continuing, long-term benefits of a reassurance about their health status and only short-term harms from service screening (discomfort, anxiety). A valuable communication of benefits and harms of screening to decision-makers, to women, and to the scientific community itself [71] should consider alongside the effectiveness and the limitations of the procedure and the relevance of such factors as trust, gratitude, and convenience that may play an important role in the informed choice to participate. It should be explicit that balance sheets (Tables 17.3 and 17.5) are the product of dedicated professionals. They are bound to set up effective health initiatives and on this basis produce communication tools that can be transparent and honest, but that cannot be neutral. There are other historical merits to be credited to MS. The leading role of the organized MS experience of the 1970s–1990s in building up the idea that there was a need for dedicated professionals with specific education, training, and expertise in BC diagnosis and treatment is rarely, if ever, remembered. The importance of interdisciplinary, collaborative management of BC by experts in senology has been advocated by the screening guidelines, at a time where senology was hardly recognized by most physicians as a field of specialization in its own right. This awareness has greatly contributed to the institution of the Breast Units system as an international standard of care. An important concluding recommendation would then be, when reminding potential harms of attending screening, to give a proportionate emphasis also to harms entailed by not attending the program: larger tumors, worse stage at diagnosis, more systemic treatment, and worse survival.

17.1.3.3 Inconsistency of the "Expired Validity" Issue

It has been shown that RCTs and service screening data proved that MS is valid and effective and that its side effects would be minor with respect to the potential benefits. At this point, the question has been arisen whether early detection through MS still holds its meaning in the new era where very effective treatments have become available and if most of the mortality reduction from BC that has been recently observed should be credited to treatment, rather than screening. This is a reasonable question in itself, but once again the answer is clear: there is substantial evidence that MS still plays an important role in BC management and cause-specific mortality reduction.

Some of this evidence has been already discussed in the above paragraphs. Of special relevance to this point are the service screening studies performed in the last 15 years [30–32, 40–43, 56, 57]. These do show net benefits for women attending MS compared to nonattenders, who still have potentially access to all the advanced treatments available in the regional health-care system. One publication [57] has brilliantly shown that screening not only retains its effectiveness in the recent years of sophisticated oncological

treatment, but in fact it contributes a favorable trend of increasingly strong reduction in mortality over time. This reminds that alongside advancements in therapy, improvement of radiological techniques also come into the picture, enhanced by the virtuous setting of quality assurance, dedicated training, and interdisciplinary collaboration in a new Breast Unit arrangement that organized MS contributes to develop.

The intuitive concept that even in an epoch when sophisticated systemic therapies are available, small, node-negative BC as those detected at screening still carry a significant survival advantage, has been confirmed by many.

Of special interest, and largely unappreciated by many physicians, is the demonstration [5] that screening detection of small tumors not only reduces the incidence of lymph node metastases but also prevents the worsening of their malignancy grade.

An Italian service screening study [73] showed an improvement in survival rates by before-after invitation period in an intention to treat analysis addressing the fact that screening changed the pattern of tumor characteristics in the population. Within the same tumor characteristic subgroups, survival was comparable, supporting the hypothesis that the difference in prognosis observed was due to early diagnosis rather than differential treatment or access to treatment.

Other experiences [42] support the idea that notwithstanding the advances of modern systemic therapy, large differences persist in prognosis by extent of disease at diagnosis. One paramount confirmation is from the Swedish experience, where individual counties had the possibility to choose 40 or 50 years as the lower age of screening. This gave the chance to measure the impact of screening in a population aged 40–49 including over 16 million women-years with 16 years of follow-up. The significant 29% decrease in BC mortality that was demonstrated for women who attended screening (RR 0.71; 95% CI 0.62–0.80) occurred in a country with uniform treatment guidelines. This proves that this mortality reduction was achieved in addition to the benefits of modern therapeutic advances [74].

It is clear that both early detection and modern treatment have merits in achieving the long-awaited for reduction in BC mortality: it would then probably be a much better way to look into the future to recognize the mutual enhancing power of the two, as early detection allows for more refined treatment options and for the adjuvant therapies, both medical and radiation based, to achieve extraordinary results in disease control. In other words, rather than keeping up a long sequence of futile controversies, it could be more advantageous to devote resources to a very appropriate topic for research: how early detection might or should change the treatment of some subgroups of BC.

17.1.4 Evolution

A positive evolution of BC screening has to build on the clear appreciation of what can already be achieved through the "classical" population-based programs. Physicians, healthcare providers, and the population alike have to understand that MS contributes a significant reduction in BC mortality and represent a major achievement and a public health intervention of demonstrated feasibility and cost-effectiveness. Future developments of screening should prove not only their absolute efficacy but also their feasibility and sustainability in terms of incremental cost-effectiveness, in order to guarantee that the new policy should not put at risk the regular management of the existing MS programs.

To date, screening has been implemented on the two strongest risk factors for BC, i.e., sex and age. However, in this epoch of personalized medicine, the concept of tailoring BC screening to different levels of risk has gained increasing interest. Mammography has been regarded as the most suitable test for screening, due to the evidence available, its reasonably high sensitivity and specificity, and low cost. It is important though to be aware of the limitations that a single screening tool entails and that while alternative breast imaging techniques have been around for decades, recent advances in digital-based diagnostic devices and information technology (IT) have widened the spectrum of imaging possibilities.

Keeping in mind the big caveats regarding (1) evidence of efficacy, (2) incremental cost-effectiveness, and (3) sustainability, one might think about screening evolution, apart from the special policies already envisaged for the population at the highest risk (the theme of the following chapter) according to the three main pathways:

(a) Tailoring the screening process on the basis of different levels of risk (low to intermediate)
(b) Introducing new screening tools (technological evolution)
(c) Increasing the effectiveness through improvements in the overall quality of the process

17.1.4.1 Tailored (Risk-Based) Screening

This involves the idea of offering customized screening policies on factors influencing the risk and/or the performance of the intervention, such as (1) age, (2) breast density, and (3) other personal risk factors. The assumption is that benefits and harms/limitations of screening vary according to BC risk, so that such tailoring of interventions may optimize their balance.

(1) Age—Besides sex, age has always been identified as the main risk factor for BC. All MS projects have been tar-

geted to those age groups where the general consensus recognized the optimal cost-effectiveness balance; these are most commonly the 50–69 years old women.

Younger and older women have always represented a subject for discussion, and in the past, there was a major debate over the appropriateness of offering MS to women in their 40s.

Arguments against screening the 40–49 years old included the lower incidence (and mortality) and the predictable lower efficiency of the screening test due to the limitations of mammography in denser breasts, both of which contributed to the lower mortality reduction observed in the RCTs. Recent data have clearly demonstrated a relevant impact on mortality also in these younger women, when offered MS. This is unequivocal in studies that can provide extended follow-up [56, 74, 75]. As to incidence, the major, abrupt increase in most western countries is obviously at the 40–44 age group, when incidence exceeds 100 cases per 100,000 women per year. Women diagnosed with BC when 40–49 account for a significant proportion of the BC mortality, in fact similar to that attributable to 50–59 and 60–69 years old women [76]. This leads to the conclusion that there is no scientific reason to exclude this age group from a screening program, beyond issues related to resources and feasibility.

Another important point to consider is that life expectancy at birth has in many countries surpassed 80 years for the female population, and for women aged 69 (the upper age target for most programs), life expectancy may exceed 15 years. This implies that stopping invitation after 69 is no longer adequate. Since diagnostic capabilities of mammography in older women are particularly good, and screening efficacy up to age 74 was proven by RCTs, also the optimal upper age limit for screening should be carefully discussed. In 2007, the Italian Society for Breast Cancer Screening (GISMa) produced a consensus document [77] that envisaged the possibility to extend screening to age groups 40–49 and 70–74, where sufficient resources were available. This has in fact been implemented in some Italian regions. A similar strategy of extended screening beyond age 70, based on self-referral of women interested, is in practice in the UK. Sweden, the home to most of the historical RCTs, has been and probably still is the country with the widest age span covered by screening: women aged 40–74 years are offered screening in many Swedish counties as opposed to 50–69 years of age in most other nations.

Another aspect strictly connected to age is the interval between screening rounds. The evidence base for current protocols lies mainly in the results of the RCTs. Considering the high proportional incidence of interval cancers in the second year after screening in the age subgroup 50–54, the Swedish option of screening ages 40–54 every 12–18 months and switching to the 18–24 months interval for ages 55–74 is arguably a better solution than the 24 months interval, starting at age 50 that is adopted by most screening guidelines worldwide. Availability of financial resources still remains one background decisive factor in determining these policies.

(2) Breast density—Breast density, being both a risk factor and a determinant of lower performance for mammography, has been the most discussed criteria to develop customized screening strategies. Many studies and proposals have been produced on this subject, actually resulting in very limited practical achievements until very recently. The subject remains extremely complex, and some issues are still to be clearly defined. Different patterns and composition of breast densities exist; the relation between density and cancer risk needs to be further understood, although it is clear that high mammographic density decreases sensitivity and the positive predictive value (PPV) of mammography, resulting in more interval cancers.

The introduction of digital mammography has already modified this situation to some extent, although the major advances are expected from the introduction in screening protocols of more modern, tomographic imaging techniques, like digital breast tomosynthesis (DBT) and automated whole-breast ultrasound (AWBU).

In recent years, modern digital technology has also made available softwares that can automatically calculate breast density values; these softwares may contribute to higher reproducibility in the classification of density levels. These measures are then used alongside personal risk factors in the definition of statistical models of BC risk. However, a precise definition and a consensus on optimal thresholds and statistical models are still lacking. In the USA, a specific legislation has made it mandatory to inform women about their breast density and the limitations of mammography in dense cases, so that women may decide to have additional examinations. From an organized screening perspective, before additional diagnostic techniques or modified protocols do not prove cost-effective, it would be questionable to stress communication on this issue, which is also generally exaggerated by the use of relative rather than absolute risks.

(3) Other risk factors—Other personal risk factors have been considered, including personal history (previous BC diagnosis or atypical hyperplasias), family history of BC, socioeconomic status (SES), comorbidities, etc. More recently, milder degrees of hereditary susceptibility to BC have been considered, as those related to the study of single nucleotide polymorphism (SNP) [78, 79].

As the overall risk cannot be calculated as a mere sum of different risk factors, it will be essential to develop and validate efficient prediction models. The availability of more sophisticated IT support will probably provide powerful tools and play a decisive role in the advancement of this line of clinical research, also through sophisticated modeling that may con-

tribute to the design of risk-stratified forms of screening, where a better balance between costs, harms, and benefit could be achieved offering adapted programs to different groups of women [80, 81]. In this framework, costs and harms may be contained also reducing screening offer to women at lower risk.

In summary, risk-based tailored evolutions of MS are at hand where revision of the age limits and frequency (1) of screening are concerned. As for factors in points (2) and (3), the general situation is that offering more intensive (or also less intensive) screening, based on one or a combination of the above factors, might indeed result in a qualified improvement in the risk/benefit balance. However, more research and clear data are warranted, as the underlying concept states that marginal gains in effectiveness have to be proven, and the big caveat remains about creating increasing motives of complexity that could eventually detract from the practical management of the screening system.

One major challenge for the future would be to devise strategies where risk-stratified screening would be offered in combination with primary prevention measures, targeting modifiable risk factors, like obesity, through interventions on diet, lifestyle, etc.

17.1.4.2 Introducing New Screening Tools (Technological Evolution)

This is the most promising pathway for BC screening evolution, given the development over the last decade of very promising, new imaging tools, sharing two common denominators: digital framework and tomographic technology. Indeed, tomography-based imaging ideally represents the optimal solution to overcome limitations of mammography in dense breasts. These techniques are (1) magnetic resonance (MR), (2) digital breast tomosynthesis (DBT), and (3) automated whole-breast ultrasound (AWBU). Since these are the subjects of the following chapters in this textbook, to these the reader is referred for extensive discussion and relevant references. At this point, only a very essential-focused comment will be given.

1. MR is by far the most powerful instrument in this series, combining excellent morphologic, three-dimensional representation with functional data. At this moment, however, its use in screening has to be limited to the very high-risk patients, mainly on cost considerations.
2. DBT has the widest literature as a potential new screening instrument. Being in fact a modified version of mammography, its introduction in the screening organization is relatively simple, and a number of studies have proven its ability to increase cancer detection rates in screening settings [82, 83]. Data on specificity are less uniform, yet promising as well. Concerns about the higher radiation dose delivered to the population will be probably overcome by technical developments and especially by the introduction of synthetic 2D images. These should dispense with the need to obtain a double exposure in order to have 2D and 3D images available for the same woman. The main research topic for DBT in MS remains the demonstration of a significant impact on the interval cancer rate. Cost issues are mainly related to the prolonged reading times of the tomographic sequence, rather than to significant modifications in the patient workflow. In fact, the extremely promising diagnostic data and its minor impact on the screening organization have led to DBT being already introduced in some screening programs, within randomized trials or pilot demonstration studies.
3. Automated whole-breast ultrasound (AWBU) takes into the diagnostic field a brilliant combination of the superior ability of sonography to read through the denser portions of the breast with the advantages of an automated procedure that is able to guarantee a more standardized coverage of the breast volume. Due to the superior sonographic potential in dense tissues (at no radiation costs) and hence also a powerful integration with mammography, this technique carries the potential for a more relevant diagnostic contribution than DBT. However, a few studies available to date in the screening setting, while confirming the expected very promising detection gain, show a substantial increase in false-positive values [84]. Moreover, the introduction of this technique in the screening context appears to be more demanding, not only for the extended radiological reading times but mainly in terms of radiographers' working time.

Another important contribution to be expected in the near future is the development of dedicated CAD (computer-assisted diagnosis) systems that will reduce the costs involved with the reading times of long series of tomographic images, be it DBT or AWBU.

17.1.4.3 Optimizing Existing Programs

It has been strongly represented how MS produces substantial benefits to the population in terms of cause-specific mortality reduction, and it has been discussed in the harm/benefit paragraph that an organized screening program provides significant advantages in terms of cost-effectiveness as compared to a spontaneous setting [72]. This reinforces the idea that optimization of the available system would be a rewarding field of evolution. Also in this field, the digital revolution of the past decades offers a number of new, interesting possibilities.

A recent, extremely detailed comparison of the costs involved by an organized service screening system [85] demonstrated significant savings both for the health system as a whole and from the women's point of view. The cost of mammography in a non-organized setting was more than

double compared to the organized program. Outside organized MS, social costs would also be higher, as those related to time lost from work, travel to the screening unit, telephone calls, administration costs, etc.

Moreover, the practical support provided to the female population by the organized setting, from the letter of invitation onward, contributes to its capacity to reach women in the lower socioeconomic categories, thus reducing inequalities in breast cancer survival. In one study [86] the lower survival rates in less-educated women before the launch of the organized MS disappeared completely in the age group invited to screening. The current design of MS has one major strength in the availability of a complex organization that embraces such aspects as detailed shared protocols and guidelines, quality assurance and audit systems, continuous evaluation, and feedback on the results to stakeholders. This is typically represented in the European Guidelines for Breast Cancer Screening [87] and in similar documents produced at the national or regional level in many countries.

Some crucial points that might be developed (and greatly gain from the introduction of digital mammography and the IT support) include:

1. Expanding the monitoring system, from the general program/unit level to the level of the individual operator, with regular personalized feedback on professional screening performance (e.g., recall rates, cancer detection rates), in order to allow for timely educational refreshments where needed. It is important that among the many performance indicators [87, 88] the most relevant will be selected for their special value. Interval cancers, representing a failure of the procedure, should be fully monitored to evaluate screening performance. The radiological revision of pertinent mammograms is a valuable tool of internal audit and a valuable occasion for training and continuing education of the screening radiologists. However, complete data on interval cancers may be difficult to collect. Large cancers (20 mm or more, i.e., T2+) that are screen detected at subsequent rounds represent an equally strong indicator of screening performance and (when combined with the T2+ interval cases) are the best early surrogate indicator of screening impact [5]. Screen-detected T2+ cancers are immediately available at the screening unit, so that their radiological revision would be more easily feasible than reviewing interval cancers—while also their educational value would be substantially similar [89]. As to the evaluation of screening performance and impact, analysis of the pathological size distribution of all BC in the population exposed to screening, expressed as absolute rates rather than percentages, should be regarded as a cornerstone.
2. Recognizing an enhanced role for dedicated education, investing on specialized courses and practical training of all the professional figures involved in the screening process, with a special emphasis on radiographers, radiologists, and pathologists. Specialized education is in many countries largely neglected, while it may probably result in the most rewarding field of investment in order to optimize screening cost-effectiveness. This process should routinely envisage the funding of National or Regional Reference Centres for Quality Assurance and Training for Breast Cancer Screening. The importance of having access to Expert Screening Training Centres is confirmed by the long-lasting experience of the Dutch National Training Centre in Nijmegen, as well as by the Swedish experience. This is effectively represented in one service screening study [90], where organized programs conducted in dedicated centers could consistently achieve mortality reductions at least as high as those observed in the RCTs. This achievement was built on the cooperation of screening centers in seven counties across Sweden, with the expert support of the leading researcher of the STC trial. Expert Reference Centres would represent the ideal site to set up and coordinate relevant research, as the Nijmegen (NL) and Falun (Sweden) experiences confirm.
3. Promoting innovative research taking advantage of the multidisciplinary context of screening. Research should be focused on the key issues of screening evaluation and risk customization. Besides that, it would be most appropriate to exploit the screening setting to foster research based on a radio-pathological cooperation. Improved standard pathologic techniques are to be implemented in order to create a better mutual understanding of the clinical significance of screen-detected lesions. Large-format histologic sections have already proven their value [91, 92] and supported the need for improved pathologic terminology that should reflect the site of origin of the lesions [93]. The integration of imaging morphology into the TNM classification of the in situ and 1–14 mm invasive tumor size range would represent a major advance. There is a considerable potential of mammographic tumor features alongside classical pathological and modern molecular prognostic factors to improve the outcome prediction of BC subgroups [94, 95]. Such radio-pathological synergy could enable the multidisciplinary team to better distinguish the less frequent subgroups with the highest fatality [94] among the small invasive cancers, thus allowing for setting up clinical trials that may identify the more successful, targeted treatment. For the majority of screen-detected, monofocal, small invasive cases that belong to the better mammographic and pathological prognostic groups [96, 97], the current use of adjuvant treatment might be reevaluated through more pertinently designed trials. This research cooperation may

eventually enable many women to forego some of the current adjuvant therapeutic regimens, without compromising their survival and avoiding the hazards of overtreatment. Finely tailored treatment protocols, based on a fuller appreciation of different parameters of tumor characterization, should make negligible any concern over the overdiagnosis of the more indolent cancer cases.

17.1.5 Discussion

The clear scientific evidence on the efficacy of MS as derivable from RCTs and its effectiveness in reducing BC mortality as confirmed by more recent studies conducted in the routine service screening situation have been reviewed and highlighted.

It has been shown how benefits achievable through MS are substantially undervalued.

This is not only the case with a number of skeptical authors, often on the basis of methodological flaws in their arguments. Also some screening advocates appear at times not to fully appreciate the size of the benefits entailed by organized screening. This can derive from:

1. The unjustified consideration paid by many to some large yet scientifically unsound studies.
2. The incomplete appreciation of many experts of the clinical peculiarities of breast tumors: especially their wide inter- and intra-tumor heterogeneity, extremely long natural history of many cases, and the concept of progressive dedifferentiation of BCs. Hence, it is not fully appreciated how MS benefits cumulate over very long times. Some screening dividends of lives saved are cashed as soon as 3–4 years after the timely detection at screening of aggressive cancers, while dividends of lives saved from more indolent cancers might still be cashed 10–15 years after screening detection. The most recent updates of the well-conducted observational studies of screening service, with the longest follow-up times, are wanted to gauge the full effect of MS on mortality (the screening dividend) and should be given prominent attention in the scientific debate. The same applies to the long-term follow-up of the best RCTs.
3. Screening harms related to false-positive recalls are unduly emphasized. It has been illustrated that the limited rate of false-positive recalls in population-based, organized screening is in fact a protection vs. the much higher rates observed in non-organized settings.
4. Neglect of the immense human and social value of MS and the diffuse, continuing real psychological reassurance it provides to the vast majority of true negative women.
5. Insufficient appreciation of the value of equity in the high-quality health-care access provided by organized MS.

It is important to state at this point one rarely, if ever remembered merit of screening. This is the leading role of the organized MS experience of the 1970s–1990s in building up the idea of a need for dedicated professionals, with specific education, training, and expertise in BC diagnosis and treatment. The importance of interdisciplinary, collaborative management of BC by experts in senology has been advocated by the screening guidelines at a time when senology was hardly recognized by most physicians as a field of specialization in its own right. This awareness has greatly contributed to the institution of the Breast Units system as an international standard of care.

There are also important, well-known limitations of cancer screening with mammography.

The lower sensitivity of mammography in dense breasts and—more generally—the traditional use of a single diagnostic tool for the early detection of a complex variety of clinical entities are obvious weaknesses. Although the use of a single test is motivated by evidence of impact, practical feasibility, and competitive cost-effectiveness, intelligent research has to be promoted to open the way to new protocols that take advantage of complementary imaging methods. The recent availability of such sophisticated technologies as DBT, AWBU, and MR will definitely accelerate this evolutionary process. The combination of the newest imaging methods with the powerful support provided by the modern IT systems is due to create a winning environment. Specially developed new CAD systems will help tackle problems related to the longer interpretation times implied by the tomographic techniques. The digital support will also play a role in the form of improved monitoring, evaluation, and educational tools, e.g., mammography test sets for training. Given the limitations of its current format, MS will have also to consider risk-based, customized screening policies, in order to maximize the cost-effectiveness of the system and the harm/benefit balance of the procedure.

So, future evolution of screening should be built on the organized setting of MS: introducing new diagnostic technologies, improving on the stratification of women and the way screening is offered (tailoring), making the most profit from modern IT technology support (simulation models, CAD, etc.), and threading along the main road of the specialized multidisciplinary units, where different specialties work together to optimize the synergies of diagnosis and treatment. Evaluation could be optimized, working on the most significant early indicators of performance (as T2+ cancer rates), refined to the individual operator level, and combined

to a more efficient system of feedback. Optimization should also be pursued of the information provided to physicians and the population and the communication tools.

The prominent importance of dedicated, specialized education, training, and research should be recognized and adequate resources provided. The organized screening framework represents an exceptional resource for producing applied research of the utmost scientific level, at competitive costs. One foremost topic of integrated research would be the innovative rethinking of the pathological classification of breast diseases, to be built on a strict collaboration of breast pathologists and screening radiologists. This new perspective could bring about a change in the fundamental concepts of BC treatment, making it negligible the concerns about screening overdiagnosis.

Conclusion

Implementing, expanding, and keeping up large, high-quality, population-based screening programs should be considered a needful strategy in order to best capitalize on modern treatment advances. In the future context of preventive medicine, innovative strategies may be devised aimed at combining risk-stratified screening with actions of primary intervention targeting modifiable risk factors. Futile controversies on the respective roles played by early detection vs. modern treatment should be abandoned, in favor of a shared awareness that these two major innovations enhance each other's benefits and of research projects on the theme of how early detection through screening might and should change the treatment of breast cancer.

17.2 High-Risk Population

Francesco Sardanelli, Franca Podo

Abstract Although breast cancer (BC) is mainly a sporadic disease, about 15% of cases are clustered in families at increased incidence. Gene mutations with autosomal dominant inheritance confer a 50–85% cumulative lifetime risk (LTR) and account for about 5% of BCs; about 50% of hereditary BCs are associated with BRCA1/2 mutations. In high-risk (HR) women, mammography has a too low sensitivity (29–50%) to be used alone as a screening tool. Nonrandomized studies showed that contrast-enhanced magnetic resonance imaging (CE-MRI) largely outperforms mammography and/or ultrasound in detecting asymptomatic BCs in HR women, reaching a sensitivity higher than 90% and a positive predictive value higher than 60%. In 2007, the American Cancer Society issued recommendations in favor of *MRI as an adjunct to mammography* for screening women with 20–25% or greater LTR, including those with a strong family history of BC or ovarian cancer or previously treated with chest radiation therapy (CRT). Recommendations in favor of MRI screening for HR women were also issued by other institutions and medical bodies. Studies suggested that MRI screening of BRCA1/2 mutation carriers should not be discontinued over 50 and that an *MRI alone* strategy could be adopted, also considering the higher sensitivity of these mutation carriers to ionizing radiation. Although randomized controlled trials are not allowed for ethical issues, evidence exists in favor of MRI screening to improve patient outcome. In cases of previous CRT, *mammography as an adjunct to MRI* is recommended, because a high incidence of ductal carcinoma in situ with microcalcifications and low neoangiogenesis limits MRI sensitivity.

17.2.1 Introduction

Exactly 30 years ago, in 1986, Sylvia H. Heywang and coworkers reported the first experience about contrast-enhanced magnetic resonance imaging (CE-MRI) of the breast [98]. Notably, only some months before, in 1985, the same author concluded a paper about unenhanced (*non-contrast*) MRI [99] saying that "possible future indications are suggested for selected cases," an elegant way to state that non-contrast breast MRI had no real clinical perspective. Conversely, when, for the first time, a gadolinium-based contrast material had been intravenously injected, "all carcinomas enhanced" and the authors concluded that "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" [98].

This was a turning point which opened a window for breast MRI to enter the clinical practice. At the beginning, even after the introduction of contrast injection, radiologists who pioneered the use of this technology (a name for all, Werner A. Kaiser, who firstly showed the value of dynamic scan for CE-MRI [100]) faced difficulties and distrusts from the established medical community working on breast cancer (BC). Even breast radiologists, who were in those days highly confident with the so-called triple assessment composed by mammography, ultrasound (US), and needle sampling, were not so favorable to MRI. Although mammography was still in the era of film-screen, US B-mode images were distant from today's quality, and needle sampling was mainly fine-needle aspiration, surprisingly breast CE-MRI did not receive a good acceptance.

Breast MRI investigators highlighted that the new method allowed BC 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 of mammography and US. Physically speaking, two completely different pieces of theory are involved: differences in photon attenuation as an effect of *electronic 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 CE-MRI side. Unfortunately, the reference to tumor-associated neoangiogenesis was reminiscent of the old thermography, an approach leading to a false hope for BC diagnosis as it was burdened by a high rate of false negatives and positives,[1] although it is still sometimes represented as a new method [101].

The main criticisms against breast MRI were based on high cost, need of 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 [102]. 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.

One clear example of this misleading use of published data is given by the comparison of two papers published in 1993–1994.[2] In 1993, a small breast MRI study from the USA [103], conducted on 30 breasts with 47 malignant and 27 benign lesions, reported a 94% sensitivity and a 37% (!) specificity; these data were included in the Abstract. A year after (1994), a group from Germany, guided by Werner A. Kaiser, reported 2053 cases, 766 with histopathological verification within 2 weeks ($n = 766$) or follow-up control up to 7 years [104]. The title was "False-Positive Results in Dynamic MR Mammography: Causes, Frequency, and Methods to Avoid." Sensitivity was 98%, specificity 97.4%, and PPV 81%. Unfortunately, these results were not reported in the Abstract, thus leading to a strong underestimation of the value of the paper [105]. Looking at the number of citations through Scopus® [106], up to April 26, 2016, the small US study [103] had 580 citations, while the huge German study [104] had only 56 citations. For decades, when researchers reported a range for breast MRI, specificity values, this notorious 37%, the lowest range limit, drew the reader's attention. *Bad news have better legs than good news*.

However, 1993 was also the year of the first report on tumor suppressor BRCA1 gene conferring a high BC risk to women carriers of a deleterious mutation [107]; the identification of a similar role for BRCA2 followed very soon [108]. This relevant new knowledge created the possibility to identify not negligible populations of women having a clearly higher risk of developing BC during their lifetime.

As a consequence, teams of breast radiologists, mostly in cooperation with geneticists, physicists, and other professionals, initiated studies in order to compare the diagnostic performance of CE-MRI with that of conventional imaging (mammography and/or US) for screening high-risk populations. In Italy, we started the discussion in the late 1990s under the coordination of the Istituto Superiore di Sanità, organ of the Italian Ministry of Health, in Rome. For more than 10 years, we guided the High Breast Cancer Risk Italian (HIBCRIT) study for the comparative evaluation of CE-MRI vs. mammography and US for early BC diagnosis among women at high genetic/familial risk. The initial results of this study were published in 2002 [109] and contributed to the initial body of evidence considered by the American Cancer Society for the first recommendation in favor of *MRI as an adjunct to mammography* for screening women with 20–25% or greater lifetime risk [110]. Interim [111] and final [112] results of the HIBCRIT study further contributed to support the use of CE-MRI for screening women with hereditary BC predisposition.

In this chapter, the *high-risk* screening issue is placed in the larger context of the screening debate, and then the evidence in favor of MRI screening protocols for women at hereditary high risk is summarized in terms of superior diagnostic value, including the *MRI alone* concept, and in terms of patient outcome. Thereafter, the special case of high risk from previous chest radiation therapy (CRT) will be considered.

17.2.2 The Context: Population-Based Screening Programs

Mammography, notwithstanding its intrinsic limitations in terms of sensitivity and specificity, remains the basic tool for population-based mass screening, being demonstrated to be effective in reducing mortality and allowing for conservative therapy [113]. The stage of BC at diagnosis significantly impacts on overall survival even in recent years, when effective systemic therapies are applied. In other words, *early diagnosis remains crucial*. This concept has been recently confirmed by a population-based study from the Netherlands Cancer Registry 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%, in 2006–2012, mortality still increased with progress-

[1]Notably, some new currently emerging technologies such as *optical imaging* and *opto-acustic 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, for example, Sella T, Sklair-Levy M, et al. (2013) A novel functional infrared imaging system coupled with multiparametric computerised analysis for risk assessment of breast cancer. Eur Radiol 23:1191–1198.

[2]This comparison was firstly reported in Amsterdam by Pascal Baltzer during the ceremony for the EUSOBI (European Society of Breast Imaging) 2014 Gold Medal to the memory of Prof. Werner A. Kaiser (*05.10.1949, † 27.12.2013).

ing tumor stage, significantly for T1c vs. T1a and independently from nodal status [114].

The International Agency for Research on Cancer (IARC) recently summarized the evidence in favor of screening mammography [59, 115]. The estimated reduction in BC mortality is 40% for those women aged 50–69 who take up the invitation and 23% when also including those not accepting the invitation. A mortality reduction has been also estimated for women aged 40–49 and 70–74, though with "limited evidence" [59]. In addition, we must note that screening mammography allows for both downscaling of the clinicopathological features of invasive BCs and reducing locoregional and adjuvant treatments [51, 116–118].

A good news of the last years is the *end of confusion*, as appropriately stated by the Society of Breast Imaging about harms from screening mammography [119]. This is a hot topic, in particular for *false-positive rate* and *overdiagnosis*. In Europe, the average risk for a false-positive recall is limited to 20% for women aged 50–69 who have ten screens in 20 years; the probability of false-positive needle biopsy is <1% per round [59]. A low rate of overdiagnosis has been calculated by the IARC working group [59], from 1 to 10% or from 4 to 11%, according to different estimation methods. Notably, *overdetection* (a radiological issue) has to be distinguished from *overdiagnosis* (which implies also an essential role of pathologists) [120], while more efforts should be dedicated to the reduction of *overtreatment*.

However, one weak point of current population-based screening programs remains the *one-size-fits-all* rule: in Europe, mammography every 2 years (every 3 years in the United Kingdom) from 49 to 69 years. Some change has been introduced when also women from 40 to 49 (mostly from 45 to 49) are invited: the periodicity is commonly reduced to 1 year only. During the last three decades, 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 [121], its masking effect results in a relevant reduction in mammography sensitivity [122]. 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, it was clear that the diagnostic performance of mammography in high-risk women was inadequate. The sensitivity ranged 29–50%, the interval cancer rate 35–50%, and the metastatic nodal involvement at diagnosis 20–56% [123]. Something different had to be proposed. A new screening strategy to be implemented had to consider four elements:

1. The need to start very early in the high-risk woman's life, accounting for the early disease onset
2. The need for closer screening events, accounting for the fast BC growth in these women
3. 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
4. Possible avoidance of ionizing radiation exposure, accounting for the higher sensitivity to radiation of BRCA mutation carriers (as explained in detail below)

This was the scenario when the first studies on MRI-including screening programs were initiated. The only change in those years and during the first decade of 2000 was the slow but progressive transition from film-screen to digital mammography, without any substantial impact for high-risk women.

17.2.3 High-Risk Screening with MRI: From a *Mission Impossible* to a Large Body of Evidence

To explore the diagnostic power of CE-MRI in a screening setting was initially a *mission impossible*. The typical objection was the following: *MRI specificity is too low, and you will be flooded by a deluge of false positives*. However, as stated by Thomas Kuhn [124], scientific research is attractive also due to "the excitement of exploring new territory, the hope of finding order, and the drive to test established knowledge".

Thus, different groups started to verify the hypothesis that CE-MRI could be useful for BC screening. For epidemiological reasoning, women at increased BC risk, especially those with hereditary predisposition, were the natural candidates for these projects. A greater expected incidence would have resulted into a higher positive predictive value (PPV) of screening modalities and a smaller sample size needed to evaluate the differences in diagnostic performance among the modalities [125]. This was also a way to begin to dismount, from the side of high risk, the *one-size-fits-all* rule.

In fact, breast radiologists had to get at least a basic information about familial/genetic predisposition to BC [126]:

- Autosomal dominant inherited BCs are only 5% of all cancers (one third of all familial BCs).
- BRCA1/2 mutations explain only about 40% of autosomal dominant inherited BCs (other genes such as TP53, STK11, PTEN, NF1, CHEK2, ATM, BRIP1, and PALP2 explain about 10%), while the remaining 50% has no gene mutation clearly identified. BRCA1/2 deleterious mutations confer a 50–85% LTR.
- Most BCs in very young women are associated with a BRCA1 mutation, a condition which 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.

This body of knowledge allows radiologists, who have the possibility to deal with a large number of women on the occasion of screening and diagnostic imaging, to identify those women whose family history indicates the possible presence of an inherited BC predisposition. Software can be used for a preliminary risk evaluation, such as that based on the Tyrer-Cuzick model [127, 128]. Anyway, *radiologists (or other professionals who suspect a BC genetic predisposition) have to refer the woman suspected to be at high risk to a specialized department/center for genetic counseling to define the possibility of genetic testing.* Importantly, in the case of strong family history of BC and/or ovarian cancer without identification of known gene mutations in the family, genetic testing is defined as *inconclusive* and the case is labeled as *BRCAX* [129]. Finally, for different reasons, including unsuitable psycho-oncologic condition, many women with strong family history prefer not to perform any genetic testing.

Thus, since the mid-1990s, the context has been enriched to comprise three basic concepts:

1. Mammography, the only established method for BC screening in general, was not working properly for screening women at high genetic/familial risk.
2. Identification of high-risk populations could be based on clearly established criteria to assess/estimate a BC genetic predisposition.
3. There was a need for several years of clinical experience with CE-MRI of the breast in the diagnostic setting, acquired in academic centers and great hospitals, to participate in suitably designed screening programs.

The first report was published by Christiane K. Kuhl in 2000 [130]. Fifteen cancers were detected in 192 women proven or suspected to be carriers of a BC susceptibility gene. Sensitivity was 33% for mammography, 33% for US, 44% for mammography and US combined, and 100% for CE-MRI; PPV 30%, 12%, and 64%, respectively. A number of studies were followed, and the body of evidence grew up in the last 15 years. When the sample size of high-risk women, the number of screening events, and the number of centers involved increased, the sensitivity of MRI slightly decreased, as expected, but the general trend for a huge difference in diagnostic power, especially in sensitivity, between MRI and the other imaging modalities was confirmed not only in terms of efficacy but also in terms of large-scale effectiveness.

High-risk screening has been the prominent application for breast MRI multicenter studies in the last 15 years, involving 7690 women who performed 18,307 MRI examinations (Table 17.6).

The evidence from prospective studies about MRI including screening protocols was summarized in 2014 [131]. Overall, nine studies [111, 132–139] enrolled more than 5500 women. A total of 392 BCs were diagnosed. Of them, 45% had a diameter ≤ 10 mm (95%; confidence interval [CI], 39–51%), 77% were invasive (95% CI 73–81%), and 52% were G3 invasive (95% CI 46–58%). Of the invasive cases with explorable axilla (not previously treated for BC), 23% had nodal metastatic involvement (95% CI 18–28%). Study-by-study details are reported in Table 17.7.

All these studies contributed to build the body of evidence in favor of the use of CE-MRI for screening women at high BC risk. National and international recommendations and guidelines accepted this indication on the basis of the superior sensitivity of breast MRI, including not only professional and scientific societies such as the American Cancer Society (already mentioned) [109], the American

Table 17.6 Multicenter breast MRI studies from 1997 to 2014

		Patients		MRI exams		Centers		Papers	Journals		Papers per country			
Study type	Studies	Total	Min Max	Total	Min Max	Total	Min Max		Imaging	Other	Europe	Europe and USA	USA	Asia
High-risk screening	10 (24%)	7690	93 2500	18,307	171 7500	157	4 30	29 (43%)	10	19	26	2	1	–
Diagnostic performance and contrast materials	14 (33%)	3989	63 969	5026	63 1652	158	3 25	18 (27%)	15	3	9	4	5	–
MR-guided biopsy/ localization	6 (14%)	2069	132 821	33,386	132 1029	51	3 20	6 (9%)	3	3	5	1	0	–
Preoperative	6 (14%)	2784	90 1623	2030	90 761	76	2 45	7 (10%)	1	6	6	0	0	1
NAT effect evaluation	6 (14%)	1029	89 746	3300	46 746	34	3 15	7 (10%)	0	7	3	0	1	–
Total	42 (100%)	20,348	63 2500	32,049	46 7500	476	2 45	67 (100%)	29 (43%)	38 (57%)	49	7	7	1

USA United States, *NAT* neoadjuvant therapy
Data from PubMed/Medline, accessed on December 22, 2014

College of Radiology [140], the European Society of Breast Imaging [141, 142], or the multidisciplinary European Society of Breast Cancer Specialists (EUSOMA) [143] but also governmental bodies such as the National Comprehensive Cancer Network [144] in the USA and the National Institute for Health and Care Excellence [145] 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 USA and higher (30% or more) in some European guidelines. However, in all guidelines MRI is proposed for screening high-risk women. Key recommendations issued by EUSOMA in 2010 [143] are summarized in Table 17.8.

Table 17.7 Prospective studies on MRI including screening of women with increased familial BC risk

First author year, study name country [Reference]	Subjects enrolled	MRI sensitivity (%)	MRI specificity (%)	MRI-detected invasive cancers ≤10 mm in diameter	Invasive cancers/all cancers	DCIS/all cancers	Invasive grade 3/all invasive cancers	Metastatic nodal involvement/all invasive cancers
Warner 2004, Canada [132]	Mut	77	95	9/16 (56%)	16/22 (73%)	6/22 (27%)	NR	2/15 (13%)
Kuhl, 2005, Germany [133]	Fam/Mut	91	97	NR	34/43 79%)	9/43 (21%)	11/24 (46%)	5/31 (16%)
Leach 2005, MARIBS UK [134]	Fam/Mut	77	81	13/29 (45%)	29/35 (83%)	6/35 (17%)	19/29 (66%)	5/26 (19%)
Hagen 2007, Norway [135]	Mut	86	NR	8/19 (42%)	21/25 (84%)	4/25 (16%)	13/21 (62%)	6/20 (30%)
Riedl 2007, Austria [136]	Fam/Mut	86	92	8/16 (50%)	16/27 (59%)	11/27 (41%)	6/16 (38%)	2/16 (13%)
Rijnsburger 2010, The Netherland [137]	Fam/Mut	71	90	30/74 (40%)	78/97 (80%)	19/97 (20%)	28/72 (39%)	22/72 (31%)
Kuhl 2010, EVA Germany [138]	Fam/Mut	93	98	9/16 (56%)	16/27 (59%)	11/27 (41%)	6/16 (38%)	NR
Sardanelli 2011, HIBCRIT, Italy [111]	Fam/Mut	91	97	15/39 (38%)	44/52 (85%)	8/52 (15%)	28/44 (64%)	11/39 (28%)
Evans 2014, MARIBS UK [139]	Fam/Mut	93-100	63	24/47 (51%)	47/63 (75%)	16/63 (25%)	29/47 (61%)	8/47 (17%)

MRI magnetic resonance imaging, *DCIS* ductal carcinoma in situ, *Fam* women at elevated familial risk of breast cancer, *Mut* women proven to carry a deleterious mutation in a breast cancer susceptibility gene (*M*), *M* mutation carriers only, *NR* not reported (From Santoro et al. 2014 [131], modified, with permission)

Table 17.8 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); and 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 the 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 (reevaluation 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, and lobular intraepithelial neoplasia, when not associated with other risk factors, do not confer an increased risk that justifies MRI screening

BC breast cancer, *LTR* lifetime risk, *MRI* contrast-enhanced magnetic resonance imaging, *US* ultrasound. From Sardanelli et al. [142], modified. Notably, the EUSOMA recommendations include also women who underwent chest radiation therapy, here discussed in the section 17.2.6.

Secondary evidence in terms of systematic reviews were published, generally confirming the introduction of annual CE-MRI for high-risk screening in terms of both diagnostic performance [146–148] and cost-effectiveness [149].

One relevant contribution came from an individual patient data meta-analysis [150], authored by a team including authors of six original studies. It was demonstrated that the addition of MRI to mammography for screening BRCA1/2 mutation carriers aged ≥50 improves screening sensitivity by a similar magnitude to that observed in younger women. This means that those guidelines which limit screening MRI in BRCA1/2 mutation carriers only up to 50 years of age should be updated to this new evidence.

17.2.4 Radioprotection Issues and the *MRI Alone* Approach

The idea of avoiding mammography in carriers of gene mutations conferring an increased BC risk is not new. It was related to the well-known role of oncosuppressor genes such as BRCA1 and BRCA2. Studies on animal model had shown that BRCA2 protein interacts with the DNA repair protein Rad51, explaining a higher radiation sensitivity [151]. Thus, also from our side [152], we suggested the possibility to abstain from doing mammography at least up to age 35, taking into consideration that, on the basis of available studies, the rate of undetected BCs was only 4%, limited to only ductal carcinoma in situ (DCIS).

This view was subsequently confirmed by statistical modeling of the risk of radiation-induced BC from mammographic screening for young BRCA mutation carriers [153] and by the empiric demonstration of more DNA double-strand breaks induced by mammographic exposure in human mammary epithelial cells sampled from patients with high than with low family BC risk, with a dose-effect exacerbated in cells from high-risk women [154].

Moreover, mammography could be avoided also from the viewpoint of a limited diagnostic performance. This was very clear especially after the results of the EVA study conducted in Germany [138] and of the HIBCRIT study conducted in Italy [111]. The EVA study, based in four academic institutions, included 687 asymptomatic women with familial high risk (LTR ≥20%) who underwent 1679 annual screening rounds composed by clinical breast examination (CBE), mammography, US, and MRI; in a subgroup of 371 women, additional half-yearly ultrasound and CBE were performed in more than 869 rounds. Of 27 BCs diagnosed (11 DCIS and 16 invasive), 3 (11%) were node positive. After a mean follow-up of 29 months, no interval cancers occurred; no cancer was identified by half-yearly ultrasound examinations. No significant difference in detection rate was observed between US (6.0%) and mammography (5.4%), with a not significant increase to 7.7% for both modalities combined. MRI alone had a significantly higher detection rate (14.9%), unchanged by adding US and not significantly increased by adding mammography (MRI plus mammography, 16.0%) , and not changed by adding ultrasound (MRI plus ultrasound, 14.9%). The PPV was 39% for mammography, 36% for US, and 48% for MRI.

Similar results were obtained by the HIBCRIT study [111], based in 18 cancer centers, universities, and general hospitals. We enrolled 501 asymptomatic women aged ≥25 who were BRCA mutation carriers, who were first-degree relatives of BRCA mutation carriers, or women with strong family history of BC or ovarian cancer, including those with previous personal BC. A total of 1,592 rounds were performed; 49 screen-detected and 3 interval cancers were diagnosed: 44 invasive and 8 DCIS; and 4 being pT2 stage, 32 G3 grade. Of 39 patients explored for nodal status, 28 (72%) were negative. Incidence per year-woman resulted significantly higher at ≥50 years of age (5.4%) than at <50 years of age (2.1%), 3.3% overall, significantly higher (4.3%) in women with previous personal BC than in those without (2.5%). The diagnostic performance of CBE, mammography, US, and their combinations is reported in Table 17.9.

At receiver-operating characteristic analysis, MRI showed a superior diagnostic performance than mammography or US (0.82), while MRI combined with mammography and/or US did not overrun MRI alone (Fig. 17.1). Of 52 cancers, 16 (31%) were diagnosed only by MRI. An example of the superior sensitivity of MRI is shown in Fig. 17.2.

Both the German and the Italian studies showed that MRI largely outperforms mammography, US, and their combination. While the EVA trial added the relevant information that US, even when performed every 6 months, does not add sensitivity, the HIBCRIT study demonstrated the effectiveness of an MRI including screening protocol on the large scale of 18 centers. The PPV values were about 50 and 60% for the two studies, respectively, a certainly good metrics in a screening setting. Of note, specificity of MRI was obviously very high in both studies, as of course expected when the probability of the true negative is overwhelming. However, only very recently the *mantra* about the low specificity of breast MRI has begun to reduce its credibility.

The key point of the superior sensitivity of MRI is due to the high detection of small cancers. In the HIBCRIT study, the sensitivity for pT1a–b BCs was 10/20 (50%) for mammography plus US vs. 95% for MRI. Moreover, in an explorative analysis, we also showed no gain in sensitivity as an effect of the transition from film-screen (17/31, 55%) to digital mammography (8/19, 42%) [112].

This new *MRI alone* paradigm, i.e., the absence of additional diagnostic power by adding other imaging modalities after a negative MRI, is due to the very high sensitivity and specificity of the method. For statistical reasons, it is quite

Table 17.9 Diagnostic performance of the different modalities in the HIBCRIT study

Modality	Sensitivity (%)	Specificity (%)	PPV2 (%)	NPV (%)	LR+	LR−
Clinical breast examination	17.6	99.4	60.0	96.1	30.9	0.83
Mammography	50.0	99.1	73.5	97.6	58.1	0.50
Ultrasound	52.0	99.2	76.5	97.7	66.0	0.48
MRI	91.3*	97.4	61.8	99.6*	35.1	0.09*
Mammography + ultrasound	62.5	98.4	65.2	98.2	39.0	0.38
MRI + mammography	93.2	97.0	58.6	99.7	31.5	0.07
MRI + ultrasound	93.3	97.1	60.0	99.7	32.0	0.07

PPV2 positive predictive value 2 (needle biopsy prompted), *NPV* negative predictive value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *MRI* contrast-enhanced magnetic resonance imaging. * indicates that the MRI value is signficantly better than each of the the other modality or their combinations.

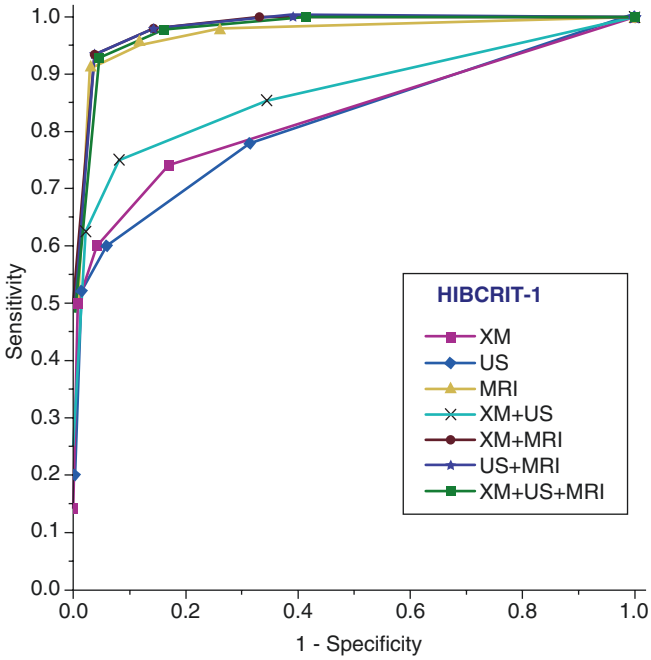

Fig. 17.1 Receiver-operating characteristic analysis of diagnostic performance of mammography (XM), ultrasound (US), MRI, and their combination for screening high-risk women. The AUC of MRI (0.97) was significantly higher than that of mammography (0.83) or US (0.82) and not significantly increased when MRI was combined with mammography and/or US. HIBCRIT study [111]

unlikely that any other technique can add significant diagnostic gain, unless a huge sample size is considered.

This approach has been reinforced by the results of a number of subsequent studies. A study from Ontario, Canada, reported on the initial evaluation of 2207 high-risk women [156]: of 35 BCs detected, none was identified by mammography alone. A study from the Netherlands considering only BRCA1 mutation carriers [157] reported on 82 invasive BCs and 12 DCIS during the study. They had four interval cancers (all invasive): MRI missed only 2 DCIS that were detected by mammography (2/94, 2%). An update from the Austrian study [158] showed that of 40 BCs 18 (45%) were detected by MRI alone and only two by mammography alone (a DCIS with microinvasion and a DCIS with <10 mm invasive areas), without leading to a significant increase in sensitivity vs. MRI alone; no cancers were detected by US alone.

Finally, an individual patient data meta-analysis including six high-risk studies [159] recently showed that in BRCA1/2 mutation carriers, adding mammography to MRI did not significantly increase sensitivity. However, the increase was 3.9% in BRCA1 but reached 12.6% in BRCA2 mutation carriers. In women with BRCA2 mutation younger than 40 years, one third of BCs were detected by mammography only. We should consider here that the inclusion of only six studies, based on the voluntary contribution of the individual patient data by the authors of the original researches, did not allow for including data from some other studies which could have reduced the rate of BCs detected on mammography only.

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:

1. MRI alone up to 35 years of age for all high-risk women
2. MRI alone for BRCA1 and p53 mutation carriers without age limitations
3. *Mammography as an adjunct to MRI* for BRCA2 mutation carriers after 35 years of age

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 [160].

17.2.5 Impact on Patient Outcome

If the principles of evidence-based medicine [161] are applied to screening programs, a high detection rate or a very good diagnostic performance of a screening tool should not

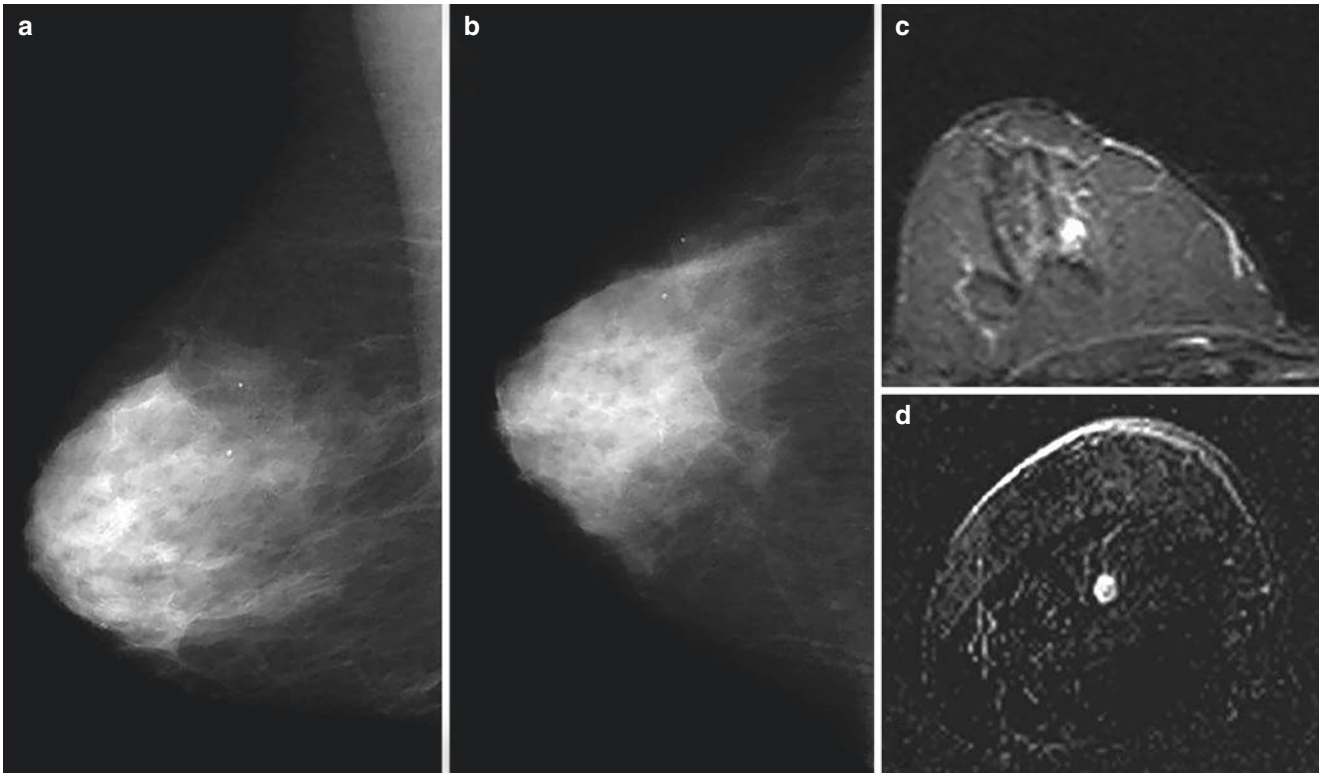

Fig. 17.2 Case from the HIBCRIT study. A 53-year-old BRCA1 mutation carrier, already treated for an invasive ductal cancer of the left breast at 33 years of age, underwent multimodal screening including clinical breast examination (CBE), mammography, US, and MRI. The left breast only showed minimal signs 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 [155], with permission)

be considered *per se* as a sufficient reason to implement this screening tool in practice. Randomized controlled trials should be performed to take into account lead time bias, length bias, and overdiagnosis, finally evaluating whether the screening under consideration has a significant impact on mortality and patient outcome overall.

This rule should be theoretically also applied to high-risk population. However, ethical issues make this approach (i.e., to obtain information from randomized controlled trials) no longer possible for what we are considering in this chapter. The demonstrated gap in sensitivity between MRI and mammography and/or US is too high to propose a randomization to a BRCA or p53 mutation carrier. We are convinced that no ethics committee would approve such a protocol.

Therefore, we had to refer to an indirect evidence. On the one side, an impact of the anticipated diagnosis obtained with MRI in a high-risk population can be inferred considering the impact of screening mammography on the general female population [114]. On the other side, relevant information began to come from the cohorts included in the above-mentioned high-risk studies.

Rijnsburger et al. [137] reported a 5-year cumulative overall survival higher in the prospective MRI screening patient series of the Dutch MRISC study (93%) than in institutional historical unselected controls, as well as in 26 published series. This result was associated with a more favorable tumor stage, particularly in a moderate-risk group.

Møller et al. [162] reported on survival of patients with BRCA1-associated BCs diagnosed in an MRI-including screening program. The 5-year BC-specific survival for women with cancer was 75%, and the 10-year survival was 69%. The 5-year survival for women with stage 1 BC was 82% compared to 98% in the general population. The authors commented that these survival rates were *less than anticipated* and *the benefit of annual MRI surveillance on reducing BC mortality in BRCA1 mutation carriers remains to be proven.*

We argue that one key point is the historical context of the cohorts of screened women, i.e., the associated effect of early diagnosis combined with that of modern treatment protocols to better exploit the advantage of an early MRI detection. When Evans et al. [139] compared three cohorts

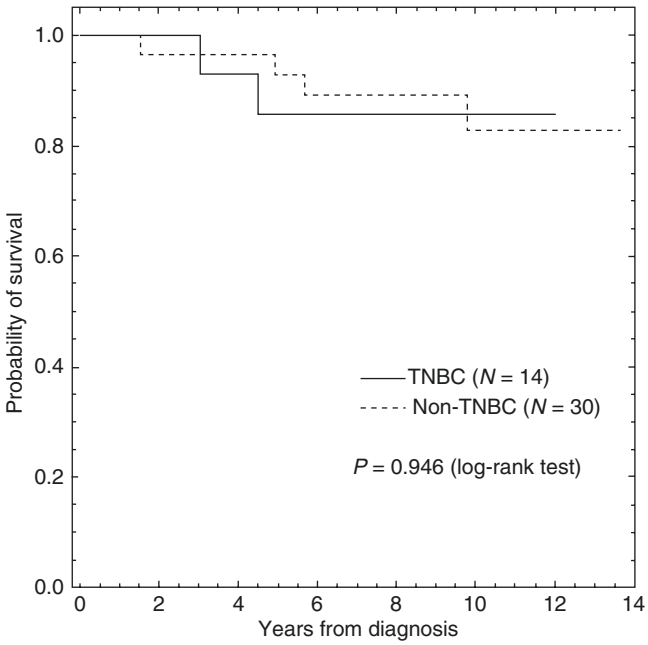

Fig. 17.3 Kaplan-Mayer analysis of overall survival of high-risk women affected with triple-negative breast cancers (TNBC) or non-TNBC during the HIBCRIT study [111] (with permission)

of high-risk women who had no screening, mammography or an MRI including program, a clear advantage of mammography vs. no screening and MRI vs. mammography or no screening is visible. However, these three cohorts are not concurrent, but subsequent and their survival should have been influenced by the progressive improvement of therapies [131].

Our contribution has been to compare phenotype features and survival of triple-negative BCs (TNBCs) vs. non-TNBCs detected during the HIBCRIT study [155], on the basis of a median of 9.7-year follow-up. The 44 invasive BCs (41 screen-detected and 3 BRCA1-associated interval TNBCs) comprised 14 TNBCs (32%) and 30 non-TNBCs (68%), without significant differences for age at diagnosis, menopausal status, prophylactic oophorectomy, or previous BC. Of 14 TNBC patients, 11 (79%) were BRCA1; of the 20 BRCA1 patients, 11 (55%) had TNBC; and of 15 patients enrolled for family history only, 14 (93%) had non-TNBCs. TNBC patients had more frequent ipsilateral mastectomy, contralateral prophylactic mastectomy, and adjuvant therapy. The 5-year overall survival was 86% ± 9% for TNBCs vs. 93% ± 5% for non-TNBCs; 5-year disease-free survival was 77% ± 12% vs. 76% ± 8%, respectively, without significant differences (Fig. 17.3). We are aware that the detection of TNBCs in BRCA (especially BRCA1) mutation carriers could have been responsible for the selection of more drastic therapies vs. those decided for noncarriers, so that the relative contribution of MRI and systemic therapies is not easily discernible [163]. At any rate, the relevant clinical message here is 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.

17.2.6 The Special Case of Previous Chest Radiation Therapy

Women who underwent chest radiation therapy (CRT) during pediatric/young-adult age (typically those treated for Hodgkin's lymphoma) have an increased BC risk, in particular those who received mantle CRT with high doses. The cumulative BC incidence from 40 to 45 years of age in these women is 13–20%, higher than that observed in the young female general population and similar to that of BRCA mutation carriers. The risk is higher for high doses delivered between 10 and 16 years of age. The BC is diagnosed on average about 15 years after CRT at about 40, to be compared with a mean age of about 61 in the general female non-exposed population [164, 165]. These BCs are similar to those encountered in the general female population in regard to histopathologic subtype, receptor status, lymphatic invasion, and nodal involvement. Of note, BCs in women who underwent CRT exhibit a preferential localization at upper external quadrants more extreme than that observed in women with hereditary predisposition (67% vs. 48%, respectively); moreover, in these women the possibilities of treatment of BC mostly exclude radiation therapy and chemotherapy with doxorubicin [166].

For women who underwent CRT, guidelines [109, 143, 167] recommend annual mammography and CE-MRI, starting from 25 years of age or, for those women who had CRT before 30, 8 years after the end of treatment. The rationale is the similar BC incidence in the young age for women who had CRT and women with hereditary predisposition associated with relatively lower sensitivity of mammography, also related to the need to start at a young age, and higher sensitivity of MRI.

In the USA, a study published in 2009 [168] reported that, of 551 women with previous CRT, 47% of those with 25–39 years of age never had a mammogram and only 37% had biannual 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.

Before the MRI introduction, the breast surveillance of women with previous CRT included annual physical examination and mammography [169]. This protocol allowed for detecting 60% of BC in the preinvasive phase or at T1 stage [170–174]. Two prospective [175, 176] and two retrospective studies [177, 178] compared mammography and MRI. Sensitivity ranged from 67 to 70% for mammogra-

phy, from 63 to 80% for MRI, with a 92% sensitivity reached only in one retrospective study, with a very small sample size for MRI [178]. Importantly, in women who underwent CRT, MRI sensitivity is relatively lower (63–80%) and that of mammography is relatively higher (67–70%) than those observed in women with hereditary predisposition, due to a higher incidence of DCIS with microcalcifications [179] and low neoangiogenesis. A sensitivity close to 95% can be obtained only using mammography as an adjunct to MRI.

An expert panel [180] recently compared the recommendations proposed by the following working groups: North American Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), Scottish Intercollegiate Guidelines Network (SIGN), and UK Children's Cancer and Leukaemia Group (UKCCLG). As a result of this comparison, a series of "harmonized recommendations" were provided: physicians, health-care providers, and women who had CRT should be informed on the treatment-related BC risk (strong recommendation); the surveillance is recommended for doses ≥20 Gy (strong recommendation); the surveillance is reasonable for doses between 10 and 19 Gy, taking into account the clinical context and further risk factors (moderate recommendation); the surveillance may be reasonable for doses between 1 and 9 Gy, taking into account the clinical context and further risk factors (weak recommendation); the surveillance implies annual check from 25 years of age or, at least, 8 years after CRT up to 50 years of age using mammography, MRI, or both of them (strong recommendation); and physical examination may be reasonable in countries where only clinical surveillance is available (weak recommendation).

Considering the available evidence, women who underwent CRT before 30 receiving a cumulative dose ≥10 Gy should be invited after 25 (or, at least, 8 years after CRT) to attend the following program [181]:

1. Dedicated interview about individual risk profile in order to define the potential of different breast imaging modalities in this specific setting
2. Annual CE-MRI using the same protocol recommended for women with hereditary predisposition
3. Annual bilateral two-view full-field digital mammography or digital breast tomosynthesis (DBT) with synthetic two-dimensional reconstructions

When reaching the age for entering population screening program, the individual risk profile should be discussed with the woman to opt for the only mammography/DBT screening or for continuing the intensive protocol including MRI.

Conclusions

More than 20 years after the identification of BRCA gene mutations and 20 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 CRT, *mammography as an adjunct to MRI* is always recommended as a high incidence of DCIS with microcalcifications and low neoangiogenesis limits MRI sensitivity.

The challenge for public health programs is to integrate these protocols for high-risk women into the general screening organization as models for a future stratification of BC screening protocols on the basis of different risk classes, up until a modulation based on the individual risk estimate will be possible, including a possible reduction of screening invitation to very low-risk women.

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