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REVIEW

The role of screening MRI in the era of next generation sequencing and moderate-risk genetic mutations

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Abstract With the advent of next-generation sequencing, the ability to rapidly analyze numerous genes simultaneously has led to the creation of large cancer gene panels. Some of these genes, like *BRCA1* and *BRCA2*, have been heavily researched and have well-established management guidelines. Other more newly established genes, like *ATM, CHEK2*, and *PALB2*, have previously had less robust research surrounding them which has limited the ability to create accurate risk estimates. With their inclusion on gene panels, there has been more pressure to produce management guidelines for patients discovered to carry pathogenic variants in these genes. For known high-risk genes, it is recommended for breast magnetic resonance imaging (MRI) and mammogram to be offered annually. This combination has been proven to be more effective at detecting breast cancer than mammography alone, with a combined sensitivity of 94% (Leach et al. in Lancet 365(9473):1769–1778, 2005). Women with a lifetime risk of breast cancer of 20% and higher have been recommended to have both breast MRI and mammography performed (Saslow et al. in CA Cancer J Clin 57(2):75–89, 2007). For women with pathogenic variants detected in moderate risk genes with lifetime breast cancer risks of at least 20%, breast MRI should be offered as part of their management. For more newly discovered genes with suspected associated risks at or above 20%, the use of breast MRI should be considered for their management as well.

Keywords Breast MRI · Hereditary cancer syndromes · Breast cancer surveillance · Moderate risk cancer genes

Introduction

The majority of breast cancers will occur sporadically and are believed to be influenced by various risk factors, including advancing age, reproductive factors, lifestyle, and possible environmental exposures. During the 1990s, researchers identified variants in *BRCA1* and *BRCA2* which predispose patients to a significantly elevated lifetime risk of breast cancer [1, 2], with initial estimates as high as 90% for *BRCA1* and 84% for *BRCA2* [3, 4]. A meta-analysis subsequently found the breast cancer risks at 57% (95% CI, 47–66%) for women with pathogenic *BRCA1* variants and 49% (95% CI, 40–57%) for *BRCA2* variants [5]. Due to this risk, the first breast cancer genetic screening test was developed and became commercially available for these two genes in 1996 [6].

Management recommendations for this high-risk population has evolved over time. The advent of magnetic resonance imaging (MRI) of the breast has proven to significantly improve the detection of breast cancer when combined with mammography versus mammography alone, with a combined sensitivity of 94% [7]. In 2007, the American Cancer Society recommended the addition of annual MRI to annual mammography in women with an elevated lifetime risk of breast cancer [8]. They specifically defined this risk to include women with known pathogenic *BRCA1, BRCA2, TP53* or *PTEN* variants, untested first degree

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relatives of individuals with pathogenic *BRCA1/2, PTEN*, or *TP53* variants, those who received radiation to the chest for lymphoma between ages 10 and 30, and those with a lifetime risk of at least 20% based on certain breast cancer risk assessment models that incorporate family history [8]. The specific models referenced at that time were the Tyrer-Cuzick model, Claus model, cancerGene, BRCAPro, and online versions of the BOADICEA model.

Since that time, options for genetic testing have expanded. Next-generation sequencing (NGS) became available, allowing the analysis of multiple different genes at once with a significant reduction in time and cost. In addition, the 2013 Supreme Court decision that disallowed patenting of genetic material opened the commercial market for genetic testing. Laboratories such as Ambry Genetics, GeneDx and others have joined Myriad Genetics in offering larger panels to those with a personal and/or family history of breast cancer. These panels now assess for a variety of genes beyond *BRCA1* and *BRCA2*. Gene panels include a spectrum of genes that have been associated with a hereditary risk for cancer, but some are newer and have less associated evidence that can provide robust estimates of risk. This leaves both patients who test positive and their providers without clear guidelines for surveillance. This paper will discuss the role of high-risk screening MRI for women with pathogenic variants in genes with moderate penetrance.

Rationale for supplemental screening MRI in high risk women

Breast MRI is a study using a magnetic field designed to produce detailed images of the breast. Cross sectional images are captured that allow for good soft tissue contrast with visualization of parenchyma, fat and lesions. A paramagnetic intravenous contrast agent using gadolinium is utilized to detect abnormal patterns of enhancement that may be reflective of underlying malignancy. The use of breast MRI in high-risk women is intended to reduce breast cancer mortality by allowing cancers to be diagnosed at an earlier stage, when tumors are more likely to be amenable to treatment.

Several studies have shown superior sensitivity with breast MRI compared to mammography or other screening tests. MRI sensitivity can range between 77–91% compared to mammography which is 40% or less [7, 9]. However, mammography has remained a more sensitive tool for the detection of ductal carcinoma in situ with a sensitivity of 83 versus 17% for MRI [10]. The positive predictive value of mammogram has been estimated to range from 48 to 100 and 28% of all biopsies performed based on a suspicious mammogram return benign [10]. The sensitivity of breast MRI combined with mammogram is highest, at 94% [7]. When other imaging modalities, such as breast sonography, have been included in the surveillance of women with *BRCA1*/2 mutations, sensitivity is similar to that of mammography [11].

The specificity of MRI is lower than mammogram, resulting in more call backs and false positives. Kriege evaluated the efficacy of mammogram and MRI in women at moderate risk (15–29% risk), high risk (30–49% risk), and high-penetrance gene mutation carriers (50–85% risk) [10]. They reported the overall detection at 9.5 cancers per 1000 woman-years at risk, with the highest levels of detection at 26.5 cancers per 1000 woman-years in known mutation carriers. MRI also resulted in a significant number of call-backs, with a two-fold increase in the number of unneeded exams and a three-fold increase in the number of unneeded biopsies. Approximately 43% of biopsies occurring as a result of MRIs with a Breast Imaging Reporting and Data System classification of 3, 4, or 5 (corresponding to an interpretation of probably benign, suspicious, and malignant until proven otherwise) were reported as benign. The positive predictive value (PPV) of MRI in this study was estimated at 60% or less, which suggests that false positive rate could be 40% or higher [10]. Kuhl also reported the results of screening MRI in high-risk women and noted the PPV to be at 50% for all high-risk women. MRI's in known *BRCA* mutation carriers were found to have the highest PPV at approximately 67% [9].

Effect of breast MRI on high risk patients

Various studies have identified the benefit of MRI screening in addition to mammography. Warner et al. followed 1275 women with a pathogenic *BRCA1/2* variant for a mean of 3.2 years and found that those who completed a high risk annual MRI as part of their routine mammographic screening were 70% more likely to be diagnosed with a Stage 0 or Stage I cancer than those without MRI surveillance [12]. There was no documented reduction in the risk of breast cancer in these patients, although MRI was successful in identifying disease at earlier stages. Kurian et al. evaluated the effect of prophylactic surgeries or surveillance on overall survival in women with *BRCA1/2* variants [13]. Although prophylactic oophorectomy at age 40 and prophylactic mastectomy at age 25 improved overall survival more than any other strategy, prophylactic oophorectomy and high-risk surveillance using both mammography and MRI showed a similar benefit in overall survival [13].

Kriege et al. also reported on the effect of MRI and mammogram screening in high-risk women [10]. Approximately 43% of cancers detected by MRI were small, at 10 mm or less in size, compared to <15% for

mammogram-detected cancers. 35% of cancers in gene-mutation carriers were measured at >2 cm in size compared to those with a moderate or high risk, where large tumors were identified in <20% of patients. Lymph node involvement was also less likely in MRI-detected cancers than those detected by mammogram (21 versus >50%). There was no significant difference in histology amongst the three groups studied (moderate risk, high risk and gene carriers) but women at moderate risk and high risk were more likely to have grade 1 disease compared to mutation carriers, whose tumors were noted to be a grade 3 on 63% of cases.

Long-term results of screening women with *BRCA1/2* variants with MRI were published in 2012 [14]. In a cohort of 496 women with harmful *BRCA1/2* variants prospectively evaluated with MRI and mammography, 57 breast cancers were detected [14]. Three of the four cancers with lymph node-positive disease were detected on the patient's first MRI screen [14]. Of the 34 cancers identified on subsequent imaging, 97% were a Stage 0 or Stage I [14]. Twenty-eight invasive breast cancers were diagnosed in women with no prior history of breast or ovarian cancer; of these, only one died from recurrent disease during a mean follow-up of 8.4 years, reflecting an overall distant recurrence rate of 3.6% and a yearly breast cancer-specific mortality of 0.5% [14]. Kuhl also reported that 92% of tumors identified by MRI only were considered minimal (ductal carcinoma in situ and/or invasive tumors <10 mm with negative lymph nodes) [9]. Of 19 cancers identified by MRI only, four were non-invasive and an additional 14 were invasive tumors of 7.5 mm in size or less.

NGS and new breast cancer risk genes

Previous genetic testing was limited by the ability to sequence only one gene at a time. This has changed with the advent of NGS, which allows for DNA sequencing of multiple genes at once. High-throughput sequencing of multiple genes enables rapid, cheaper testing, leading to faster test turnaround times. Most laboratories offering NGS for hereditary cancer syndromes organize gene panels based on cancer risks. This strategy increases test specificity by cutting down on discovery of variants of uncertain significance (VUS), which are genetic test results with uncertain impact on health [15–17]. Variants of uncertain significance are challenging to incorporate into medical management as they have the potential to be reclassified as benign or pathogenic, and generally a VUS should not be managed the same as a pathogenic result [18]. When patients with breast cancer were tested using a 25 gene cancer susceptibility panel, around one-third of women (33.2%) were detected to carry at least one variant of uncertain significance [19]. Increasing the number of genes tested increases the likelihood of detecting a VUS.

Clinical application is increased with targeted panels as well, because healthcare providers have greater ability to incorporate the result into the understanding of the case [15]. Utilizing larger gene panels over *BRCA1/2* analysis alone increases the number of pathogenic variants detected. It allows for inclusion of other high risk breast cancer genes, such as *PTEN, TP53, STK11*, and *CDH1*, and moderately penetrant variants in genes, such as *PALB2, CHEK2*, and *ATM*, and can be easily analyzed as well [19, 20]. When over 35,000 women with a single diagnosis of breast cancer were molecularly tested, around half (48.4%) of the pathogenic variants detected were present in *BRCA1/2* [20]. The other half were in other more established, high-risk genes, like *TP53*, or newer, moderate-risk genes, such as *CHEK2* [20].

Clinical interpretation can be a challenge with pathogenic variants in some of the newly identified genes [20]. Well-established guidelines have been created for management of individuals with pathogenic changes in high risk genes, like *BRCA1/2*, due to the extensive evidence that has accumulated over time [21]. For example, the National Comprehensive Cancer Network (NCCN) Guidelines outline when and what surveillance should be completed for men and women with *BRCA1/2* variants. Alternatively, evidence of risk with newly-discovered genetic variants is limited currently (Table 1). This is a rapidly changing field though, and understanding of the impact these variants have on health is refined as evidence evolves over time. *BRIP1* (*BRCA1* interacting protein C-terminal helicase1) has been included on breast cancer gene panels, with initial reports that truncating variants were associated with a 20% risk of breast cancer and missense variants not associated with an elevated risk [22]. Newer evidence, however, now suggests that truncating variants do not significantly increase risk for breast cancer [23]. Additional research will continue to refine our knowledge of these genes.

Breast cancer risks

The research that has been completed demonstrates that aside from *BRCA1/2*, pathogenic variants increasing risk for breast cancer are most commonly identified in *CHEK2, ATM*, and *PALB2* [20]. Most research on the cancer risk associated with *CHEK2* has been completed on the c.1100delC variant. A meta-analysis of individuals with this variant determined that women have a 37% risk to develop breast cancer by age 70 [24]. The cumulative risk for breast cancer for women with pathogenic variants in *ATM* is estimated at 33% by age 80 [25]. Pathogenic

Table 1 Breast cancer susceptibility genes and associated risks

Gene	Breast cancer risk (95% CI)*	Comment	References
ATM	33% (24–40)[4]		Marabelli et al. [25]
	52% (28–80)[2a]		Bernstein et al. [46]
BRCA1	57% (47–66)[2]		Chen and Parmigiani [5]
BRCA2	49% (40–57)[2]		Chen and Parmigiani [5]
CHEK2	20% (18–22)[5^b]	No affected 1st or 2nd degree relative	Han et al. [43]
	20%[5]	Affected 2nd degree relative	Cybulski et al. [44]
	28%[5]	Affected 1st degree relative	
	34%[5]	Affected 1st and 2nd relative	
	44%[5]		
	37% (26–56)[2c]		Weisher et al. [24]
CDH1	52% (29–94)[3]		Kaurah et al. [34]
	39% (12–84)[5]		Pharoah et al. [33]
NBN	33% (22–48)[5d^]		Zhang et al. [41]
PALB2	35% (26–46)[2]		Antoniou et al. [26]
	33% (25–44)[2]	No affected relatives	
	58% (50–66)[2]	Two 1st degree relatives affected at age 50	
PTEN	77% (59–91)[2]		Bubien et al. [42]
	85% (71–99)[5]		Tan et al. [30]
	25–50%[5]		Pilarski [31]
STK11	32–54%[2]		van Lier et al. [36]
	45% (27–68)[2]		Hearle et al. [35]
TP53	49%[1]		Masciari et al. [29]
	79% (53–115)[5^]		Ruijs et al. [27]

*95% Confidence interval presented if available

^Values based on relative risk multiplied by general population risk for breast based on SEER Cancer Statistics Review (Howlader et al. [28])

[1]Breast cancer risk by age 60

[2]Breast cancer risk by age 70

[3]Breast cancer risk by age 75

[4]Breast cancer risk by age 80

[5]Lifetime risk

[a]*ATM*c.7271T>G variant

[b]*CHEK2*p.I157T variant

[c]*CHEK2**1100delC variant

[d]*NBN**657del5 variant

variants in *PALB2* are estimated to create a risk of 35% for female breast cancer by age 70 [26].

There are many more high and moderate risk genes associated with increased risk for breast cancer that are frequently included on NGS panels. Risk for breast cancer for women with pathogenic variants in *TP53* has been reported as 6.4 times higher than women in the general population [27]. *TP53*-associated breast cancer risk by age 60 has also been reported much lower at 49% [29]. *PTEN* variants may increase breast cancer risk as high as 85% [30], but lower risks, around 25–50%, were commonly cited previously [31]. *CDH1* mutations, which are known to confer an increased risk of gastric cancer, have also been reported to raise risk of breast cancer, specifically lobular carcinoma [32]. Reported lifetime risks for breast cancer have ranged from 39% [33] to 52% [34]. *STK11*, the gene associated with Peutz-Jegher syndrome, has been noted to carry a 32–54% risk of breast cancer by age 70 [35, 36].

Women with neurofibromatosis type 1 (NF1) have been reported to have an elevated risk for breast cancer up until around age 50 [37, 38]. Relative breast cancer risk for women with NF1 has been reported as 6.5 between ages 30–39 and 4.4 for women aged 40–49 [38]. For women with NF1 in the age group of 20–49, the unadjusted standardized incidence ratio for breast cancer was reported as 2.68 [37]. Another newly characterized breast cancer gene is *NBN*. It is believed that the *NBN**657del5 variant

increases risk for breast cancer, but risks for other variants have not been studied as much [39–41].

It is difficult to apply blanket management guidelines for each gene as cancer risks can differ based on the specific genetic variant. For example, the *ATM* c.7271T>G variant is expected to increase for breast cancer more significantly than the majority of pathogenic variants in *ATM*. Also, many genetic risk studies have been completed on truncating variants; clinical interpretation for some suspected pathogenic missense variants could create new challenges for clinicians [24, 25]. Missense variants sometimes affect gene function differently than truncating variants which could increase or decrease associated cancer risk. The risk for a second primary breast cancer is also unknown for many of these genes. In some instances, multiple genetic changes may be required to result in greatly increased risk for breast cancer [45]. This would differ from the high breast cancer risk that is gained by having a single pathogenic variant in a high risk gene, like *BRCA1*. A low risk allele could be much harder to interpret and more difficult to incorporate into medical management.

Conclusion

Mammography remains the screening tool of choice among women at general-population risk for breast cancer. Following the identification of a subset of women at particularly high risk, clinicians questioned whether this limited-sensitivity screening modality should be acceptable as the only surveillance option for this particular population, especially given the newer availability of breast MRI. Studies have documented that while MRI has a superior sensitivity to mammography, the combination of mammography and MRI has the greatest ability to detect disease [7, 9, 11].

Studies of MRI screening in high-risk women have confirmed an improvement in the ability to diagnose cancer; however, the data also raise several additional questions. The specificity of MRI is lower than that of mammography and the PPV has been estimated around 60% or less (except in mutation carriers). Studies have confirmed that although there is an improvement in diagnosis, this comes at a cost of additional imaging and biopsies, many of which are benign but still contribute to the cost of medical care and the patient's overall anxiety.

In addition, many of the cancers detected are smaller in size and more likely to be associated with negative lymph nodes. While this may reflect an ability to downgrade the staging at diagnosis (and thus improve mortality), there is a predominance of grade 1 tumors in moderate-to-high risk, non-mutation carriers and an increased likelihood of identifying grade 3 tumors or tumors of greater size in known carriers of highly-penetrant genes. These data suggest the possibility that the additional tumors detected by routine MRI surveillance may not carry the same biological and pathologic implications and that improvements in staging and survival may be caused not only by the lower stage at diagnosis but on the presence of a less aggressive, better prognosis tumor. The possibility of over diagnosis is also generated by the presence of non-invasive disease among these MRI-detected lesions.

In 2007, the American Cancer Society recommended the addition of breast MRI to annual mammography for those women with an elevated lifetime risk of breast cancer based on family history. Known pathogenic variants in certain high risk genes were included in this subset of women. The group also included women with a confirmed elevated risk (>20%) based on certain mathematical models that are largely based on family history, which affirms the belief that disease risk is at least partly dependent on hereditary factors [8].

Since that time, knowledge of the genetic factors that affect risk has expanded with newer gene panels. Studies to date suggest that *BRCA1/2* pathogenic variants may account for approximately half of the known genetic cases, with the other known half caused by pathogenic variants in other genes including *ATM, CHEK2, PALB2, PTEN, CDH1, STK11*, and *TP53* [16, 19]. The presence of pathogenic variants in these newer genes remains uncommon, with *CHEK2* variants having the highest reported incidence (1.3%) after *BRCA1/2* [16]. This complicates the ability to formally assess the specific gene-associated lifetime risks for breast cancer and increases the number of women who are documented to possibly harbor a genetic predisposition to cancer. Analysis of the lifetime risks associated with the more common pathogenic gene variants, in *PALB2, CHEK2*, and *ATM*, as well as, the less common *CDH1, NF1, NBN*, and *STK11*, suggest that their lifetime risks are comparable to the risk values outlined in the 2007 American Cancer Society publication.

Early estimates of lifetime risk associated with these genes are 20% or higher. If one considers the use of annual surveillance MRI for all carriers, there is a possibility of increased detection at the cost of a significant increase in downstream procedures (including invasive measures such as surgery) and increase in the phenomenon of over diagnosis for patients who may never go on to develop clinically-significant disease. Alternatively, one can take a new approach by analyzing the data that is currently available, stratifying patients by risk, and considering alternative surveillance programs for those with moderate risk mutations and high risk mutations. Current data on the increased likelihood of identifying cancer in high-penetrance mutation carriers and the significant likelihood of higher grade disease or larger tumor size at diagnosis all suggest that these

mutation carriers may benefit from shorter surveillance intervals than those with lower risk.

Despite advances in medical research, there are still significant gaps in knowledge. These include the identification and confirmation of absolute and age-specific risks associated with newly identified and testable genes. Additional research is also needed to understand the role of MRI in patient outcomes. It is unclear whether improvements in detection with MRI lower mortality and recurrence rates or if this is reflective of other factors such as improvements in treatment. It should also be considered whether alternative screening intervals or alternative imaging modalities can be used for those at varying levels of risk. Furthermore, additional research to identify the optimal threshold of risk for high-risk screening should be completed. Creation of comprehensive management guidelines that incorporate other, non-genetic risk factors, such as atypical hyperplasia, lobular carcinoma in situ, or breast density could be beneficial also. This method could allow us to provide more individualized management. Investigation into the benefits, risks and limitations of using a multifaceted system is warranted.

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