Appendix 2. Genetic Risk Factors for Early Onset Breast Cancer

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INTRODUCTION

This document focuses on genetic risk factors for early onset breast cancer (EOBC), including racial or ethnic groups that may have a genetic predisposition to early onset disease; the efficacy of additional testing or screening; and the major society and health service guidelines on how to manage women with genetic predisposition to EOBC.

1. Which groups have genetic predisposition for EOBC? How strong are these risks?

- **African American**
- **Hispanic**
- **Ashkenazi Jewish**
- **Other groups**

P – Patient, Problem, or Population. I – Intervention. C – Comparison, Control, or Comparator. O – Outcome(s) (PICO)

P: Frequency of genetic variant carriage that increase the risk of EOBC (defined as <46 y) in different populations

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- African American
- Hispanic
- Ashkenazi Jewish
- Other ethnic or racial groups living in the United States with known increased risk

I: Frequency of carriers of pathogenic genetic variants that increase the risk of EOBC (eg, BRCA, PALB2, CHEK2, ATM, p53, PTEN) across different ethnic or racial groups.

C: In groups with genetic predisposition, is additional testing or screening beneficial? What are the most effective testing or screening approaches?

O: Uptake of screening or testing in ethnic/racial groups and any measured effects on clinical or other important outcomes.

2. What are current major society and health service guidelines for identification, screening, and management of women with genetic predisposition for EOBC?

PICO

P: Women with personal or family history indicating suspected known genetic risk that increases their likelihood of developing EOBC.

I: Screening and identification of women with genetic predisposition to EOBC; management of women identified with a genetic predisposition of EOBC.

C: Use of surveillance or risk reduction to improve outcomes, as defined below.

O: Appropriate risk assessment leading to early detection, risk reduction, or reduced mortality due to EOBC.

METHODS

Using the above statements and questions, the ACOG clinical reference staff searched the Cochrane, MEDLINE, and PubMed databases for all relevant references. There was also a review for relevant guidelines published by the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society, the National Comprehensive Cancer Network (NCCN), the American Society of Breast Surgeons (ASBS), the Society of Surgical Oncology, the American College of Radiology, the U.S. Preventive Services Task Force (USPSTF), and the American Society of Breast Disease. References within included papers were reviewed for additional publications of relevance. References were included if they addressed genetic predisposition to EOBC.

This review focuses on screening, identification of gene mutations that substantially increase the risk of EOBC (eg, autosomal dominant single gene mutations), and differences in genetic risk among ethnic or racial populations. Major society and health service guidelines were also reviewed to determine the current recommendations for screening, identification, and testing for genetic risk, including advice on surveillance and risk reduction methods.

Inclusion Criteria

- Women aged 18–45 years

- United States and Canadian studies only, or United Nations Health Development Index
- Major society or health service guidelines, systematic review, meta-analysis, cohort study, case-control study, randomized controlled trial
- Studies comparing populations of interest
- English-language studies only

Exclusion Criteria

- Average-risk women
- Genetic risk not addressed
- Theoretical or simulated design
- Laboratory methodology papers
- Discussed only prognosis of EOBC
- Addressed only patients older than age 45
- Only addressed prenatal genetic testing after diagnosis
- Pregnancy
- Pregnancy-associated breast cancer
- Male subjects only
- Unavailable in English
- Case series or reports
- Studies exclusively outside United States

RESULTS

The literature review returned 179 results. There were 16 Level I reviews (12 systematic reviews and 4 randomized controlled trials); 129 Level II studies; and 32 Level III (2 guidelines and 30 reviews). Two additional studies addressed sensitivity and specificity of genetic risk factors. Of the 179 results, 29 met the criteria and were included, whereas 150 studies did not meet the criteria. In addition, guidelines from USPSTF (2014), NCCN (2019), the American College of Medical Genetics (2015), and ACOG (2017) were included. All of the guidelines addressed recommendations for screening and testing (USPSTF does not address criteria for testing, only the value of testing), while other guidelines also address management recommendations (ACOG and NCCN).

Which groups have genetic predisposition for early onset breast cancer? How strong are these risks?

- **African American**
- **Hispanic**
- **Ashkenazi Jewish**
- **Other groups**

Single gene pathogenic variants (PVs, also called deleterious mutations) result in a substantial increase in the lifetime risk of breast and other cancers. BRCA 1 and BRCA 2 are the most common single gene PVs associated with breast cancer, representing more than 50% of such genes. There is a substantially higher risk of EOBC (prior to age 46) in women who carry a PV in BRCA 1 or BRCA 2. In the United States, the prevalence of BRCA 1 and BRCA 2 is estimated at 1 in 400 persons.[1,2] However, these genes occur more frequently in certain populations, most notably Ashkenazi Jews, in whom the prevalence is 1 in 40

(2.5%).[3,4] Ashkenazi Jews are of central or Eastern European descent, from the regions that are now Belarus, Latvia, Lithuania, Moldova, Poland, Russia, and Ukraine. In this population, three specific mutations, two in BRCA 1 (185delAG and 5382insC) and one in BRCA 2 (6174delT), have been identified These three PVs are called "founder mutations," which derive from a small group of founding families centuries ago and were perpetuated in this population by infrequent intermarriage.[5] As a result of this relatively high rate of carriage, most consensus guidelines recommend routine BRCA founder mutation screening for individuals of Ashkenazi Jewish descent, regardless of personal or family history of cancer.[6,7] Numerous studies indicate that using family history criteria alone in this population will miss more than one half of the BRCA PVs.[8,9] A recent study evaluating Ashkenazi Jewish patients who had testing for BRCA 1 and BRCA 2 at a large clinical laboratory demonstrated that additional nonfounder PVs were found in 7.2–13% of these patients.[10] While some other ethnic groups appear to have founder mutations—including certain French Canadian, Polish, and Icelandic populations—their carrier rate risk is less than that of Ashkenazi Jews, and the clinical implications of these increased risks are unclear.[1–3]

While African American women have a lower incidence of breast cancer than do Caucasian women in the United States, their mortality rates are higher.[4] A disproportionate number of African American women with breast cancer are younger (<46 years of age) compared with Caucasian women, with 30–40% of breast cancers in African American women diagnosed prior to the age of 50, compared with about 20% of breast cancers in Caucasian women. The reasons are not entirely clear, as there is not a difference in incidence of single gene mutations (eg, BRCA 1, BRCA 2) in these two populations. Another biologic factor that appears to contribute to the higher mortality in African American women is the substantially higher rate of triple-negative (TN; estrogen receptor-, progesterone receptor-, and

hormone epidermal growth factor 2-receptor-negative) tumors, which are biologically more active with substantially higher recurrence rates.[6] A U.S. study in the Carolinas found the highest prevalence of TN (39%; 38/97 invasive cancers) in premenopausal African American women, a substantially higher rate than seen in postmenopausal African American women (14%) or Caucasian women (16%) (P<0.001 for both comparisons).[7] This high prevalence of TN breast cancers in African American women has been found in other parts of the United States,[11–14] including Philadelphia,[15] Boston,[16] Georgia,[10] and Michigan.[17] Genome-wide association studies have explored these differences. Dozens of single nucleotide polymorphisms have been identified in TN tumors, though a clear pattern of single nucleotide polymorphisms leading to a clinical testing scenario for women at risk has not been developed.[15] There are other potential genetic mechanisms that may contribute to EOBC in certain ethnic or racial groups. As an example, genomic copy number alterations are common in breast cancer and are likely associated with specific cancer subtypes such as TN tumors. Early studies have demonstrated copy number alterations differences in African American and Caucasian women with TN tumors, which may be one of the mechanisms contributing to the poorer outcome in African American women.[16] There may be other biologic differences between TN breast cancers in African American women and Caucasian women. One study compared the transcriptional profiles from TN breast cancer tumors in African American women with those of Caucasian women. The gene expression signature in the TN breast cancer tumors from the African American women demonstrated more

- loss of BRCA 1 expression;
- increased activation of insulin-like growth factor 1 receptor; and
- increased expression of vascular endothelial growth factor-activated genes.[17]

Among all women with breast cancer, genetic mutations account for about 5–10% of cases.[18] Table 1 shows the likelihood of carrying a BRCA 1 or BRCA 2 PV, based on races or ethnicity, in the United States.

Table 1. Likelihood of Carrying a BRCA PV Among Women With Breast Cancer, by Race or Ethnicity

Race/Ethnicity	BRCA 1	BRCA 2
Caucasian	2–3%	2%
African American	1%	3%
Hispanic	4%	No data
Asian American	<1%	No data
Ashkenazi Jewish	8–10%	1%

Data from Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Res 2006;66:8297-308; *and* John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 2007;298:2869-76.

A study from the National Cancer Institute's Surveillance, Epidemiology, and End Results database comparing the median age of onset of breast cancer in the United States by race/ethnicity found the median age of breast cancer diagnosis in the United States from 1973 to 2010 was as follows:[19]

- Caucasian: 59 years (interquartile range [IQR]: 51–67 years)
- Black: 56 years (IQR: 49–65 years)
- Hispanic: 55 years (IQR: 48–64 years)
- Asian: 56 years (IQR: 48–64 years)

While these median ages appear somewhat similar, current USPSTF recommendations to start screening at age 50 would result in a disproportionate number of black and Hispanic women not diagnosed compared with Caucasian women. In other words, according to the study authors, "to achieve a similar capture rate for nonwhite patients as current guidelines do for Caucasian patients at 50 years of age, screening ages would need to decrease to 47 years for black, 46 years for Hispanic, and 47 years for Asian patients." In addition, this analysis demonstrated that a larger proportion of black and Hispanic women were diagnosed with advanced (regional or distant) disease (46.6% and 42.9%, respectively) than were Caucasian or Asian patients (37.1% and 35.6%, respectively; $P<0.001$ for all).

DISCUSSION

Widespread genetic counseling and testing is increasingly recommended in the United States and can clearly reduce morbidity and mortality from EOBC. However, studies are incomplete regarding the specifics of who is screened, the ideal of risk assessment versus the reality of busy medical practices, the absence of well-established screening tools, and the cost-effectiveness of the various practices. While certain ethnic groups have more frequent gene mutations (Ashkenazi Jewish) and strategies have been developed to address these (eg, three-site testing), both the widespread implementation and the effectiveness of these strategies in terms of mortality reduction and cost efficacy are uncertain or incompletely studied or both. Other ethnic groups with populations living inside the United States (eg, certain French Canadian, Icelandic, and Polish populations, among others) also harbor founder mutations in BRCA 1 and BRCA 2. However, the lower frequency of these mutations relative to

Ashkenazi Jews results in uncertainty as to which, if any, strategy should be employed for screening in persons with these ethnic backgrounds.

African American women are known to have both more frequent EOBC and substantially more aggressive biology (ie, more TN tumors) than other racial groups, resulting in higher breast cancer mortality than Caucasian women. The scientific understanding of these biologic differences and genetic underpinnings in African American women with EOBC remains elusive, but does not appear to be caused by simple higher carriage rate of single gene mutations such as BRCA 1 and BRCA 2. As a result, challenges remain in identifying specific strategies to address screening, prevention, risk reduction, or improved treatments in this at-risk population. Additionally, qualitative studies have shown that while mammography rates are high among African American women, genetic testing rates appear to be lower compared with Caucasian women. A case-control study of 408 women with a family history of breast cancer found that African Americans were significantly less likely to undergo genetic testing compared with Caucasian women (odds ratio: 0.22, 95% confidence interval: 0.12–0.40).[20]

In groups with genetic predisposition, is additional testing or screening beneficial? What are the most effective screening or testing approaches?

To date, population-based screening for cancer genes in the absence of other risk factors is not broadly recommended, given the rarity of a PV (approximately 1 in 400) and the uncertainty of benefit and value of large-scale testing.[14] However, there is general consensus that in certain high-risk groups, namely individuals of Ashkenazi Jewish origin, founder mutation testing is recommended.[21] Because the

prevalence in the population is 10 times higher than that of the general population, testing in this group is similar to recommendations for testing individuals using other established high-risk criteria (eg, family history or personal history).[22] Because about 90% of the carrier risk among Ashkenazi Jewish individuals includes the three founder PVs, the consensus recommendation is to perform three-site testing rather than entire BRCA 1 and BRCA 2 sequencing. This recommendation has been added to the draft recommendations from the USPSTF.[23] There is no consensus of opinion regarding genetic testing for other ethnic groups (eg, French Canadian, Icelandic, and Polish, among others), where the risk of BRCA 1 and BRCA 2 mutations falls between that of the general and Ashkenazi Jewish populations. As such, risk assessment based on family history is recommended in those groups.[21,24] (Screening based on family history is covered further in Appendix 3, Family History as a Risk Factor for Early Onset Breast Cancer.)

What are current major society or health service guidelines for identification, screening, and management of women with genetic predisposition for EOBC?

Several national guidelines exist for risk identification, screening, and management of women with a genetic predisposition for EOBC.[22,21,24]

Identification

A number of national consensus groups have made specific recommendations to identify women (and men) for further genetic counseling or genetic testing based on several factors, including the following:

- Personal history of various cancers (eg, breast, ovarian, tubal, pancreatic, or prostate) and either age of onset of these cancers or other cancer-specific factors that increase the likelihood of carrying a PV in an EOBC gene (eg, TN tumors at a young age)
- Family history that suggests a pattern consistent with an autosomal dominant cancer gene pattern of inheritance

Several national groups have created guidelines for who should be referred for genetic counseling or offered genetic testing based on personal or family history (Table 2).[21-25] Recently, the ASBS released a consensus statement recommending BRCA 1 and BRCA 2 testing in all women with breast cancer.[24]

Table 2. Summary of Recommended Guidelines*

Guideline Group	Identification Recommendations	Screening and Management Recommendations	Frequency of Guideline Updates	Most Recent Update
National Comprehensive Cancer Network†	Yes	Yes	Annual	2019
American College of Obstetricians and Gynecologists‡	Yes	Yes	Periodic	September 2017
U.S. Preventive Services Task Force§	Yes	SO*	Periodic	December 2013
American Society of Breast Surgeons‖	Yes	SO*	Periodic	January 2019
American College of Medical Genetics¶	Yes	No	Periodic	January 2015

*Both the U.S. Preventive Services Task Force and the American Society of Breast Surgeons defer to other guidelines for management recommendations.

† Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 12, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

‡ Data from Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110-26.

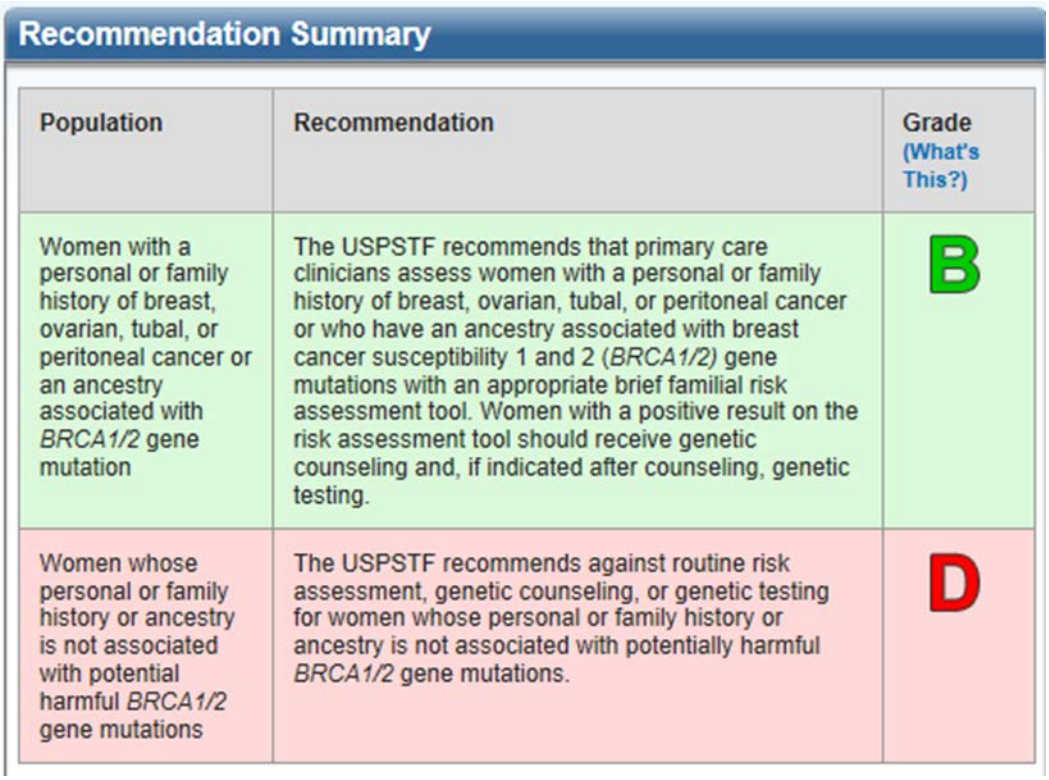
§ Data from Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-Related Cancer: US Preventive Services Task Force recommendation statement. JAMA 2019;322:652-65.

|| Data from American Society of Breast Surgeons. Consensus guideline on genetic testing for hereditary breast cancer. Columbia, MD: ASBrS; 2019. Available at: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Retrieved October 21, 2019.

¶ Data from Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. Genet Med 2015;17:70-87.

The USPSTF recommends that women who have family members with breast, ovarian, tubal, or primary peritoneal cancer should be screened by primary care providers with one of several screening tools designed to identify family history that may be associated with BRCA 1 or BRCA 2 mutations. Further, they recommend that those who screen positive should receive genetic counseling and, if indicated, genetic testing.[22]

Figure 1. USPSTF Recommendations



Recommendation Summary

Population	Recommendation	Grade (What's This?)
Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with *BRCA1/2* gene mutation	The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1/2*) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.	B
Women whose personal or family history or ancestry is not associated with potential harmful *BRCA1/2* gene mutations	The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations.	D

Reprinted from U.S. Preventive Services Task Force. BRCA-related cancer: risk assessment, genetic counseling, and genetic testing. Rockville, MD: USPSTF; 2019. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing1. Retrieved October 28, 2019.

Other Genes Associated With Early Onset Breast Cancer Risk

Although BRCA 1 and BRCA 2 are the primary genes associated with an increased breast cancer risk in women, they are not the only ones. Like BRCA 1 and BRCA 2, these other genes behave in an autosomal dominant fashion, meaning only one mutated allele needs to be acquired to confer increased risk (heterozygosity), though with varying degrees of penetrance. Some of these genes (TP 53, PALB 2, CDH 1) are highly penetrant, with an increased breast cancer risk similar to that of BRCA 1 or BRCA 2. Most are moderately penetrant, increasing risk to a lesser degree. Additionally, while these mutations increase the lifetime risk of breast cancer, the impact on breast cancer incidence among women younger than age 46 is less established. Because of this, screening and risk-reduction strategies vary based on the mutation, and strength of evidence differs for these strategies. Table 3 includes most of the recognized high-risk genes with their estimated lifetime risk of breast cancer.[26] Over the past several years, panel genetic testing for EOBC has become more widely available and typically includes these genes. While it is important for providers and patients to know that most genes associated with breast cancer increase the risk of other cancers as well, discussion of these other cancer risks is beyond the scope of this document.

Table 3. Genes Associated With Increased Risk of Breast Cancer

Gene	Estimate Lifetime Risk of Breast Cancer
BRCA 1	40–75%
BRCA 2	40–60%
ATM	17–52%

CHEK 2	20–37%
STK 11	32–54%
PALB 2	33–58%
PTEN	40–70%
CDH 1	39–60%
NBN	20–30%
TP53 (p53)	50+%
RAD 51	26%
BARD 1	20–25%
NF 1	40–50%

Data from National Cancer Institute. BRCA mutations: cancer risk and genetic testing. Bethesda, MD: NCI; 2018. Available at: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Retrieved October 22, 2019.

Management Strategies for Women at Increased Risk for Early Onset Breast Cancer Caused by Genetic Mutation

Management strategies for women at genetically increased risk for EOBC fall into two broad categories: Increased surveillance in an effort to detect breast cancer at earlier stages and risk reduction to prevent breast cancer. Studies of these strategies have focused on BRCA carriers. There is less complete understanding of the penetrance and age of onset for those with non-BRCA genes associated with

breast cancer. Table 4 provides an overview of common genes included in panel testing, along with recommendations for surveillance and risk reduction.[21]

Table 4. Management of Women With Breast-Cancer-Associated Genes*

Gene	Screening Recommendation†			Risk Reduction	
BRCA1	**CBE‡**	**Mammography**	**MRI**	**Chemoprophylaxis With Tamoxifen**	**RRM**
	Start: Age 25 y Frequency: Every 6–12 mos	Start: Age 30 y Frequency: Annual§	Start: Age 25 y Frequency: Annual§	Limited data to support tamoxifen.‖	Discuss option of RRM.¶
BRCA2	Start: Age 25 y Frequency: Every 6–12 mos	Start: Age 30 y Frequency: Annual§	Start: Age 25 y Frequency: Annual§	Limited data to support tamoxifen.‖	Discuss option of RRM.¶
ATM	No recommendations provided	Start: Age 40 y Frequency: Annual	Consider start: Age 40 y Frequency: Annual	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on

					family history.
CHEK2	No recommendations provided	Start: Age 40 y Frequency: Annual	Consider start: 40 y Frequency: Annual	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
PALB2	No recommendations provided	Start: Age 30 y Frequency: Annual	Consider start: 30 y Frequency: Annual	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.‖
PTEN	Start: Age 25 y Frequency: Every 6–12 mos	Start: Age 30 y Frequency: Annual§	Start: Age 30 y	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM.‖

			Frequency: Annual[§]		
STK11	Start: Age ~25 y Frequency: Every 6 mos[#]	Start: Age ~25 y Frequency: Annual[#]	Start: Age 25 y Frequency: Annual[#]	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history[‖]
NF1	No recommendations provided	Start: Age 30 y Frequency: Annual	Consider from 30–50 y Frequency: Annual	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
NBN	No recommendations provided	Start: Age 40 y Frequency: Annual	Consider Start: Age 40 y	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be

			Frequency: Annual		considered based on family history.
TP53 (P53)	Start: Age 20 y[‡] Frequency: Every 6–12 mos	Start: Age 30 y Frequency: Annual[§]	Start: Age 20 y or earlier if family history of younger-onset breast cancer Frequency: Annual[§]	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM. [¶]
CDH1	No recommendations provided	Start: Age 30 y Frequency: Annual	Consider start: Age 30 y Frequency: Annual	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM (no data on benefit). [¶]

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* CBE, clinical breast examination; MRI, magnetic resonance imaging; RRM, risk reduction mastectomy

† The age for starting breast screening may be earlier depending on earliest age of diagnosis in the family (if before age 30).

‡ Self-breast awareness (also called breast awareness) is recommended. It is defined as women being familiar with their breasts so they can promptly report any changes to their health care provider.

§ Mammography and MRI are recommended to age 75; breast imaging beyond that age should be individualized.

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¶ Mastectomy counseling includes degree of protection, reconstruction options, and risks of procedures.

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SURVEILLANCE

Individuals who carry a single gene PV that increases the lifetime risk of breast cancer are generally recommended to undergo intensive surveillance, characterized by three different components: earlier-onset surveillance; additional imaging modalities; and more frequent clinical breast examination by a licensed provider. Breast magnetic resonance imaging (MRI) has demonstrated substantially improved breast cancer detection and lower rates of node-positive disease compared with mammography alone. In one large prospective study of women with more than a 15% lifetime risk of breast cancer resulting from a family history of genetic risk, clinical breast examination, mammography, and MRI were used on an annual basis. Among women ultimately diagnosed with breast cancer through this intensive surveillance program, the sensitivity of clinical breast examination, mammography, and MRI for detecting invasive breast cancer was 17.9%, 33.3%, and 79.5%, respectively.[27,28] Moreover, the proportion of invasive tumors that were 10 mm or less in diameter was significantly greater in the intensive surveillance group (43.2%) than in age-matched control groups with breast cancer who were not enrolled in intensive surveillance with MRI (14%, $P<0.001$, and 12.5%, $P=0.04$, respectively). Finally, there was a lower incidence of positive axillary nodes or micro-metastases in the MRI group compared with age-matched control groups diagnosed with breast cancer but not undergoing imaging surveillance (21.4%, as compared with 52.4%, $P<0.001$, and 56.4%, $P=0.001$, respectively). Despite these encouraging results, longer-term studies demonstrating improved mortality have not yet been conducted.

Strategies for intensive surveillance have largely been based on studies in women with BRCA 1 and BRCA 2 PVs and are summarized in Table 5.[27,28] Some consensus guidelines have extended some elements of these recommendations to women with other high-risk breast cancer gene PVs but without direct study in these high-risk populations.

Table 5. Current Recommendations for Intensive Surveillance for Women With Known PVs in BRCA 1 and BRCA 2*

Type of Surveillance	Age to Start (y)	Frequency
Mammography	30	Annual
Breast MRI	25	Annual
Clinical breast examination	25	1–2 times/y

*Certain non-BRCA breast-cancer-associated PVs have later-onset disease, so intensive surveillance with mammography or MRI is recommended to start at later ages (eg, imaging screening recommended to start at age 40 with ATM PVs).

Data from Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. Magnetic Resonance Imaging Screening Study Group. N Engl J Med 2004;351:427-37; *and* Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317-25.

The decision to delay mammography until age 30 is based on three factors: 1) younger women have denser breasts, reducing sensitivity of mammography; 2) exposure to radiation in younger women may cause a higher rate of radiation-induced DNA damage; and, 3) most EOBC is detected by MRI alone.[29] This latter observation must be tempered by the knowledge that for certain specific gene PVs (eg, BRCA 2), up to one third of early cancer detection results from mammography alone.[30] Other pathogenic gene mutations have been observed to have later onset of disease and penetrance; therefore, screening and management recommendations vary.

Risk Reduction

Risk reduction approaches in women at increased genetic risk for EOBC can be divided into three categories: chemoprophylaxis; surgical risk reduction; and so-called lifestyle risk reduction.

Chemoprophylaxis. While there are multiple agents approved by the U.S. Food and Drug Administration for breast cancer chemoprophylaxis (eg, tamoxifen, raloxifene, exemestane), only tamoxifen is approved in premenopausal women. Though it has clearly been shown to decrease risk in menopausal women at high risk for developing breast cancer, the evidence in BRCA carriers has been mixed.[31] However, there have been several studies in women with BRCA mutations and unilateral breast cancer who take tamoxifen with an intact contralateral breast. These demonstrate a 40–75% reduction in contralateral breast cancer compared with controls.[32,33]

Surgical Prophylaxis. Surgical prophylaxis with bilateral mastectomy is frequently considered by women at high risk for EOBC. Studies evaluating the efficacy of bilateral mastectomy in women with PVs have demonstrated a 90–95% risk reduction.[34,35] Many women choose surgical risk reduction to reduce their lifetime risk of breast cancer mortality and to avoid long-term increased surveillance, with its associated anxiety, cost, and occasional false-positive results. Furthermore, some women choose to undergo surgical prophylaxis to avoid the treatment that is associated with a diagnosis of breast cancer. Importantly, a meta-analysis demonstrated that the two strategies of intensive surveillance and surgical risk reduction result in similar disease-specific mortality.[36] Therefore, after careful counseling, many women will choose either surveillance or risk reduction based on their individual values and preferences.[37]

Other Factors

Paradoxically, a recent meta-analysis showed a decrease in the risk of breast cancer in BRCA 1 mutation carriers who delivered their first child after age 30 compared with BRCA1 carriers who delivered their first child at or before age 30 (pooled effect estimate of 0.65; 95% confidence interval: 0.42–0.99).[38]

DISCUSSION

Very few well-designed studies show unequivocal advantage in disease-specific mortality with a specific strategy for identification, testing, and management, Therefore, precise recommendations made by various groups (eg, NCCN or ACOG) are based on consensus or lower-level evidence. The more recent

recommendations by ASBS to offer genetic testing to all women with breast cancer are based on consensus, but there is very little scientific data to support these recommendations.

Gaps in Information Pertinent to Making Recommendations

Like most studies on cancer mortality, which may occur 10 or more years after diagnosis, clear evidence of disease-specific mortality improvement often requires decades of follow-up. Because there are numerous different approaches to management and the field of cancer genetics is changing rapidly, awaiting data for precise evidence-based recommendations might result in the missed opportunity to diagnosis cancer early through lower-level recommendations of intensive surveillance and risk reduction methods.

Therefore, adopting thorough consensus guidelines that are updated by experts on a regular basis (eg, NCCN) is a good interim strategy while awaiting newer research to clarify unanswered questions.

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