

### **Appendix 3. Family History as a Risk Factor for Early Onset Breast Cancer**

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#### **INTRODUCTION**

Assessment of family history is essential when evaluating young women accessing primary care. Review of a woman's family history of breast cancer can help identify individuals at elevated risk for hereditary breast cancer or women who would benefit from increased breast cancer surveillance. The American College of Obstetrics and Gynecology (ACOG), Society of Gynecologic Oncologists (SGO), U.S. Preventive Services Task Force (USPSTF), National Institute of Health Care Excellence (NICE), and National Comprehensive Cancer Network (NCCN) have published guidelines recommending assessment of family history and screening of patients at increased risk of breast cancer. For example, ACOG advises that screening should include, at minimum, a personal cancer history and first- and second-degree relatives' cancer history, to include a description of the type of primary cancer, the age of onset, and the lineage of the family member. The NCCN's clinical guidelines recommend genetic assessment for all first- and second-degree relatives diagnosed with breast cancer younger than age 50. It is generally accepted by all major societies that women with a lifetime risk of breast cancer greater than 20% by any model are at high risk. This review evaluates the literature addressing early onset breast cancer (EOBC) screening, diagnosis, and treatment for women aged 45 years and younger. The goals of this review are as follows:

1. Evaluate the data showing elevated risk of breast cancer for women with a family history of breast cancer.
2. Stratify this risk regarding first-, second-, and third-degree relatives.
3. Determine the accuracy of self-reported family history and the accuracy of risk assessment models for women with positive family history without known genetic mutations.
4. Evaluate the appropriate breast cancer screening intervention for women at increased risk of breast cancer based on family history without genetic mutation.

The ACOG literature search sought to address the following questions:

1. **Is the BRCAPRO computer model more accurate in assessing increased risk of breast cancer in patients with family history of breast cancer compared with the Tyrer-Cuzick model (also called the International Breast Cancer Intervention Study [IBIS] breast cancer risk evaluation tool)?**
2. **Are patients with one affected first-degree relative (FDR) at increased risk of breast cancer compared with patients without an FDR affected by breast cancer between the ages of 18 and 45? Are patients with two affected FDRs at increased risk of breast cancer compared with patients without any FDRs with breast cancer between the ages of 18 and 45? Are patients with a second-degree relative (SDR) at increased risk of breast cancer compared with patients without an SDR with breast cancer between the ages of 18 and 45?**
3. **In patients with a positive family history of breast cancer, does more intensive mammographic and magnetic resonance imaging (MRI) screening detect breast cancer earlier than in low-risk**

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**women who are screened according to current guidelines? In patients with a family history of breast cancer, is breast cancer screening with breast MRI screening as effective as mammography? Is breast MRI indicated as an adjunct to screening with mammography?**

4. **Do women with a positive family history of breast cancer have an increased risk of being diagnosed with EOBC compared with women without a family history of breast cancer?**

Table 1 describes the literature search criteria.

**Table 1. Literature Search Criteria**

Patient/Population	Intervention	Comparison	Outcome(s)
Patients with family history of breast cancer	Computer model (eg, BRCAPRO)	<ul style="list-style-type: none"> <li>● Tyrer-Cuzick (IBIS)</li> <li>● Claus</li> </ul>	<ul style="list-style-type: none"> <li>● Increased risk of breast cancer</li> <li>● Accuracy</li> <li>● Sensitivity/specificity</li> <li>● Positive/negative predictive value</li> </ul>
Patients	<ul style="list-style-type: none"> <li>● With one FDR</li> <li>● With two FDR</li> <li>● With one SDR</li> </ul>	<ul style="list-style-type: none"> <li>● No FDR</li> </ul>	Increased risk of breast cancer
Patients with family history of breast cancer	<ul style="list-style-type: none"> <li>● Mammography</li> <li>● Breast MRI</li> <li>● Clinical breast examinations</li> </ul>	<ul style="list-style-type: none"> <li>● No screening</li> </ul>	<ul style="list-style-type: none"> <li>● Diagnosis of breast cancer</li> <li>● Cost-effectiveness</li> <li>● Sensitivity/specificity</li> <li>● Positive/negative predictive value</li> </ul>
Patients with family history of breast cancer	<ul style="list-style-type: none"> <li>● Mammography</li> </ul>	<ul style="list-style-type: none"> <li>● Breast MRI</li> </ul>	<ul style="list-style-type: none"> <li>● Diagnosis of breast cancer</li> <li>● Cost-effectiveness</li> <li>● Sensitivity/specificity</li> <li>● Positive/negative predictive value</li> </ul>
Patients	Family history of breast cancer	No family history of breast cancer	<ul style="list-style-type: none"> <li>● Diagnosis of all breast cancer (all ages)</li> <li>● Diagnosis of EOBC</li> </ul>

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## **METHODS**

The ACOG literature search committee searched MEDLINE through Ovid, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PubMed articles from January 1, 2010 to February 7, 2019. The search included patients with a positive family history of breast cancer (including first-, second-, and third-degree relatives, one and more family members, both maternal and paternal). Studies of patients with known genetic mutations were excluded. (These patients are covered in Appendix 2, Genetic Risk Factors for Early Onset Breast Cancer.)

The literature search found 106 articles meeting the search criteria, then reviewed the titles and abstracts of all of them. Studies then deemed to have relevant objectives, study design, and participant characteristics were reviewed in full. The literature search also included 20 guidelines from ACOG and other national organizations. Following review, the search committee evaluated three of the ACOG guidelines and three guidelines from other major societies:

- ACOG Guidelines for Women's Health Care<sup>1</sup>
- ACOG Committee Opinion No. 478, Family History as a Risk Assessment Tool<sup>2</sup>
- ACOG Practice Bulletin No. 182, Hereditary Breast and Ovarian Cancer Syndrome<sup>3</sup>
- Risk Assessment, Genetic Counseling and Genetic Testing for BRCA Related Cancers in Women.

A Systematic Review for the USPSTF<sup>4</sup>

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- NICE Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People With a Family History of Breast Cancer<sup>5</sup>
- NCCN Practice Guidelines in Oncology Genetic/Familial High-Risk Assessment: Breast and Ovarian<sup>6</sup>

The reference lists of the guidelines pertaining to breast cancer family history were manually reviewed.

When a reference was determined to be relevant to the stated research aim, the full article was reviewed.

## **RESULTS**

Of the initial 106 titles and abstracts, 93 articles were excluded on the grounds that they did not address the specific research aims of evaluating family history or studied patients with genetic mutations that increase the risk of breast cancer. Of the 13 manuscripts reviewed in their entirety, 7 were excluded, leaving 6 articles which are covered in the summary of findings from the initial literature search. A second search turned up 218 titles, only 2 of which were reviewed in greater detail. After deciding to review data prior to 2010, the committee found five additional articles; they are discussed in the section “Summary of Findings From Research Before 2010.”

### **Summary of Findings From Initial Literature Search**

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One study evaluated the validity of self-reported family history in women younger than age 35 with a personal history of breast cancer in Sweden.<sup>7</sup> Self-reported and registry-reported information regarding FDR with cancer was collected with information regarding tumor characteristics. Standardized questionnaires covering family history of all malignant types of cancer were sent to the breast cancer patients or relatives, as was a questionnaire regarding risk factors. Information regarding the fate of the cancer diagnosis and tumor characteristics of the primary breast cancer was retrieved from the Southern Swedish Regional Tumor Registry and the OnkGen Register at Skane University in Lund. There was concordance ( $K=0.92$ ) between self-reported and registry-reported information regarding first-degree family history of breast cancer.<sup>7</sup>

The second article was a consecutive cohort study, performed in the Netherlands, of 464 proven nongenetic mutation carriers who had FDRs with a pathogenic mutation such as BRCA.<sup>8</sup> These proven nongenetic mutation carriers were monitored for risk of developing breast cancer. By age 50, the breast cancer risk in proven noncarriers was 6.4% (95% confidence interval [CI]: 2.9–9.8%), which is significantly higher than the average risk of 2.4% by age 50 for women. The number of breast cancers among noncarriers in BRCA 1 families was higher than expected for the general population (standardized incidence ratio or 2.0, 95% CI: 1.1–3.3). By age 60, the noncarriers had a breast cancer risk of 9.5% (95% CI: 5.0–14.1), whereas women in the general population had a risk of 4.2%. At all ages, the breast cancer risk was higher in the proven noncarriers than in the age-matched cohort from the general population.<sup>8</sup>

The third paper reported on a prospective cohort study conducted in Norway that included women aged 25–59 who had a positive family history of breast cancer without a known BRCA mutation in the family.<sup>9</sup> A detailed history of affected first- and second-degree relatives was obtained by genetic counselors and validated with review of medical records. The selected patients underwent annual mammography screening. In the women with affected families without a known genetic mutation, 64 breast cancers were diagnosed, compared with 34 expected ( $P<0.01$ ), arriving at a 7.9% cumulative risk at age 60 compared with 4% in the general or average-risk population (relative risk [RR] = 2.0). Women with only one FDR (a mother or sister affected at age 50 years or younger) and no other relatives with breast cancer did not exhibit increased risk (no cancers observed and 0.6 expected at age 40; 11 cancers observed and 7.9 expected at age 60,  $P>0.05$ ). The highest cumulative risk at age 60 was 11.4% among women with two affected family members (first or second degree) less than 56 years old (RR = 2.8).<sup>9</sup>

The fourth article was part of the FH01 study, a single-arm study of annual mammography in women aged 40–49 with a moderate family history of breast cancer. Specifically, a cohort study enrolled 6,710 women younger than 50 with a moderate family history of breast cancer between 2003 and 2007 in 76 centers in the United Kingdom to receive annual screening mammography until 2009.<sup>10</sup> “Moderate family history” was the classification used for women with the following risk factors (among others):

- One FDR with breast cancer at age 40 or younger
- One FDR female with bilateral breast cancer at age 50 or younger
- Two FDR or one FDR and one SDR (female) on the same side of the family who both had breast cancer at age 60 or younger
- One FDR or SDR with breast or ovarian cancer before age 60

- Three FDR or SDR relatives on the same side with breast or ovarian cancer diagnosed at any age
- One FDR male relative with breast cancer at any age

Study endpoints were size, node status and histological grade of invasive tumors, and estimated mortality. A total of 136 women were diagnosed with breast cancer, with 77% diagnosed at screening with mammography and 21% diagnosed symptomatically in between screening intervals. Another 2% of women were diagnosed after failing to attend their last mammography appointment. Invasive tumors in screening were significantly smaller ( $P=0.0094$ ), less likely to be node-positive ( $P=0.0083$ ), and of more favorable grade ( $P=0.0072$ ) than those in the control groups. The mean Nottingham prognostic index score was significantly lower in the FH01 cohort than in the control group of the United Kingdom Age trial ( $P=0.00079$ )<sup>11</sup> or the Dutch study ( $P<0.0001$ )<sup>8</sup>. After adjustment for underlying risk, predicted 10-year mortality was significantly lower in the FH01 cohort (1.10%) than in the control group of the U.K. Age Trial (1.38%), with RR of 0.80 (95% CI: 0.66–0.96;  $P=0.022$ ).<sup>10</sup>

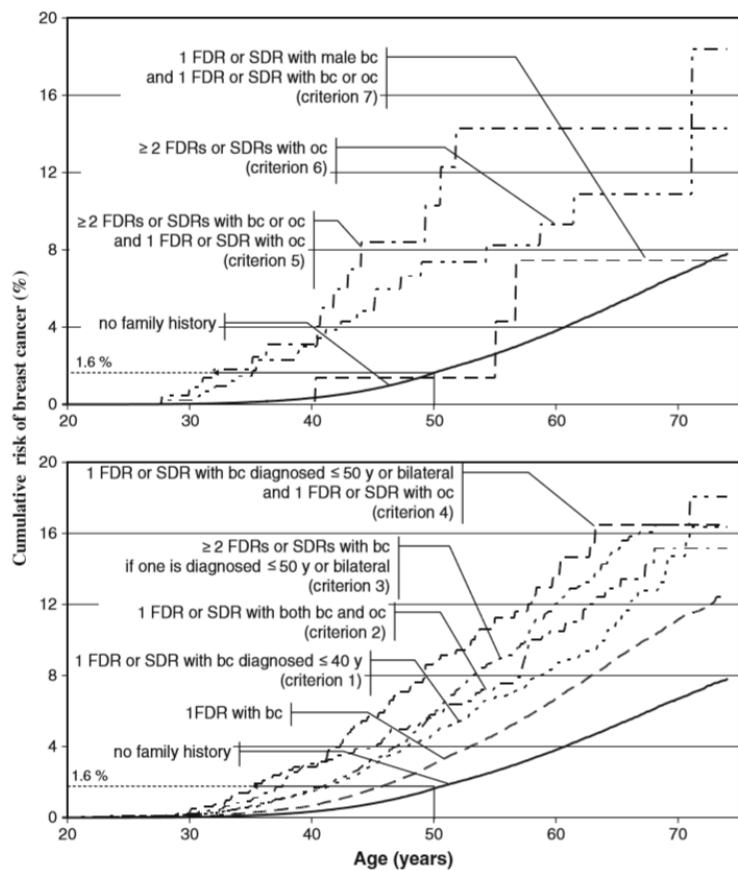
The fifth study was a large population-based assessment in which women age 50 or younger attending a mammographic screening program in the United Kingdom were given a questionnaire that collected family history and other risk factors for breast cancer.<sup>12</sup> The NICE guidelines and the Tyrer-Cuzick model were used to estimate risk for the women. The number of cancers detected in the “moderate-to-high” risk groups were compared with numbers in the whole population. Of the 4,360 completed questionnaires for women between the ages of 46 and 49 years, 30 women (0.7%, 95% CI: 0.5–1.0%) were at high risk and 130 (3.0%, 95% CI: 2.5–3.5%) were at moderate risk, according to the NICE guidelines. There were 37 cancers detected by mammography in the entire group, 5 of which were

found in the moderate-to-high risk group, giving a 3.2-fold increase in detection compared with the standard risk group. Using the Tyrer-Cuzick model, more women were assigned to the moderate- or high-risk group (N=384), but the number of cancers in this group was not appreciably elevated (N=8).<sup>12</sup>

The sixth study was a population-based study in which women in the Swedish Family Cancer Database were categorized by family history into high-risk and average-risk groups, based on first- and second-degree relatives.<sup>13</sup> The authors sought to determine how many years earlier high-risk women reach a defined risk, compared with women lacking a family history. This study had seven criteria, based on the cancers in FDRs and SDRs. The RR of breast cancer was estimated as hazard ratios (HR), which ranged from 1.50 (one FDR or SDR with male breast cancer and one FDR or SDR with breast cancer or ovarian cancer) to 5.99 (two or more FDRs or SDRs with breast cancer or ovarian cancer and one FDR or SDR with ovarian cancer). The number of women affected by breast cancer before the age of 50 was higher than that for women diagnosed later. The HRs were also higher for the young diagnostic group for any of the criteria; the highest HR was 8.98. Figure 1 represents the cumulative risk of breast cancer according to the criteria. The solid curves in the bottom show the cumulative risk of women without a family history; in these curves, the cumulative risk at the age of 50 years (1.6%) is marked.

**Figure 1. Cumulative risk of breast cancer.**

**Fig. 2** Cumulative risk of breast cancer for women who fulfilled high-risk criteria for breast and ovarian cancer syndrome



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Table 2 shows the cumulative risk of breast cancer by ages 50 and 70, while Table 3 shows the age at which women meeting high-risk criteria reach the cumulative risk of women lacking a family history at the ages of 40 and 50 years. The cumulative risks ranged from 1% to 10% by age 50. The age to

reach the same cumulative risk as women lacking a family history at the age of 50 years ranged between 32 and 40.8 years.<sup>13</sup>

**Table 2. Cumulative Risk of Breast Cancer by Age 50 and 70 Years**

Criterion	50 years			70 years		
	CR(%)	95% CI		CR (%)	95% CI	
1 FDR <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> diagnosed $\leq$ 40 years	4.7	4.1	5.4	14.7	12.0	17.5
1 FDR or SDR with both bc and oc <sup>d</sup>	5.8	4.2	7.4	15.2	11.3	19.0
$\geq$ 2 FDRs or SDRs with bc if one is diagnosed $\leq$ 50 years or bilateral	5.8	4.9	6.8	16.5	14.2	18.7
1 FDR or SDR with bc diagnosed $\leq$ 50 years or bilateral and 1 FDR or SDR with oc	8.9	6.4	11.4	16.5	12.0	20.9
$\geq$ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	10.3	4.0	16.5	14.3	6.2	22.3
$\geq$ 2 FDRs or SDRs with oc	7.4	3.9	10.8	10.9	5.7	16.1
1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc	1.4	0.0	4.0	7.5	0.0	16.0
1 bc in FDR, none of criteria 1–7	3.0	2.9	3.2	11.1	10.7	11.6
1 bc in SDR, none of criteria 1–7	2.1	1.8	2.4	10.1	7.8	12.4
1 oc in FDR, none of criteria 1–7	2.7	2.4	3.0	8.8	8.0	9.5
1 oc in SDR, none of criteria 1–7	2.3	1.6	3.0	8.3	3.1	13.5
No family history	1.6	1.6	1.7	6.7	6.5	6.9

<sup>a</sup> First-degree relative (parent, sibling)

<sup>b</sup> Second-degree relative (grandparent, aunt/uncle, half-sibling)

<sup>c</sup> Breast cancer

<sup>d</sup> Ovarian cancer

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**Table 3. Age at Which High-Risk Women Reach the Same Cumulative Risk as Women Without a Family History of Breast Cancer at the Ages of 50 and 40 Years**

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**Table 3** Age at which women who fulfilled high-risk criteria for breast and ovarian cancer syndrome reach the cumulative risk of women lacking a family history at the age of 50 and 40 years

Criterion		50 years				40 years			
		N <sup>e</sup>	Age <sup>f</sup>	95% CI	Age difference	N <sup>e</sup>	Age <sup>g</sup>	95% CI	Age difference
1	1 FDR <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> diagnosed $\leq$ 40 years	110	40.8	39.4–42.3	9.2	27	32.8	31.4–33.8	7.3
2	1 FDR or SDR with both bc and oc <sup>d</sup>	18	37.0	35.3–38.8	13.0	4	31.4	28.7–34.3	8.6
3	$\geq$ 2 FDRs or SDRs with bc if one is diagnosed $\leq$ 50 years or bilateral	66	40.4	38.8–41.9	9.6	17	32.8	31.4–34.1	7.3
4	1 FDR or SDR with bc diagnosed $\leq$ 50 years or bilateral and 1 FDR or SDR with oc	14	35.1	33.4–38.4	14.9	4	30.0	29.0–32.9	10.0
5	$\geq$ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	4	32.0	30.0–41.8	18.0				
6	$\geq$ 2 FDRs or SDRs with oc	6	35.4	32.1–41.1	14.6				
7	1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc								
	1 bc in FDR, none of criteria 1–7	952	45.2	44.8–45.7	4.8	153	35.9	35.3–36.8	4.1
	1 bc in SDR, none of criteria 1–7	512	47.3	46.5–48.5	2.7	246	38.2	37.5–38.6	1.8
	1 oc in FDR, none of criteria 1–7	172	45.4	44.5–46.8	4.6	22	33.3	31.7–37.1	6.7
	1 oc in SDR, none of criteria 1–7	84	48.5	47.3–51.3	1.5	47	39.2	38.0–41.1	0.8

<sup>a</sup> First-degree relative (parent, sibling)

<sup>b</sup> Second-degree relative (grandparent, aunt/uncle, half-sibling)

<sup>c</sup> Breast cancer

<sup>d</sup> Ovarian cancer

<sup>e</sup> Number of cases until ‘Age’

<sup>f</sup> Age to reach the same risk as women lacking a family history at the age of 50 years

<sup>g</sup> Age to reach the same risk as women lacking a family history at the age of 40 years

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### Summary of Findings From Research Before 2010

The first article was a systematic review and meta-analysis of articles from 1966 to 1997 and found on MEDLINE as a result of a search to identify all of the published studies that had quantified the risk of breast cancer associated with a family history of breast cancer.<sup>14</sup> The review identified 74 published studies (52 case-control studies and 22 cohort studies). Of these, 26 reported the risk of breast cancer associated with having a history of breast cancer in any relative (unspecified). All but one of the studies

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found a positive association, with RRs ranging from 0.9 to 3.6. The pooled RR estimate was 1.9 (CI=1.7, 2.0). The age-specific effects were described in four studies but varied, with only one of the studies finding that the risk was higher if the relative had been diagnosed before age 45 (RR=2.2) compared to a RR of 1.6 if the relative had been diagnosed at age 45 or older. Thirty-eight studies evaluated the risk of breast cancer in women with a history of breast cancer in at least one FDR. The RR estimates ranged from 1.2 to 2.8. The pooled RR estimate was 2.1 (CI= 2.0, 2.2).

Of the five studies in the systematic review that reported risk by the relative's age at diagnosis, four showed the risk of breast cancer to be slightly higher for women whose relatives were diagnosed at a younger age, and one study found the relative's age at diagnosis to have no effect. The risk of breast cancer in women whose mother had breast cancer was reported in 18 studies. All of these studies showed an elevated risk, with RRs ranging from 1.3 to 8.2, although the RR was not always significantly different from unity. The estimate of RR obtained from combining all studies was 2.0 (CI = 1.8, 2.1).

Twenty-two studies in the systematic review evaluated the risk of breast cancer among women who had a sister with breast cancer. Most studies estimated a risk of between 2 and 3. The pooled estimate of risk was 2.3 (CI= 2.1, 2.4). The effect of having two affected FDRs was reported in five studies, with a range of risk estimates from 2.5-13.6. The pooled risk estimate was 3.6 (CI= 2.5, 5.0). Ten studies reported on the risk conferred by a family history of breast cancer in an SDR. These were generally lower than the risk associated with having an affected FDR, with risk estimates ranging from 1.2 to 1.9. The summary risk estimate was 1.5 (CI=1.4, 1.6).

The second manuscript compared the efficacy of MRI with that of mammography for screening high-risk women in the Netherlands.<sup>15</sup> These women had a cumulative lifetime risk of breast cancer of 15% or more according to the Claus model or familial or genetic predisposition. The women were divided into three categories: mutation carriers, high-risk group, and moderate-risk group. The high-risk group was defined as having a cumulative risk of 30–49%, while the moderate-risk group was defined as having a cumulative risk of 15–29%. These women underwent CBEs every 6 months, annual breast MRI, and annual mammography between November 1, 1999, and October 1, 2003.<sup>15</sup>

The study included 1,909 women. The overall rate of detection for all breast cancer was 9.5 per 1,000 woman-years at risk (95% CI: 1–12.3), with the highest rate (26.5 per 1,000) in the group with genetic mutations (see Table 4). The sensitivity of CBE, mammography, and MRI for detecting invasive breast cancer was 17.9%, 33.3%, and 79.5% respectively, and the specificity was 98.1%, 95%, and 89.8% respectively.<sup>15</sup>

**Table 4. Table on Breast Cancer by Risk Group**

Table 2. Detection of Cases of Breast Cancer (Including Ductal Carcinoma in Situ) According to Risk Group.								
Risk Group	No. of Women	Woman-Years at Risk	No. of Cases Detected by Screening		No. of Cases Detected between Screenings		Rate of Detection (95% CI)*	
			Total	Invasive	Total	Invasive	All Cancers no./1000	Invasive Cancers no./1000
Mutation carriers	358	867	19	16	4	4	26.5 (15.3–39.4)	23.1 (14.1–35.6)
High-risk group	1052	2968	15	15	1	1	5.4 (3.1–8.8)	5.4 (3.1–8.8)
Moderate-risk group	499	1414	11	8			7.8 (3.9–13.9)	5.7 (2.4–11.1)
Total	1909	5249	45	39	5	5	9.5 (7.1–12.3)	8.4 (6.1–11.3)

\* CI denotes confidence interval. Rates shown are per 1000 woman-years at risk.

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The third and fourth articles reviewed drew from the Nurses' Health Study, which was established in 1976 when 121,701 female nurses in the United States aged 30–55 responded to a mailed questionnaire that inquired about risk factors for breast cancer, including family history of breast cancer.<sup>16–18</sup> The risk factors have been updated in repeat questionnaires obtained every 2 years. The most recent article obtained data up to 2006. Overall, 15.38% of women in this study reported a family history of breast cancer diagnosed in a mother or sister; 3.4% had a family history with first diagnoses before the age of 50, and 11.94% had first diagnosis at age 50 or older. Compared with women with no family history of breast cancer, those whose mother was diagnosed before age 50 had an adjusted RR of 1.69 (95% CI: 1.39–2.05) and those whose mother was diagnosed at age 50 or older had a RR of 1.37 (95% CI: 1.22–1.53). The difference between these RRs was borderline significant ( $P=0.06$ ). The RR for those with a sister diagnosed before the age of 50 was 1.66 (95% CI: 1.38–1.99), and for those diagnosed at age 50 or older the RR was 1.52 (95% CI: 1.29–1.77). The difference in the RR was not significant ( $P=0.43$ ).<sup>16</sup>

### **National Guideline Recommendations**

From the evaluation of clinical practice guidelines from ACOG, SGO, USPSTF, NICE, NCCN, the American College of Medical Genetics and Genomics (ACMG), and the National Society of Genetic Counselors, nine relevant articles from the reference lists of the guidelines were identified and manually reviewed. All of

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the guidelines recommend an assessment of family history to evaluate patients for elevated risk of breast cancer.

In general, the various national guidelines were consistent in describing what an at-risk family history entails. For example, the NICE guidelines recommend that women without a personal history of breast cancer be referred to genetic counseling if they have any of the following:<sup>5</sup>

- One female FDR diagnosed with breast cancer at age younger than 40
- One male FDR diagnosed with breast cancer at any age
- One FDR with bilateral breast cancer, with the first primary diagnosed before age 50
- Two FDRs or one FDR and one SDR with breast cancer at any age
- One FDR or SDR diagnosed with breast cancer at any age and one FDR or SDR diagnosed with ovarian cancer at any age
- Three FDRs diagnosed with breast cancer at any age

These NICE criteria are quite consistent with SGO guidelines.

Other organizations describe family history of concern beyond breast cancer diagnosis. The ACMG practice guidelines state that a patient with three or more cases of breast, ovarian, pancreatic, or aggressive prostate cancer, or some combination, in close relatives, including the patient, should be referred for genetic counseling.

For risk assessment, ACOG defers to the ACMG and the National Society of Genetic Counselors guidelines. The NCCN guidelines state that individuals without a personal history of breast cancer are considered at higher risk if they have the following family history:<sup>6</sup>

- First- or second-degree relatives with breast cancer at age 45 years or younger, ovarian cancer, male breast cancer, pancreatic cancer, or metastatic prostate cancer
- Two or more breast cancer primaries in a single individual
- Two or more individuals with breast cancer primaries on the same side of the family, with at least one diagnosed at age 50 or younger.
- Personal or family history or both on the same side of the family of three or more cases of breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, diffuse gastric cancer, and others, especially if diagnosed at age 50 or younger.

The literature search did not find the data to support these detailed family history guidelines. The references cited in this section of the NCCN guidelines described familial risk stratification tools that have been validated to identify women with an increased probability of testing positive for a genetic mutation such as BRCA, with the presumption that this mutation increases their risk of breast cancer. The focus of these cited articles was the identification of women with high-risk mutations. Several addressed risk assessment tools:

- Family history assessment tool<sup>19,20</sup>
- Pedigree assessment tool<sup>21</sup>
- Manchester scoring system<sup>21</sup>

- Referral Screening Tool<sup>23</sup>
- BOADICEA genetic prediction model<sup>24</sup>
- BRCAPRO genetic prediction model<sup>25</sup>

Two articles looked at the validity of various models.<sup>25,26</sup>

**Is the BRCAPRO computer model more accurate in assessing increased risk of breast cancer in patients with family history of breast cancer compared with the Tyrer-Cuzick model?**

In general, multiple validated models exist that could be used to determine one's probability of a genetic mutation that increases the risk of breast cancer. There was no consensus to recommend one superior model. Two studies evaluated the validity of different risk assessment models to determine the probability of a patient having a genetic mutation that increased their risk of breast cancer. Parmigiani et al looked at seven different models in their predictions.<sup>26</sup> The measurement of discrimination between individuals testing positive for a mutation in BRCA 1 or BRCA 2 from those testing negative is the c-statistic—the probability that a randomly chosen test-positive patient will have a higher probability (or prediction score) of a BRCA mutation than a randomly chosen negative patient. This study reported that the better performing models have a c-statistic around 80%. BRCAPRO had the most favorable c-statistic overall at 82%, although the margin over other models was narrow in many strata. Panchal et al also compared seven models, reporting that the Penn II model most closely met their criteria regarding sensitivity, applicability, and tendency towards ease and efficiency.<sup>25</sup> The sensitivity

and specificity to identify women with a breast cancer mutation reported were 0.93 and 0.31, respectively, for the Penn II model. However, no data specifically evaluated the prediction of EOBC.

**Are patients with one affected FDR at increased risk of breast cancer compared with patients without an FDR affected by breast cancer between the ages of 18 and 45? Are patients with two affected FDRs at increased risk of breast cancer compared with patients without any FDRs with breast cancer between the ages of 18 and 45? Are patients with an SDR at increased risk of breast cancer compared with patients without an SDR with breast cancer between the ages of 18 and 45?**

The NICE and SGO guidelines were consistent in identifying the most concerning patterns of positive family history. For example, they are consistent on the need for women with two FDRs at any age to undergo genetic testing for breast cancer mutations. Generally, having multiple family members of any age or FDRs diagnosed at earlier ages is most concerning. Women in breast-cancer-positive families without a known BRCA mutation had about twice the risk of breast cancer at any age compared with women in the general population. However, on deeper analysis, having only one early affected mother or sister was not associated with a significantly increased risk for EOBC. An affected family with multiple young breast cancer cases (before age 50) had close to three times the low or average population-based risk.<sup>9</sup>

In the Nurses' Health Study, women with a family member diagnosed with breast cancer before the age of 50 carried increased risk for breast cancer compared with women of the same age with family members diagnosed at older ages. Compared with women with no family history, those whose mother

was diagnosed before age 50 had an adjusted RR of 1.69 (95% CI: 1.39–2.05), and those whose mother was diagnosed at 50 or older had a RR of 1.37 (95% CI: 1.22–1.53). In addition, having a sister with diagnosed breast cancer was associated with increased RR of 1.66 (95% CI: 1.38–1.99) for those with a sister diagnosed before 50 and 1.52 (95% CI: 1.29–1.77) for those whose sister was diagnosed at age 50 or older.<sup>16</sup>

In the systematic review and meta-analysis, a history of breast cancer in at least one FDR resulted in RR estimates ranging from 1.2 to 8.8, with most studies showing RR between 2 and 3. The pooled risk estimate for having two affected FDRs was 3.6 (95% CI: 2.5, 5.0). The RR for women with an SDR ranged from 1.2 to 1.9, with the summary risk estimate being 1.5 (95% CI: 1.4, 1.6).<sup>14</sup> However, many of the older Nurses' Health Study findings noted in the systematic review and meta-analysis did not factor out genetic mutations.

**In patients with positive family history of breast cancer, does more intensive mammographic and MRI screening detect breast cancer earlier than in low-risk women who are screened according to current guidelines? In patients with family history of breast cancer, is breast cancer screening with MRI as effective as mammography? Is MRI indicated as an adjunct to screening with mammography?**

The NCCN recommends that women with an estimated lifetime risk of breast cancer of 20% or more according to models largely based on family history (BOADECIA, Claus, BRCAPRO, Tyrer-Cuzick) be offered annual mammography screening starting at the age of 30 and annual breast MRI screening starting at the age of 25.<sup>6,27</sup> One article compared the efficacy of MRI with mammography screening in

high-risk groups. Women in this study were divided into three groups: women with genetic mutations, women with cumulative lifetime risk of 30–49%, and women with cumulative lifetime risk of 15–29%.<sup>15</sup> In this study, MRI appeared to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to breast cancer. However, both the specificity and the positive predictive value of MRI were lower than with mammography.<sup>15</sup> The prospective, single-arm FH01 study evaluated whether screening with yearly mammography in women younger than 50 with a clinically significant family history of breast cancer affected the stage at diagnosis and thus projected mortality.<sup>10</sup> The data suggested that annual mammography in women with increased familial risk of breast cancer is likely to be effective in preventing deaths from breast cancer.

**Do women with a positive family history of breast cancer have increased risk of being diagnosed with EOBC compared with women without a family history of breast cancer?**

Women with deleterious genetic mutations tend to present with breast cancer at an earlier age. Three studies in the literature search suggested that women with a positive family history and no known genetic mutation were at increased risk of developing breast cancer compared with those in the general population who did not have a known mutation.<sup>8,9,13</sup> These women also were noted to develop breast cancer at an earlier age in comparison to the general population. Similar findings were noted in the Nurses' Health Study and the systematic review and meta-analysis.<sup>14,16</sup> However, those studies did not specifically test for genetic mutations and thus genetic mutations were not excluded.

**DISCUSSION**

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As noted, the initial literature search identified 6 studies out of the 106 that directly or indirectly addressed the research questions. An additional three studies were assessed after review of the initial data. Most of the data from those studies were classified as level II or level III evidence. Most of the articles excluded investigated families with genetic mutations such as BRCA. Risk assessment models in these studies estimated the likelihood of BRCA mutations and have been used to guide patient referrals to genetic specialists and breast cancer specialists and to stratify patients at high or moderate risk who should consider more intensive screening regimens. The secondary literature search identified 2 relevant articles out of 218. These two articles simply stated that women with a family history of breast cancer may benefit from regular breast cancer screening.

These models have been used to indirectly extrapolate the presumed elevated risk of women with a positive family history of breast cancer and no genetic mutations identified. Only two articles specifically investigated the breast cancer risk of women in noncarrier families.<sup>8,16</sup>

The Gail model is well-known and has been used previously for breast cancer risk assessment. The model employs several parameters, such as personal and family history, with other parameters to assess risk. It is limited and generally not used because its data set does not account for family history of ovarian cancer, age of onset of breast cancer diagnosis of relatives, or second- and third-degree relatives. It is also used in women over the age of 35. The Gail model does not factor in any male breast cancer among relatives. The BRCAPRO model includes age-specific, positive and negative family history for breast and ovarian cancer from paternal and maternal sides.<sup>19</sup>

The search found no study that specifically addressed the effectiveness of familial risk assessment tools for noncarrier women, nor did the search uncover studies investigating the impact of risk stratification and the need for more intensive screening based on family history alone. There are many variations within the various risk assessment models, and an exhaustive review of the models is not within the scope of this review. There is no consensus of the preferred risk assessment tool amongst the various organizations. Current data do not make it possible to recommend one model over others.

There are frustratingly limited data on outcomes for women with an elevated risk of breast cancer by family history without an established familial genetic mutation. Two articles suggested that women with a positive family history without a known genetic mutation are at increased risk of breast cancer at an earlier age. Recommendations from national guidelines are consistent regarding the importance of gathering a thorough family history of breast cancer. However, these guidelines are limited in their ability to estimate lifetime and age-based breast cancer risk for women in families without genetic mutation carriers. Many of the current guidelines relating to this population appear to be based on expert opinion and studies of family history that were published prior to genetic testing for mutations such as BRCA 1 and BRCA 2.

It is generally agreed that women who have an elevated lifetime risk of breast cancer, defined as 20% by any currently available familial risk assessment model, should be offered increased breast cancer screening surveillance.

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