Appendix 6. Prior History Risk Factors for Early Onset Breast Cancer

Primary reviewer: Dana Scott, MD

Secondary reviewer: Laura Bozzuto, MD

Tertiary reviewer: Amy Young, MD

INTRODUCTION

A woman's prior health history affects her lifetime risk of early onset breast cancer (EOBC). This literature review specifically addressed questions about the relationship between prior history and EOBC.

1. What prior histories (eg, breast disease, prior breast or ovarian cancer, hormonal contraceptives, and radiation exposure) are risk factors for EOBC? How strong are these risks?

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

P: Adult women aged 18–45 with prior histories of proliferative breast disease, prior breast or ovarian cancer, hormonal contraceptive use, or radiation exposure.

I: Having a potential risk factor:

- Breast disease (ie, atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ (LCIS), pleomorphic lobular carcinoma in situ, complex sclerosing

Chelmow D, Pearlman MD, Young A, Bozzuto L, Dayaratna S, Jeudy M, et al. Executive summary of the Early-Onset Breast Cancer Evidence Review Conference. Obstet Gynecol 2020;135.
The authors provided this information as a supplement to their article.

lesions, or radial scars; hereafter, the term *proliferative breast disease* refers to any of these lesions)

- Past or present use of hormonal contraception (HC, ie, oral contraception, contraception, progestin intrauterine device/system, progestin implant, medroxyprogesterone injection; hereafter, the term *HC* refers to any of these contraceptive choices)
- Past or present use of fertility treatments (ie, ovulation induction medications, ovarian stimulation for in vitro fertilization; hereafter, the term *fertility treatments* refers to these fertility treatment methods)
- Radiation exposure (ie, radiation therapy [RT], chest radiation, mantle radiation, breast radiation, and axillary radiation; hereafter, the term *chest radiation* refers to any of these radiation exposures)
- Prior breast cancer or ovarian cancer

C: Women with:

- A risk factor versus no risk factors
- A history of proliferative breast disease versus past or present use of HC
- A history of proliferative breast disease versus past or present use of fertility treatments
- A history of proliferative breast disease versus history of breast or ovarian cancer
- A history of proliferative breast disease versus history of chest radiation
- Past or present use of HC versus history of breast or ovarian cancer
- Past or present use of HC versus history of chest radiation

- Past or present use of HC versus past or present use of fertility treatments
- Past or present use of fertility treatments versus women with a history of chest radiation
- Past or present use of fertility treatments versus women with a history of breast or ovarian cancer
- A history of breast or ovarian cancer versus history of chest radiation

O: Breast cancer diagnosis before age 46, increased risk of breast cancer (relative risk [RR] or odds ratio [OR]).

2. In women with prior history risk factors for EOBC, is screening beneficial? What are the most effective screening approaches?

PICO

P: Women aged 18–45 with history of proliferative breast disease, past or present use of HC, past or present use of fertility treatments, history of chest radiation, or history of breast or ovarian cancer

I: Breast cancer screening (ie, mammography, breast MRI, or breast ultrasonography).

C: Mammography at younger age versus routine screening (mammography starting at age 40), breast MRI at younger age versus mammography starting at age 40, breast ultrasonography at younger age versus mammography at age 40.

O: Stage at diagnosis, survival rate.

3. What are current major society or health services guidelines for screening or management of women with prior history risk factors for EOBC (eg, contraceptive choices)?

PICO

P: Women aged 18–45 with history of proliferative breast disease, past or present use of HC, past or present use of fertility treatments, history of chest radiation, or history of breast or ovarian cancer

I: Breast cancer screening, mammography, breast MRI, breast ultrasonography, breast cancer risk reduction, tamoxifen, raloxifene, mastectomy, or any combination of these

C: Mammography versus breast MRI, mammography versus breast ultrasonography, breast MRI versus breast ultrasonography, tamoxifen versus raloxifene, medication versus no medication, medication versus mastectomy, mastectomy versus no mastectomy.

O: Recommended by National Comprehensive Cancer Network (NCCN), U.S. Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists (ACOG), or American Cancer Society

METHODS

The literature review searched the Cochrane Library, MEDLINE through Ovid, and PubMed by using the search strategy created by the ACOG Resource Center librarians. The literature search was supplemented by examining the bibliographies of included studies and bringing in other notable, pertinent works not identified by the primary search. A manual search identified relevant guidelines

from the following organizations: American Cancer Society, American Society of Clinical Oncology, European School of Oncology (ESO), European Society of Medical Oncologists (ESMO), European Society of Breast Cancer Specialists (EUSOMA), International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), National Cancer Institute, NCCN, National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists, USPSTF, and the American Society for Reproductive Medicine (ASRM).

Inclusion and exclusion criteria were created for each question. Studies were included if they were English-language major society or health services guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, or case–control studies evaluating women aged 18-45. Studies were excluded if they were unavailable in English, were case series or reports, or if they evaluated men, average-risk women, or pregnancy-associated breast cancer. A single investigator reviewed the title and abstracts of all identified articles and guidelines, then examined the full text of those articles that met eligibility criteria.

RESULTS

Of the 27 published guidelines reviewed, 19 were excluded because they were not pertinent to the research question. The eight remaining guidelines were reviewed in further detail and included in this review. The literature search returned 293 total citations, of which 250 papers were excluded after review of the title and abstract, leaving 43 for review. An additional 17 papers were excluded after

further review, and another 17 papers were included after reviewing the references of the included papers.

What prior histories (eg, breast disease, prior breast or ovarian cancer, hormonal contraceptives, and radiation exposure) are risk factors for EOBC? How strong are these risks?

History of Proliferative Breast Disease

While there are substantial data evaluating the effect of proliferative breast disease on a woman's lifetime risk of breast cancer, there is a paucity of data regarding the risk of EOBC specifically. This review addresses lifetime risk of breast cancer and, therefore, must be extrapolated to young patients with caution.

Women with atypical hyperplasia of the breast (atypical ductal hyperplasia or atypical lobular hyperplasia) have a significantly increased future risk of breast cancer. These breast lesions have previously been discussed in the ACOG Practice Bulletin Diagnosis and Management of Benign Breast Disorders.[1] Atypical hyperplasia is a fairly common finding, occurring in approximately 10% of all benign breast biopsies.[2] Typically, atypical ductal hyperplasia is excised because of an approximately 20% or higher risk of concurrent ductal carcinoma in situ (DCIS) or invasive malignancy. Atypical lobular hyperplasia is associated with a lower risk of concurrent in situ or invasive cancer (<5%), and therefore can be monitored closely rather than excised when the imaging is concordant and there are no other high-risk lesions requiring excision.[3] A diagnosis of atypical hyperplasia confers an increased lifetime risk

of breast cancer, with an RR of approximately 4. Future breast cancer diagnosis is slightly more common in the ipsilateral breast, but can occur in either breast.[2,4]

Lobular carcinoma in situ (LCIS) differs from DCIS in that it is not considered a precursor lesion to invasive breast cancer. It is, however, a marker for future breast cancer risk, and confers a significantly increased risk of breast cancer (RR: 6.9–11,[5] absolute risk: 7.1% over 10 years[6]). Pleomorphic LCIS is a subtype of LCIS with increased nuclear pleomorphism, which may carry an increased risk of breast cancer compared with classic LCIS. There are not enough data to make recommendations for the management of pleomorphic LCIS as a separate entity from classic LCIS.[7]

Radial scars and complex sclerosing lesions (RS/CSLs) are proliferative lesions typically diagnosed on core-needle biopsy of a spiculated mass or mammographic asymmetry. The reported risk of identifying a concurrent in-situ or invasive malignancy at the time of excision of RS/CSLs varies widely in the literature, with most studies reporting an 8–15% risk of upstaging.[3,8,9] While certain characteristics may be associated with upstaging (eg, patient age, lesion size, imaging appearance, or presence of a palpable mass), the literature is somewhat inconsistent regarding how predictive these findings are.[3,8,10,11] As such, most RS/CSLs are excised, though some small, imaging-concordant lesions may be safely observed.[3,10,12] Following excision, the radial scar is no longer thought to contribute to a patient's risk of breast cancer.[1,11,12]

Past or Present Use of Hormonal Contraception

The effect of HC on breast cancer risk has been studied extensively since shortly after oral contraceptive pills (OCs) became widely available in the United States. Many case–control and cohort studies have revealed conflicting data, with some studies showing a small increased risk of breast cancer with OC use[13,14] and others showing no effect.[15,16] A large meta-analysis in 1991 revealed a small increased risk of breast cancer among women currently using OCs and for the first 10 years after discontinuation (RR: 1.07, 99% confidence interval [CI]: 1.05–1.09).[17] In December 2017, a large population-based Danish cohort study evaluated the effect of HC on the risk of breast cancer prior to age 50 among approximately 1.8 million women. Because of its extremely large sample size, the study was able to control for confounding risk factors (eg, family history, reproductive risk factors) and to detect even small associations. Most notably, women using any form of HC had a significantly elevated RR of breast cancer compared with never-users (RR: 1.20, 95% CI: 1.14–1.26). Similar risk level was seen in women using OCs, specifically (RR: 1.19, 95% CI: 1.13–1.26). There was no increased risk among women who used HC for fewer than 5 years. Beyond 5 years of use, however, the RR increased with duration of use. This increased risk persisted for 5 years after discontinuation, at which point risk returned to baseline. There was no difference in risk based on specific OC formulation. Given the extremely large sample size, these statistically significant findings suggest a very small absolute risk increase. Among all women, this risk translates to one additional case of breast cancer for every 7,690 women using HC each year. Among women younger than age 35, there was one additional breast cancer case for every 50,000 women using HC each year.[18] HC usage is not clearly associated with a specific breast cancer hormone receptor status.[19,20] The effect of OC use on breast cancer risk among BRCA 1 or BRCA 2 mutation carriers has been somewhat controversial.[21,22] Modern OCs, however, do not appear to further increase

the risk of breast cancer among BRCA 1 or BRCA 2 mutation carriers and have significant benefit in terms of ovarian cancer risk reduction.[21,23,24]

There are limited data evaluating the effect of other HC options on breast cancer risk. While the large, population-based Danish study reported an increased risk of breast cancer among women who used levonorgestrel intrauterine systems (LNG-IUS) (RR :1.21, 95% CI: 1.11–1.33),[18] multiple other well-done case–control/cohort studies and systematic reviews have shown no increased risk of breast cancer with LNG-IUS.[25-27] A single case–control study demonstrated an increased risk of breast cancer among women who had recently used depo-medroxyprogesterone (DMPA) injections for more than 12 months (OR: 2.2, 95% CI: 1.2–4.2), but not for shorter duration or more distant use.[28] Other larger case–control studies have shown no increased risk of breast cancer with DMPA.[27] There is no evidence of increased breast cancer risk with the etonogestrel implant.[27]

It is important to note that HC has numerous benefits, which must be considered whenever discussing potential risks. For example, HC prevents unplanned/undesired pregnancies, which have significant health, social, and economic consequences, including approximately $21 billion of direct and indirect health care costs per year.[29] Additionally, the maternal mortality rate is roughly twice the rate of excess breast cancer on HC identified in the recent Danish population study (26.4 deaths per 100,000 pregnancies in the United States in 2015).[30] Additionally, HC, particularly OCs, has been shown to reduce the risk of ovarian and endometrial cancers.[20] Women using OCs for 5–10 years experienced a significantly decreased risk of ovarian cancer (hazard ratio [HR]: 0.72, 95% CI: 0.59–0.88 at 5–9 years of use; HR: 0.60, 95% CI: 0.47–0.76 for 10 or more years of use) and endometrial cancer (HR: 0.84, 95% CI:

0.73–0.97 at 5-9 years or use; HR: 0.66, 95% CI: 0.56–0.78).[31] When accounting for the possible increased risk of breast cancer with OC use, there still seems to be a net negative cancer risk among women using OCs, reflecting the significant reduction in ovarian and endometrial cancers.[32]

Past or Present Use of Fertility Treatments

Many fertility treatments cause an increase in circulating estrogen and progesterone levels, which raises a theoretical concern for an increased risk of breast cancer in the future. Clomiphene citrate (CC), however, is a selective estrogen-receptor modulator frequently used for ovulation induction. Other selective estrogen-receptor modulators, namely tamoxifen, are used for breast cancer treatment and risk reduction. Many studies have attempted to evaluate the risk of breast cancer following various fertility treatments, but results are somewhat inconsistent and these studies have been limited by their retrospective nature, lack of long-term follow-up, potential for recall and detection bias, and lack of differentiation between different fertility medications.[33] Additionally, many features of infertility (eg, nulliparity, older age at first delivery) are also independent risk factors for breast cancer, potentially confounding results.

Despite the limitations noted above, most studies published on this topic have demonstrated either no effect or a decrease in the risk of breast cancer following fertility treatments. As such, the ASRM has issued a statement that there is "fair evidence that fertility drugs are not associated with an increased risk of breast cancer (Grade B)."[33] Few studies have examined the specific risk of EOBC in this population. The Two Sister Study is a retrospective study evaluating various environmental and genetic

risk factors in pairs of women with EOBC (defined in the study as diagnosis before age 50) and an unaffected biologic sister. Overall, women exposed to either CC or both CC and follicle-stimulating hormone exhibited a non-statistically significant decrease in EOBC compared to nonusers.[34]

While the majority of data does not suggest an increased risk of breast cancer, there are specific populations in which fertility treatments may be associated with an increased risk. In one study, women exposed to high cumulative doses and multiple cycles of CC demonstrated an increased risk of breast cancer (HR: 1.27; 95% CI: 1.02–1.59 for women with cumulative dosage of 2,251 mg or more and six or more cycles). This study did not demonstrate an increased risk among women who had used shorter courses or lower doses of CC or among those treated with gonadotropins (even after previous CC exposure).[35]

Looking at in vitro fertilization (IVF) specifically, one recent study did not identify any difference in breast cancer rate among women who underwent IVF compared with those who underwent other fertility treatments. However, women who underwent IVF at a young age (<24 years) did have a significantly increased risk of breast cancer in the future (HR: 1.59, 95% CI: 1.05–2.42). This effect remained after adjusting for age at first delivery and multiple gestations (HR 1.56, 95% CI: 1.01–2.40).[36]

History of Radiation Exposure

Therapeutic radiation to the chest before age 30 is a well-established risk factor for EOBC.[37,38] It has also been suggested that frequent diagnostic ionizing radiation exposure at a young age is associated with an

increased risk of breast cancer, but the magnitude of risk is uncertain and is beyond the scope of this review.[39] Research has classically focused on the effects of mantle RT for Hodgkin's lymphoma, which delivers the highest dose of radiation to the chest and breast tissue. However, moderate-dose chest radiation, such as mediastinal and lung fields for non-Hodgkin's lymphoma, leukemia, bone malignancies, and pediatric solid tumors (eg, Wilms tumor, neuroblastoma, soft-tissue sarcoma), also increases a woman's future risk of breast cancer. While not used in practice today, RT to treat benign skin conditions, such as hemangiomas, is also associated with an increased risk of breast cancer.[40]

For women with a history of chest radiation before age 30, the majority of available data estimates the cumulative incidence of invasive breast cancer by age 40–45 years at 13–20%, but some reports are as high as 35% by age 45.[41] This risk level is similar to that seen in BRCA 1/2 mutation carriers.[42,43] In contrast, the cumulative incidence of breast cancer by age 45 in the general population is only 1–2%.[41] Breast cancers following chest radiation are more likely to occur in the upper outer quadrant (in the area with the highest exposure to ionizing radiation during mantle RT), be bilateral, treated with mastectomy, be high grade, and be hormone-receptor negative compared with primary nonradiation-associated breast cancers.[44-46] There are conflicting data about the impact that age of chest radiation has on breast cancer risk, with some reports stating the risk is highest if treatment occurs around puberty (10–16 years of age).[45] Others do not find a difference in risk based on relationship of treatment timing to puberty.[42] The increased risk of breast cancer is evident starting 8–10 years after completion of therapy.[41-43] Importantly, this risk does not appear to plateau at any point following completion of radiation, and the cumulative incidence of breast cancer 25–30 years after treatment is 12–26%.[41,42]

The risk of breast cancer is modified by a few factors, most notably radiation dose, additional cancer therapies, and family history. There appears to be a dose-response effect, with the greatest breast cancer risk seen in women treated with 40 Gy or more.[42,43] The limited data that have stratified breast cancer risk for lower radiation doses suggest a lower OR of breast cancer for women treated with 20–30 Gy (OR: 6.0–9.0) compared with 40 Gy or more (OR: 10.8, 95% CI: 3.8–31),[42,47] but the exact risk magnitude by radiation dose is not well established. Therapy-induced primary ovarian insufficiency, such as that resulting from high-dose alkylating chemotherapy or pelvic RT, appears to mitigate the increased breast cancer risk from chest RT.[42,48] Additionally, a family history of breast cancer appears to further increase risk in women with a history of chest radiation.[42]

Prior Breast Cancer or Ovarian Cancer

Women with a prior history of breast cancer remain at risk for a second breast cancer in the ipsilateral or contralateral breast, but the risk for a second EOBC in women diagnosed with their first cancer prior to age 46 has not been studied. The following data pertains to the lifetime risk of a second breast cancer diagnosis among women diagnosed with their first breast cancer at any age and, therefore, must be extrapolated to young patients with caution. In women without a known cancer gene mutation, the risk of a second breast cancer is approximately 3% and 7% at 10 and 15 years after diagnosis, respectively.[49] Women with a pathogenic BRCA 1 or BRCA 2 mutation have a significantly higher risk of a second breast cancer (26% and 39% at 10 and 15 years, respectively). Treatment with tamoxifen and bilateral oophorectomy significantly reduces the risk of a second breast cancer in both BRCA 1 or BRCA 2 gene

mutation carriers and noncarriers.[49,50] The risk of a contralateral breast cancer is not affected by the surgical treatment for the first breast cancer (breast conservation versus mastectomy).[41] There are no data to quantify the risk of second breast cancer in other high-risk women, such as those with prior history of chest radiation.

An extensive literature review did not reveal any articles addressing risk of EOBC in women with ovarian cancer in childhood, adolescence, or early adulthood.

In women with prior history risk factors for EOBC, is screening beneficial? What are the most effective screening approaches?

Breast cancer screening strategies for each specific risk factor are addressed below. To optimize sensitivity and specificity in young women undergoing screening, mammography and breast MRI should be performed early in the menstrual cycle (days 1–14 for mammography, days 6–13 for breast MRI).

History of Proliferative Breast Disease

There are very limited data regarding the potential benefit of breast MRI in patients with high-risk breast lesions, and there are no data to recommend any specific screening strategies in young women to detect EOBC.[38] In a single retrospective study evaluating 378 patients with a history of LCIS or atypical hyperplasia, women underwent screening with either mammography alone or mammography and breast MRI. Women included in the study ranged in age from 25 to 90 years, but women screened with

MRI tended to be younger (mean age of 52 years vs 59 years) and have a stronger family history of breast cancer than those who did not undergo MRI screening. Breast MRI detected six cases of breast cancer that were not visualized on recent mammography, all in patients with LCIS. There were no mammographically-occult MRI-detected malignancies among those with atypical hyperplasia. Additionally, breast MRI generated more biopsies than mammography, with cancer being detected in 4 of 46 MRI-generated biopsies.[51]

Past or Present Use of Hormonal Contraception

After extensive literature review, there are no specific data regarding breast cancer screening efficacy specifically in women with a history of HC use. It is noted that the sensitivity and specificity of breast MRI is not affected by HC use.[52]

Past or Present Use of Fertility Treatments

After extensive literature review, there are no specific data regarding breast cancer screening efficacy specifically in women with a history of fertility treatments.

History of Radiation Exposure

Early initiation of breast cancer screening is effective for detecting breast cancers at an earlier stage in women with a history of chest radiation prior to age 30.[42] The specific recommendations regarding

screening strategies and age at which to initiate screening are described in the next section. Screening most commonly consists of a combination of mammography, breast MRI, clinical breast examinations and, less commonly, screening breast ultrasonography. In one prospective cohort of women treated with chest radiation before age 30, breast MRI was found to be extremely sensitive for detecting breast cancer (100%; 95% CI: 93–100%), but had only an 80% specificity (95% CI: 68–88%). In contrast, mammography is less sensitive (73%; 95% CI: 39–94%), but more specific for diagnosis (99%; 95% CI: 98–100%).[53] Other reports have emphasized the importance of mammography, however, as 25% of breast cancers in this patient population present as microcalcifications.[44,45] Additionally, mammography is the only surveillance method with a clearly established reduction in breast cancer mortality.[43] The highest sensitivity for detection, therefore, has been seen with a combination of mammography and breast MRI.[45] While mammography is associated with radiation, the radiation dose with standard imaging provides a small incremental increase in radiation exposure to women previously treated with therapeutic radiation.[43] Neither clinical breast examinations nor screening breast ultrasonography have a high sensitivity for detecting breast malignancies in this setting (36%, 95% CI: 11–69%, and 55%, 95% CI: 23–83%, respectively).[53]

Prior Breast Cancer or Ovarian Cancer

Extensive literature review did not reveal any articles addressing breast cancer screening efficacy specifically in women with a prior history of breast or ovarian cancer.

What are current major society or health services guidelines for screening or management of women with prior history risk factors for EOBC (eg, contraceptive choices)?

History of Proliferative Breast Disease

The NCCN is the only professional society or health system with published guidelines for screening following a diagnosis of atypical hyperplasia or LCIS.[38] As noted, these guidelines apply to women of any age and do not specifically address screening for EOBC. The NCCN recommends the following for patients with a history of LCIS or atypical hyperplasia:

- Annual mammography starting at age of diagnosis or age 30, whichever is later. Consider tomosynthesis instead of traditional two-dimensional mammography.
- Consider annual breast MRI starting at age of diagnosis or age 25, whichever is later.
- Have clinical breast examinations every 6–12 months.
- Breast self-awareness.

As previously stated, there is not enough evidence to make separate guidelines for pleomorphic LCIS.[38] The EUSOMA does not have complete screening guidelines for atypical hyperplasia or LCIS. However, it recommends against screening breast MRI for atypical hyperplasia or LCIS without other risk factors because of potential harms (e.g. callbacks and unnecessary biopsies) and lack of evidence of benefit.[52] There are no screening guidelines for patients with a history of RS/CSLs. Given that the risk of breast cancer returns to baseline following excision of RS/CSLs, it is unlikely that intensive surveillance would be beneficial.

Past or Present Use of Hormonal Contraception

After extensive literature review, there are no specific screening guidelines in place for women with past or present use of HC.

Past or Present Use of Fertility Treatments

After extensive literature review, there are no specific screening guidelines in place for women with past or present use of fertility treatments.

History of Radiation Exposure

Multiple professional societies and health services have published guidelines regarding breast cancer screening in women with a prior history of chest RT. Screening recommendations most commonly consist of a combination of clinical breast examination, mammography, and breast MRI. There is slight variation among the guidelines regarding age to start any screening and, more specifically, the age to begin mammography screening. In general, screening is recommended for women who received 20 Gy or more total dose chest radiation prior to age 30.[38,43,52,54] Screening can be considered in women who received lower-dose RT, but the benefit of screening in that setting is unclear.[43] The most comprehensive guidelines selected and included in this review are published by the NCCN, EUSOMA, and IGHG. The ESO and ESMO have published the ESO-ESMO 3rd International Consensus Guidelines for

Breast Cancer in Young Women, which affirm the NCCN guidelines for post-chest RT screening, but do not provide novel guidelines.[54] Box 1 summarizes these guidelines and indicates areas of disagreement.

There is limited data to suggest superiority of one screening protocol over others. Shared decision making, including the discussion of risks of false positives and negatives, is recommended when deciding upon a screening strategy. The National Comprehensive Cancer Network guidelines are updated on a scheduled annual basis, so may reflect updated evidence sooner than other guidelines.

Box 1. Comparison of Guidelines for Screening Women With a History of Radiation Exposure*

NCCN†

- Start screening at **age 25** or **10 years** after completion of radiation therapy, whichever is later.
- Begin annual breast MRI starting at **age 25.**
- Begin annual mammography starting at **age 30**. Consider tomosynthesis instead of traditional two-dimensional mammography.
- Undergo clinical breast examinations **every 6–12 months.**
- Engage in breast self-awareness.
- For women under the age of 25 who had radiation therapy 10 or more years ago, annual clinical breast examination and breast self-awareness are recommended.

EUSOMA‡

- Start screening at **age 30** or **8 years** after completion of radiation therapy, whichever is later. Can discuss risks and benefits of initiating screening at age 25.
- Begin annual breast MRI starting at **age 30.**
- Begin annual mammography starting at **age 35.**
    - Mammography is not recommended before age 35 because of concerns about cumulative diagnostic radiation exposure and subsequent breast cancer risk.
- Clinical breast examinations are **not recommended.**

IGHG[§]

- Start screening at **age 25** or **8 years** after completion of radiation therapy, whichever is later.
- Undergo annual breast MRI, mammography, or both.
    - There is no definitive recommendation because of the lack of evidence for an optimal screening protocol.
- Clinical breast examinations are **not recommended.**

*****Areas of disagreement are highlighted in boldface type.

[†]Data from Bevers TB, Helvie M, Bonaccio E, Calhoun KE, Daly MB, Farrar WB, et al. Breast cancer screening and diagnosis, version 3.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(11):1362–89. doi: 10.6004/jnccn.2018.0083.

[‡]Data from Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48(18):3355–77. doi: 10.1016/j.ejca.2012.10.004.

[§]Data from Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the international late effects of childhood cancer guideline harmonization group. Lancet Oncol. 2013;14(13):e621–9.

Prior Breast Cancer or Ovarian Cancer

Following breast cancer treatment, a patient requires regular clinical follow-up and breast imaging to evaluate for recurrence but still requires screening for second breast malignancies. Both the NCCN and EUSOMA have published guidelines regarding breast cancer screening in this population, but neither specifically addresses screening for a second EOBC in women diagnosed with their first breast cancer before age 46. Both guidelines recommend annual mammography and consideration of breast MRI in high-risk women. Box 2 summarizes these guidelines and indicates areas of disagreement.

Box 2. Comparison of Guidelines for Screening Women With Prior Breast or Ovarian Cancer*

NCCN[†]

- Begin annual mammography starting **6–12 months after completion of radiation therapy.**
- Consider breast MRI if at high risk for second breast cancer (eg, BRCA 1 or BRCA 2 mutation carriers).
- Undergo clinical breast examination every 4–6 months for the first 5 years after treatment.

EUSOMA[‡]

- Begin annual mammography starting at **age 35.**
- Consider breast MRI if at high risk for second breast cancer (eg, BRCA 1 or BRCA 2 carriers).
- Clinical breast examination and screening breast ultrasonography **are not recommended**.

*****Areas of disagreement are highlighted in boldface type.

[†]Data from Goetz MP, Gradishar WJ, Anderson BO, Abraham J, Aft R, Allison KH, et al. NCCN Guidelines insights: breast cancer, version 3.2018. J Natl Compr Canc Netw. 2019;17(2):118–26. doi: 10.6004/jnccn.2019.0009.

[‡]Data from Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48(18):3355–77. doi: 10.1016/j.ejca.2012.10.004.

Summary of Recommendations

HISTORY OF PROLIFERATIVE BREAST DISEASES

Recommend treatment and screening as outlined by the NCCN:

- Radial scars should be excised. Following excision, patient can return to routine screening.
- Women with atypical hyperplasia or LCIS should undergo annual mammography (not before age 30) and clinical breast examinations every 6–12 months. Data are unclear about the benefits of

breast MRI in this population. An annual breast MRI is reasonable to offer, particularly if a patient has other risk factors for breast cancer, such as a strong family history or very young age at diagnosis.

- Currently, pleomorphic LCIS is considered higher risk than classic LCIS, but there are no established guidelines to recommend management distinct from that of classic LCIS.

History of Hormonal Contraception

There are no screening guidelines that specifically address exposure to HC. While it appears as though there is a small increased risk of breast cancer among current and recent HC users, the absolute risk is small, particularly among women under the age of 35. In the absence of other risk factors for EOBC, routine breast cancer screening is recommended for women with a history of HC use.

History of Fertility Treatments

The majority of available evidence does not suggest an increased risk of breast cancer among women exposed to fertility treatments. An increased risk has been suggested in those patients exposed to high cumulative dosages and multiple cycles of CC and those who underwent IVF prior to age 25, but these results have not been confirmed. There are no screening guidelines that specifically address fertility treatment exposure. In the absence of other risk factors for EOBC, routine breast cancer screening is recommended for women with a history of fertility treatments.

History of Chest Radiation

Numerous professional societies have published guidelines regarding breast cancer screening in women with a history of chest radiation. While the guidelines vary slightly, they all recommend a combination of mammography and breast MRI. As such, the following are recommended:

- Initiation of screening 8–10 years after completion of RT
- Annual breast MRI starting at age 25, with consideration of deferring MRI until age 30
- Annual mammography starting at age 30, with consideration of deferring mammography until age 35 if concerned about risk of radiation exposure, though the cumulative diagnostic radiation dose is small compared with the overall radiation exposure from therapeutic chest radiation
- Annual clinical breast examinations
- Breast self-awareness

History of Breast or Ovarian Cancer

Women with a prior history of breast cancer who have not undergone bilateral mastectomy require breast cancer screening, both for recurrence of the first breast cancer as well as development of a second breast cancer. The risk of a second breast cancer is quite low among women without other strong risk factors for breast cancer (eg, BRCA 1 or BRCA 2 mutation), though this risk specifically in young patients with breast cancer is unknown. As such, annual mammography and clinical breast examination every 4–6 months is recommended. Breast MRI is not recommended in the absence of other risk factors.

DISCUSSION

History of Proliferative Breast Diseases

Strengths

There are robust observational data regarding various benign breast lesions and the future risk of breast cancer. Additionally, the NCCN has developed specific guidelines for certain high-risk lesions.

Weaknesses

Because there are numerous subtypes of benign breast diseases, there are not definitive risk associations for each type of breast lesion. More specifically, while pleomorphic LCIS appears to be higher risk than classic LCIS, definitive data regarding the risk magnitude and tailored management recommendations are lacking. Additionally, there are limited data regarding optimal screening strategies, particularly in young women.

Gaps in Information Pertinent to Making Recommendations

There is a significant lack of information regarding the efficacy of breast MRI screening in women with atypical hyperplasia and LCIS. A single retrospective cohort published in 2007 is the basis of current

understanding of breast MRI in this population. More specific to this review, none of the available data specifically address screening in young women with proliferative breast diseases to identify EOBC. Nevertheless, consideration of breast MRI screening is recommended, but data regarding risks, benefits, efficacy, and cost-effectiveness of MRI screening are lacking.

Availability/Quality of Sources

As noted, there are numerous high-quality, case–control and cohort studies evaluating the risk of breast cancer with various benign breast lesions, but data regarding optimal screening protocols are lacking, particularly in young women.

Additional Comments

While from a risk standpoint patients with atypical hyperplasia and LCIS qualify for breast MRI screening (lifetime risk >20%), it is unclear whether they truly benefit from breast MRI in addition to mammography given the lack of data.

History of Hormonal Contraception

Strengths

Hormonal contraception and breast cancer risk has been studied very extensively, but data were previously fairly conflicting. More recently, there has been a clearer delineation of the breast cancer risk among users of OCs and other HCs. In addition to numerous large, population-based studies, there are multiple systematic reviews and meta-analyses on this topic.

Weaknesses

Data are relatively lacking for HC other than OCs. There are multiple studies evaluating LNG-IUS, but very minimal data regarding the DMPA injections or etonogestrel implant. There are no studies available evaluating breast cancer screening and HC use.

Gaps in Information Pertinent to Making Recommendations

After an extensive literature review, there were no data regarding breast cancer screening modalities after HC exposure.

Availability/Quality of Sources

There are numerous very high-quality systematic reviews, meta-analyses, case–control, and cohort studies regarding HC and breast cancer risk. As noted previously, data are relatively lacking for HC options other than OCs.

Additional Comments

Based on the lack of any data regarding breast cancer screening and HC, it appears as though HC users without other risk factors fall into routine breast cancer screening guidelines.

Past or Present Use of Fertility Treatments

Strengths

Breast cancer risk related to fertility treatments has been studied fairly extensively, including multiple meta-analyses and systematic reviews, and ASRM has a published a statement regarding these risks.

Weaknesses

The existing studies are limited by their retrospective nature, lack of long-term follow-up, potential for recall and detection bias, and lack of differentiation between different fertility medications. Additionally, many features of infertility (eg, nulliparity and older age at first delivery) are also independent risk factors for breast cancer, potentially confounding results.

Gaps in Information Pertinent to Making Recommendations

After an extensive literature review, there were no data regarding breast cancer screening modalities in women with a history of fertility treatments.

Availability/Quality of Sources

There are numerous studies evaluating this topic, including a thorough review guideline publication by ASRM.

History of Chest Radiation

Strengths

Chest radiation is a well-established risk factor for breast cancer, and there were numerous well-done studies and systematic reviews evaluating breast cancer incidence. Because of the breadth of data available, multiple health societies have released guidelines for management.

Weaknesses

Despite there being many studies evaluating the effects of radiation on breast cancer risk, there is a lack of data showing survival benefit from intensive surveillance. High-risk breast cancer screening is recommended given the increased risk of breast cancer in this population, but some of the

recommendations are extrapolated from other high-risk groups (eg, BRCA 1 and BRCA 2 mutation carriers).

Gaps in Information Pertinent to Making Recommendations

As noted, there is a lack of data establishing a survival benefit from high-risk screening in this population. While malignancies appear to be diagnosed at an earlier stage with screening, it is unclear whether this translates to survival benefit or just lead-time bias. Additionally, there is evidence that a variety of risk factors (eg, radiation dose, radiation field, family history, and ovarian function) modify the magnitude of risk posed by chest radiation, but these relationships are not well established enough to individualize a patient's screening recommendations.

Availability/Quality of Sources

As noted, there are numerous high-quality systematic reviews, case–control, and cohort studies establishing the risks of breast cancer following chest radiation. Additionally, there are thorough summary guideline reviews available.

Additional Comments

This is a well-studied topic with many guidelines already available.

History of Breast or Ovarian Cancer

Strengths

The two studies included in this section are very well-done multicenter studies.

Weaknesses

There are fairly minimal data establishing the risk of second breast malignancy among patients with a prior history of breast cancer, and there are even fewer data evaluating the risk of a second breast cancer diagnosis prior to age 46. There were no published reports of breast cancer risk following ovarian malignancy in young women.

Gaps in Information Pertinent to Making Recommendations

As noted, there were minimal data on breast cancer risk after breast cancer and no data on breast cancer risk after ovarian cancer. There are no screening recommendations specifically for women with a prior diagnosis of breast cancer without other risk factors, particularly for women under the age of 46.

Availability/Quality of Sources

As noted, the two studies included in this section are well-designed with robust data.

REFERENCES

1. Diagnosis and management of benign breast disorders. Practice Bulletin No. 164. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;127:e141-56.
2. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med 2015;372:78-89.
3. American Society of Breast Surgeons. Consensus guideline on concordance assessment of image-guided breast biopsies and management of borderline or high-risk lesions. Columbia, MD: ASBrS; 2016. Available at: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Concordance-Assessment-of-Image-Guided-Breast-Biopsies.pdf. Retrieved October 21, 2019.
4. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. Breast Cancer Res Treat 2015;149:569-75.
5. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. Nat Rev Clin Oncol 2015;12:227-38.
6. Chuba PJ, Hamre MR, Yap J, Severson RK, Lucas D, Shamsa F, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. J Clin Oncol 2005;23:5534-41.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 29, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

8. Linda A, Zuiani C, Furlan A, Londero V, Girometti R, Machin P, et al. Radial scars without atypia diagnosed at imaging-guided needle biopsy: how often is associated malignancy found at subsequent surgical excision, and do mammography and sonography predict which lesions are malignant? AJR Am J Roentgenol 2010;194:1146-51.
9. Patterson JA, Scott M, Anderson N, Kirk SJ. Radial scar, complex sclerosing lesion and risk of breast cancer. Analysis of 175 cases in Northern Ireland. Eur J Surg Oncol 2004;30:1065-8.
10. Nakhlis F, Lester S, Denison C, Wong SM, Mongiu A, Golshan M. Complex sclerosing lesions and radial sclerosing lesions on core needle biopsy: low risk of carcinoma on excision in cases with clinical and imaging concordance. Breast J 2018;24:133-8.
11. Bunting DM, Steel JR, Holgate CS, Watkins RM. Long term follow-up and risk of breast cancer after a radial scar or complex sclerosing lesion has been identified in a benign open breast biopsy. Eur J Surg Oncol 2011;37:709-13.
12. Rungruang B, Kelley JL 3rd. Benign breast diseases: epidemiology, evaluation, and management. Clin Obstet Gynecol 2011;54:110-24.
13. Meirik O, Lund E, Adami HO, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. Lancet 1986;2:650-4.
14. Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, et al. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev 2010;19:2496-502.
15. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, et al. A case-control study of oral contraceptive use and breast cancer. J Natl Cancer Inst 1984;72:39-42.

16. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346:2025-32.
17. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347:1713-27.
18. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017;377:2228-39.
19. Beaber EF, Malone KE, Tang MT, Barlow WE, Porter PL, Daling JR, et al. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiol Biomarkers Prev 2014;23:755-64.
20. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update 2010;16:631-50.
21. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46:2275-84.
22. Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C, et al. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Hereditary Breast Cancer Clinical Study Group. Breast Cancer Res Treat 2014;143:579-86.
23. Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110-26.
24. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. No. 329-Canadian Contraception Consensus part 4 of 4 chapter 9: combined hormonal contraception. J Obstet Gynaecol Can 2017;39:229-268.e5.

25. Dinger J, Bardenheuer K, Minh TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. Contraception 2011;83:211-7.
26. Jareid M, Thalabard JC, Aarflot M, Bovelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. Gynecol Oncol 2018;149:127-32.
27. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, et al. Progestin and breast cancer risk: a systematic review. Breast Cancer Res Treat 2016;155:3-12.
28. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res 2012;72:2028-35.
29. Sonfield A, Kost K. Public costs from unintended pregnancies and the role of public insurance programs in paying for pregnancy-related care: national and state estimates for 2010. New York, NY: Guttmacher Institute; 2015. Available at: https://www.guttmacher.org/report/public-costs-unintended-pregnancies-and-role-public-insurance-programs-paying-pregnancy. Retrieved October 22, 2019.
30. Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. GBD 2015 Maternal Mortality Collaborators [published erratum appears in Lancet 2017;389:e1]. Lancet 2016;388:1775-812.
31. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. JAMA Oncol 2018;4:516-21.

32. Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. Ann Epidemiol 2015;25:193-200.
33. Fertility drugs and cancer: a guideline. Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2016;106:1617-26.
34. Fei C, Deroo LA, Sandler DP, Weinberg CR. Fertility drugs and young-onset breast cancer: results from the Two Sister Study. J Natl Cancer Inst 2012;104:1021-7.
35. Brinton LA, Scoccia B, Moghissi KS, Westhoff CL, Niwa S, Ruggieri D, et al. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2014;23:584-93.
36. Stewart LM, Holman CD, Hart R, Bulsara MK, Preen DB, Finn JC. In vitro fertilization and breast cancer: is there cause for concern? Fertil Steril 2012;98:334-40.
37. Gynecologic issues in children and adolescent cancer patients and survivors. ACOG Committee Opinion No. 747. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e67-77.
38. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis. V.1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 22, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.
39. Simony A, Hansen EJ, Christensen SB, Carreon LY, Andersen MO. Incidence of cancer in adolescent idiopathic scoliosis patients treated 25 years previously. Eur Spine J 2016;25:3366-70.

40. Haddy N, Dondon MG, Paoletti C, Rubino C, Mousannif A, Shamsaldin A, et al. Breast cancer following radiotherapy for a hemangioma during childhood. Cancer Causes Control 2010;21:1807-16.
41. National Cancer Institute. Breast cancer prevention (PDQ®)–health professional version. Bethesda, MD: NCI; 2019. Available at: https://www.cancer.gov/types/breast/hp/breast-prevention-pdq. Retrieved October 22, 2019.
42. Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 2010;152:44-54.
43. Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013;14:e621-9.
44. Allen SD, Wallis MG, Cooke R, Swerdlow AJ. Radiologic features of breast cancer after mantle radiation therapy for Hodgkin disease: a study of 230 cases. Radiology 2014;272:73-8.
45. Koo E, Henderson MA, Dwyer M, Skandarajah AR. Management and prevention of breast cancer after radiation to the chest for childhood, adolescent, and young adulthood malignancy. Ann Surg Oncol 2015;22(suppl 3):S545-51.
46. Sadler C, Goldfarb M. Comparison of primary and secondary breast cancers in adolescents and young adults. Cancer 2015;121:1295-302.
47. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27:3901-7.

48. Krul IM, Opstal-van Winden AW, Aleman BM, Janus CP, van Eggermond AM, De Bruin ML, et al. Breast cancer risk after radiation therapy for Hodgkin lymphoma: influence of gonadal hormone exposure. Int J Radiat Oncol Biol Phys 2017;99:843-53.
49. Pierce LJ, Levin AM, Rebbeck TR, Ben-David MA, Friedman E, Solin LJ, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437-43.
50. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328-35.
51. Port ER, Park A, Borgen PI, Morris E, Montgomery LL. Results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia. Ann Surg Oncol 2007;14:1051-7.
52. Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77.
53. Terenziani M, Casalini P, Scaperrotta G, Gandola L, Trecate G, Catania S, et al. Occurrence of breast cancer after chest wall irradiation for pediatric cancer, as detected by a multimodal screening program. Int J Radiat Oncol Biol Phys 2013;85:35-9.
54. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso MJ, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast 2017;35:203-17.

