Appendix 10. Risk Reduction for Early Onset Breast Cancer

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INTRODUCTION

This review focused on what interventions may be effective for reducing the risk of early onset breast cancer (EOBC), defined as breast cancer before age 46. To address this issue, the following questions were used to direct a literature search.

1. What interventions (eg, chemoprevention, surgery, health behaviors) are effective for risk reduction in women at risk for EOBC?

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

P: Women aged 18-45 at high risk of breast cancer

I: Medications (eg, tamoxifen, raloxifene, aromatase inhibitors, metformin, nonsteroidal antiinflammatory drugs, statins, deslorelin, and fenretinide), surgery, behavior change

C: Medication versus surgical intervention, medication versus behavior change intervention, surgical intervention versus behavior change intervention, one medication versus another medication, risk reduction intervention versus no intervention

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O: Development of breast cancer before age 46

2. What are the current major society or health services guidelines for risk reduction in women with prior history risk factors for EOBC?

PICO

P: Women aged 18–45 at high risk of breast cancer

I: Medications (eg, tamoxifen, raloxifene, aromatase inhibitors, metformin, nonsteroidal antiinflammatory drugs, statins, deslorelin, and fenretinide), surgery, behavior change

C: Medication versus surgical intervention, medication versus behavior change intervention, surgical intervention versus behavior change intervention, one medication versus another medication, risk reduction intervention versus no intervention

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

METHODS

Using the PICO criteria, ACOG clinical reference staff performed a search in the Cochrane, MEDLINE, and PubMed databases for all relevant references. Additional review was carried out for relevant guidelines published by ACOG, American Cancer Society, NCCN, American Society of Breast Surgeons, Society of Surgical Oncology, American College of Radiology, USPSTF, and American Society of Breast Disease.

Additional relevant publications were identified from the references within the included papers and for subgroup analyses of young patients and short-term cancer incidence.

References were included if they addressed interventions for risk reduction in women aged 18–45 for the purpose of reducing risk of EOBC. They were excluded if they addressed risk in pregnancy, pregnancy-associated breast cancer, male breast cancer, postmenopausal or lifetime risk of cancer exclusively, or were unavailable in English.

RESULTS

The literature review found no guidelines specific to reducing the risk of EOBC. There was one published guideline on general breast cancer risk reduction from the NCCN.[1] A USPSTF recommendation statement on medication to reduce the risk of breast cancer is currently being updated.[2] This statement addresses overall lifetime risk of breast cancer and not EOBC specifically. There were two guidelines for screening recommendations for patients who underwent mantle irradiation, though these guidelines only discussed cancer detection strategies and lifetime risk of breast cancer.[3,4]

The literature review found 128 publications, of which 6 addressed the proposed question. Of these, 2 were Level 1 systematic reviews.[5,6] Four publications were Level 3 evidence reviews.[7–10] Two additional publications were included after review of the references of included papers.[11,12]

After title and abstract review, 109 references were excluded, primarily because they addressed risk reduction among cancer survivors or were about patient decision making regarding health or risk reduction behaviors, risk perception, or screening. An additional 13 references were excluded after full-text review for similar reasons: wrong population (cancer patients, over age 45), wrong outcome (patient decision making, nonclinical measure), or wrong intervention (screening).

What interventions (eg, chemoprevention, surgery, health behaviors) are effective for risk reduction in women at risk for EOBC?

Risk-Reducing Surgery

Risk-reducing bilateral mastectomy should be considered in women with a genetic mutation conferring a high risk of breast cancer.[1] This recommendation is not specific to prevention of EOBC, and there are no guidelines or studies comparing the age at which this surgery should be undertaken. For patients with BRCA mutations, age-related risk estimation tables may be useful to guide and counsel patients on the timing of prophylactic procedures.[13] There is no evidence for age-based recommendations for interventions for lower-risk genes or based on nongenetic risk factors alone.

There is no evidence to support bilateral salpingo-oophorectomy for the purposes of preventing EOBC. The use of bilateral salpingo-oophorectomy to prevent lifetime risk of breast cancer has been estimated to be as high as 50% for BRCA 1 and BRCA 2 carriers, although more recent publications question that these results may be biased to show a larger effect.[14]

Chemoprevention

There are no guidelines or studies for the use of risk-reducing agents (eg, tamoxifen, raloxifene, anastrozole, exemestane) expressly for the purpose of reducing the risk of EOBC.

Tamoxifen is the only agent indicated for use in premenopausal women at increased risk of breast cancer, generally defined as 5-year risk of 1.7% or higher. Tamoxifen is not recommended for women younger than 35 in part because of the risk of birth defects in pregnancy, and the benefit in women younger than 35 is not known.[1] The majority of the large trials in chemoprevention were performed in older women who had completed menopause. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial did enroll premenopausal patients but, notably, for the mean age at enrollment was 47 years. The NSABP P-1 trial found a 44% decrease in cancer among women aged 49 and younger treated with tamoxifen for chemoprevention.[12]

Data are limited regarding the magnitude of risk reduction with the use of tamoxifen for BRCA 1 and BRCA 2 mutation carriers or women with prior thoracic radiation. However, cohort data suggest there may be a benefit for women with BRCA 2 mutations, with the NSABP P-1 study showing a 62% decrease relative to placebo (relative risk: 0.38, 95% confidence interval [CI]: 0.06–1.56).[1,12] While other, European studies have shown mixed effects, this overall reduction is supported by a review of trials showing a 44% decrease in the risk of breast cancer for women younger than 50 across multiple prevention trials (hazard ratio: 0.66, 95% CI: 0.52–0.85).[15]

Health Behaviors

There are no guidelines for health behaviors to reduce the risk of EOBC specifically.

Three studies did analyze other risk factors for BRCA carriers, but none were specific to EOBC.[5–7] A meta-analysis by Friebel et al assessed numerous risk factors for BRCA carriers.[5] Later age at first live birth showed a decreased lifetime risk of breast cancer for BRCA 1 carriers (effect size [ES] for age ≥30 y vs <20 y = 0.65, 95% CI: 0.42–0.99). There was no effect of age at first birth for BRCA 2 carriers. Breastfeeding also appeared to be protective for lifetime risk of cancer for BRCA 1 carriers, though study heterogeneity meant that no meta-analysis could be performed. Reported effects based on case–control studies showed a 32–50% decreased risk associated with breastfeeding lasting longer than 1 year compared with never breastfeeding. Additionally, three or more live births appeared to have a protective effect in meta-analysis for BRCA 1 carriers (ES=0.57, 95% CI: 0.39–0.85) as well as BRCA 2 carriers (ES=0.52, 95% CI: 0.30–0.86) when compared with nulliparity. For BRCA 1 and BRCA 2 carriers, there were no significant or reliably duplicated effects of alcohol consumption, oral contraceptive use, or smoking.[5,6]

In a literature review on breast cancer and alcohol consumption for all women, there was no reliable effect seen of alcohol consumption on premenopausal breast cancer.[11] There is no convincing evidence for a decreased lifetime risk of breast cancer by modification of dietary factors.[8]

What are the current major society or health services guidelines for risk reduction in women with prior history risk factors for EOBC?

There are no guidelines specific to the prevention of EOBC. Those that may be considered relevant address lifetime breast cancer risk reduction, largely among women over age 35.

The NCCN Breast Cancer Risk Reduction Panel recommends tamoxifen, 20 mg per day for up to 5 years, for women age 35 and older with a high 5-year risk of breast cancer (defined as 1.7% or higher in 5 years using the Gail model, or lobular carcinoma in situ).[1] NCCN guidelines advise a healthy lifestyle for reduction of risk for breast cancer, though the magnitude of this reduction and whether it reduces the risk of EOBC or premenopausal breast cancer is unknown.[1] Elements of healthy lifestyle advised by the NCCN include limited alcohol consumption, vigorous physical activity, and breastfeeding.

In its draft recommendations on medication use for the risk reduction of primary breast cancer in women, the USPSTF offered the following:[2]

- Grade B Recommendation: Women at increased risk of breast cancer should engage in shared decision making about the use of risk-reducing medications.
- Grade D Recommendation: Women not at increased risk should not routinely take risk-reducing medications.

DISCUSSION

There is limited evidence for risk modification specific to the outcome of EOBC, and there are no guidelines specific to reducing risk of EOBC. The evidence for risk reduction among younger women is most robust for BRCA mutation carriers. For these patients, there is good evidence that surgical prophylaxis decreases the risk of breast cancer. Among other high-risk women, chemoprophylaxis may be beneficial, though there are no studies or approved medications for use in women younger than age 35. The potential benefits of tamoxifen should be balanced by the lack of data in very young women and its known teratogenic effects, which may necessitate that women taking it delay childbearing. In addition, decreased medication adherence, in part because of side effects, is a known issue in this population, and it merits further study. Finally, many studies do not specifically examine the risk for young women developing breast cancer, which may physiologically develop along different mechanisms or by different exposures than postmenopausal breast cancer.

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