Appendix 8. Tools for Assessing Risk of Early Onset Breast Cancer

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INTRODUCTION

This review focused on validated tools for identifying risk factors or estimating risk for early onset breast cancer (EOBC), or breast cancer onset before age 46. A literature search and review was guided by the following questions.

1. What validated tools or best practices are available for identifying risk factors or estimating risk for EOBC?

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

P: Women aged 18–45

I: Validated risk assessment tools (eg, family history questionnaire, pedigree, Gail model, Breast Cancer Genetics Referral Screening Tool [B-RST], Families Sharing Health Assessment and Risk Evaluation [Families SHARE]) and risk factors (ie, family history, race/ethnicity, overweight/obesity, age at first pregnancy, breastfeeding history, alcohol use, smoking, hormone replacement therapy, lack of exercise, and diet)

C: Women with identified risk factors versus women without identified risk factors

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The authors provided this information as a supplement to their article.

O: Development of breast cancer before the age of 45

2. What are the current major society or health services guidelines for assessing risk factors or estimating risk for EOBC?

PICO

P: Women aged 18–45

I: Guidelines for validated risk assessment tools (eg, family history questionnaire, pedigree, Gail model) and risk factors (ie, family history, race/ethnicity, overweight/obesity, age at first pregnancy, breastfeeding history, alcohol use, smoking, hormone replacement therapy, lack of exercise, and diet)

C: Guidelines from one source versus another source

O: National Comprehensive Cancer Network (NCCN), U.S. Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists (ACOG), American Cancer Society, American College of Radiology, American Society of Breast Disease, American Society of Breast Surgeons, and Society of Surgical Oncology

METHODS

Using the PICO criteria defined, a search was performed in 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.

References were included if they addressed tools for assessing risk in women aged 18–45. They were excluded if they addressed tools for assessing risk in pregnancy, pregnancy-associated breast cancer, or male breast cancer or if they were not available in English.

References from all included papers were reviewed to identify additional relevant publications, and there was a further review of practice bulletins, along with a content review of validated models.

RESULTS

The literature review found no guidelines specific to assessing risk of EOBC. The search turned up 29 publications, none of which addressed the use of tools to assess risk of EOBC. The majority of references (20) from the resulting literature search were excluded after title and abstract review. Of these, nine were not about assessing risk factors, nine were not about cancer development, one was about risk modification, and one addressed tools to assess prognosis after cancer. Full review excluded five more articles. Two of these addressed populations over age 45, one did not examine EOBC, another examined prediction of genetic mutations in cancer patients, and the fifth did not use a validated tool.

Three publications were relevant to the topic but not specific to EOBC. BRCAPRO is an approved statistical program to estimate individual carrier probabilities based on family history. It is not specific to any age category and does not directly estimate the risk of EOBC. Rather, it estimates the risk of carrying a BRCA 1 or BRCA 2 mutation. Antonucci et al's comparison of BRCAPRO versions 5.1 and 6.0 found decreased sensitivity in the 6.0 model but increased specificity for both BRCA 1 and BRCA 2 mutations.[1]

Two studies addressed risk factors that may be associated with the risk of breast cancer, but did not discuss tools for assessment of these risk factors and were retrospective in assessing the risk of premenopausal breast cancer. Farvid et al did see an association with increased red meat consumption in adolescence and increased risk of premenopausal breast cancer in the Nurses' Health Study, but this finding was retrospective and associative.[2] Harris et al similarly looked at proinflammatory diets in adolescence, which were also associated with premenopausal breast cancer.[3]

Additional review of practice bulletins as well as content review of breast-related NCCN guidelines revealed some relevant materials, though none directly addressed the question. Most guidelines were for genetic testing for high-risk genetic lesions.

The NCCN guidelines on breast cancer risk reduction are not specific to the development of EOBC, but do provide guidance on risk assessment for women in general. They recommend assessing family history and referral to genetic counseling when appropriate, as well as use of the Gail or Tyrer-Cuzick models to assess risk for women over age 34.[4] NCCN has also published guidelines to establish criteria for genetic testing for high-risk mutations.[5] These guidelines recommend assessment based on family history not earlier than age 18. No specific tool is recommended, and the recommendations are not specific to reducing the risk of EOBC.

The National Institute for Health and Care Excellence Clinical Guideline 164 on familial breast cancer advises assessment of risk using family history and referral to genetic counselors for formal assessment if familial risk is identified.[6] No specific tool is recommended.

The USPSTF recommendation statement on BRCA risk assessment also advocates that primary care providers screen patients every 5–10 years for family history of BRCA-associated cancers to identify patients for genetic counseling and screening.[7] USPSTF recommends assessing patients starting at age 18 using one of the following validated tools to aid in eliciting a focused family history: the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool (B-RST), Pedigree Assessment Tool, and FHS-7. The USPSTF found insufficient evidence to recommend one tool over another or a risk threshold at which to recommend testing.

To date, ACOG has published two relevant Practice Bulletins and two Committee Opinions on breast cancer risk.[8–11] None are specific to assessing risk of EOBC. All advocate family history assessment to identify those patients at increased risk of genetic mutations in order to direct referral for genetic testing.

There are multiple published validated tools for assessing the risk of breast cancer or BRCA mutation. The three most widely used tools for assessing BRCA risk are BRCAPRO, BOADICEA, and Penn II. BRCAPRO and BOADICEA also provide cancer risk estimates. These models may be useful to stratify women at increased risk of genetic mutations correlated to high-risk of early onset disease, to direct genetic testing and counseling. Additional widely validated models to assess cancer risk include the Tyrer-Cusik, Gail, and Breast Cancer Surveillance Consortium models. None specifically assess risk of EOBC or premenopausal breast cancer, although most provide 5- or 10-year cancer risks as well as lifetime risks of breast cancer. Of note, no models used validation cohorts with patients younger than age 20. The Gail model is not validated for use in patients below age 35. The Stanford risk assessment

tool for BRCA carriers may help aid in decision making for preventive measures based on risk assessment.[13]

Based on these findings, the following recommendations can be made:

What validated tools or best practices are available for identifying risk factors or estimating risk for EOBC?

There are no validated tools or best practices specific to identifying risk factors or estimating risk of EOBC, but there are multiple tools that may be helpful to identify short-term risk in younger patients.

Family history should be collected and updated to identify those patients who may be at increased risk of predisposing genetic mutations. Tools that may aid in collecting family history are the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool (B-RST), Pedigree Assessment Tool, and FHS-7. There is no evidence to recommend one method over another. Patients who screen positive or who meet published guidelines for qualifying family histories should be referred for genetic counseling and testing.[5]

Breast cancer risk assessment tools may be considered to assess short-term risk in young patients. Use of the Gail model may be considered in women 35 and older to assess 5-year cancer risk. The use of the Tyrer-Cusik model may be considered in women over age 20 to assess 10-year cancer risk. The Breast Cancer Surveillance Consortium risk calculator may be used for women older age 35 to provide 5- and

10-year risks and includes breast density in the calculation.[12] There are limited data on the use of these models to specifically address cancer risk reduction in young women.

What are current major society or health services guidelines for assessing risk factors or estimating risk for EOBC?

There are no guidelines or best practices for identifying risk factors or estimating risk of specific to EOBC. Three entities—ACOG, USPSTF, and the National Institute for Health and Care Excellence—recommend assessment of family history as part of routine care. These assessments should be updated regularly to identify patients who may be at risk of predisposing genetic mutations. The USPSTF advocates use of either the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool (B-RST), Pedigree Assessment Tool, or FHS-7 to screen for patients who may benefit from genetic counseling and testing. The USPSTF recommends screening patients every 5–10 years for BRCA-related cancers. Other organizations do not advocate use of any specific tool.

DISCUSSION

There are no published tools nor any guidelines specific to assessing the risk of EOBC. Current best practices aim to identify patients at risk of familial cancer syndromes based on family history, to direct genetic testing. There are numerous validated models to assess the risk of breast cancer, but these are not specific to early onset of disease, nor have they been validated for patients at very young ages.

Strengths

The strengths of this review are the comprehensive nature of the evidence review and guideline review.

Weaknesses

The weaknesses of this review are the relative lack of evidence in this area to inform recommendations. There are no tools specific to the assessment of risk for EOBC.

Gaps in Information Pertinent to Making Recommendations

Additional research is needed to develop tools specific to assessing the risk of EOBC. Many risk factors in the current models include factors not relevant to young women, such as age of menopause. Additionally, the risk factors for developing premenopausal breast cancer may be different and may not be adequately captured in these existing models, which were validated in largely older populations with longer lifetime risk horizons.

REFERENCES

1. Antonucci I, Provenzano M, Sorino L, Balsamo M, Aceto GM, Battista P, et al. Comparison between CaGene 5.1 and 6.0 for BRCA1/2 mutation prediction: a retrospective study of 150 BRCA1/2 genetic tests in 517 families with breast/ovarian cancer. J Hum Genet 2017;62:379-87.
2. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Adolescent meat intake and breast cancer

risk. Int J Cancer 2015;136:1909-20.

3. Harris HR, Willett WC, Vaidya RL, Michels KB. An adolescent and early adulthood dietary pattern associated with inflammation and the incidence of breast cancer. Cancer Res 2017;77:1179-87.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Risk Reduction. V.1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 12, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 22, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.
6. National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical Guideline CG164. London, UK: NICE; 2017. Available at: https://www.nice.org.uk/guidance/cg164/evidence. Retrieved October 22, 2019.
7. U.S. Preventive Services Task Force. BRCA-related cancer: risk assessment, genetic counseling, and genetic testing. Final Recommendation Statement. Rockville, MD: USPSTF; 2019. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing1. Retrieved October 23, 2019.
8. Breast cancer risk assessment and screening in average-risk women. Practice Bulletin No. 179.

American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e1-16.

9. Family history as a risk assessment tool. Committee Opinion No. 478. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:747-50.
10. Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110-26.
11. Hereditary cancer syndromes and risk assessment. Committee Opinion No. 634. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;125:1538-43.
12. Vachon CM, Pankratz VS, Scott CG, Haeberle L, Ziv E, Jensen MR, et al. The contributions of breast density and common genetic variation to breast cancer risk. J Natl Cancer Inst 2015;107:10.1093/jnci/dju397.
13. Kurian AW, Munoz DF, Rust P, Schackmann EA, Smith M, Clarke L, et al. Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 2012;30:497-506.

