commentaries

Reducing Breast Cancer Incidence and Mortality: Rethinking an Approach to Risk Assessment and Prevention

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A comprehensive approach to breast cancer prevention encompasses individualized risk assessment and implementation of risk-reduction strategies, which include lifestyle modification, preventive endocrine medications, surveillance breast imaging, genetic counseling and testing, and for those with a hereditary breast cancer mutation, consideration of risk-reducing surgery (mastectomy and/or salpingo-oophorectomy). Recent agency guidelines promote preventive endocrine medications (selective estrogen receptor modulators, and aromatase inhibitors [AIs]) that are shown to reduce development of favorable, hormone receptor–positive cancers but have not affected breast cancer–related mortality.[1]

In the article that accompanies this editorial, Chlebowski et al[2] propose a reexamination of breast cancer risk-reduction strategies incorporating a low-fat diet dietary modification and consideration of use of oral conjugated equine estrogen (CEE) to reduce breast cancer mortality. The authors discuss the results of two large randomized trials, the Women's Health Initiative (WHI) Dietary Modification randomized trial and WHI randomized trial with CEE alone in women with prior hysterectomy, both of which demonstrated a reduction in breast cancer mortality.[3,4]

Advances in our understanding of tumor biology and breast cancer prognostic categories demonstrate how more favorable hormone receptor–positive (estrogen receptor [ER]–positive and progesterone receptor [PR]–positive) breast cancers are associated with a lower mortality as compared with less favorable tumor biology, such as ER-positive and PR-negative or triple-negative tumors, which have a poor prognosis.[2] To date, breast cancer prevention trials that evaluated the benefit of tamoxifen and AIs (exemestane and anastrozole) have not been powered to assess breast cancer mortality and only showed reductions in breast cancer incidence of the favorable, hormone receptor–positive breast cancers.[5] Long-term follow-up of the tamoxifen prevention trials showed a higher breast cancer–related mortality in the tamoxifen group despite a reduction in breast cancer incidence.[6]

On the basis of available observational studies, the benefits of dietary modification on breast cancer risk has been unclear. However, results from the well-designed, randomized WHI Dietary Modification (DM) Trial demonstrated that after a 19.6-year follow-up, nutrition matters and that a low-fat dietary lifestyle with an increase in vegetables, fruits, and grains reduces breast cancer mortality among postmenopausal women.[7] There was also a significant reduction in worse-prognosis ER-positive PR-negative breast cancer occurrence in the low-fat dietary intervention arm. Metabolic syndrome is associated with a higher risk of breast cancer. In a subgroup analysis in the WHI DM Trial, there was a lower incidence of metabolic syndrome and lower mortality in the low-fat intervention arm.[7-9]

In the WHI randomized trial of CEE versus placebo in postmenopausal women with prior hysterectomy, CEE alone significantly reduced incidence of poor-prognosis (ER-positive, PR-negative) breast cancer. There was also an observed reduction in breast cancer–related mortality (hazard ratio, 0.6; 95% CI, 0.37 to 0.97; $P = .04$).[4] The relationship of menopausal hormone therapy (HT) and breast cancer risk is complex and likely depends on many factors including type, dose, and formulation of HT and patient factors including, but not limited to, lifestyle, genomics, and epigenetics. The WHI CEE-alone trial findings refute the notion that all HT increases the risk of breast cancer for all women. In fact, high-dose estrogen had previously been used to treat hormone-dependent breast cancer in menopausal women before introduction of tamoxifen.[10] Further study is needed to determine optimal estrogen formulation, dose, duration, and target population as breast cancer prevention modalities. Meanwhile, clinicians should individualize their treatment plans through shared decision making for symptomatic women in menopause for example, those < 60 years and within 10 years of their final menstrual period, as it relates to HT treatment.[11]

Since most patients are likely seen in a busy primary care clinical practice, there is a need for easily accessible, efficient, and accurate personalized risk assessment tools. Currently available computerized risk calculation tools have limitations in their ability to provide population-based risk assessment and, as

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Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 5, 2021 and published at ascopubs.org/journal/op on September 7, 2021: DOI https://doi.org/10.1200/OP.21.00551

highlighted by the article, are not capable of estimating risk of breast cancer–related death. In fact, data from the Breast Cancer Surveillance Consortium showed that women with lower 5-year risk estimates of breast cancer on the basis of the BRCAT tool actually had higher breast cancer mortality.[12] Enhancements to current tools that incorporate lifestyle factors, medication use, family history, and reproductive risk factors would not only estimate risk for breast cancer but also potentially identify those more likely to develop a poor-prognosis breast cancer. Additionally, such tools may help to improve compliance and uptake of risk-reducing strategies.

It is prudent that the goals of personalized risk assessment prioritize improved uptake of known strategies that not only reduce the risk of breast cancer occurrence but also reduce breast cancer mortality. It is critical to partner with our patients and asses for barriers to implementation, hence the importance of taking into account social determinants of health especially motivation centered around dietary change. Furthermore, effective education of clinicians to empower them to counsel patients regarding the various risk-reducing strategies thus allows women to make informed choices to manage their risk and feel confident about lifestyle changes and to improve uptake of preventive medications. We need to swiftly start studying the impact of CEE or estrogen alone in eligible patients as a new risk-reducing pharmacologic agent.

How do clinicians implement dietary modification in the day-to-day lives of patients to ensure compliance? The way forward includes not only counseling patients but also empowering them to be advocates for their own health and providing them with practical tools such as mobile technology to assist with implementing lifestyle modifications. The use of mobile technology is a highly effective form of digital support that can be individualized and taken directly to the patient; however, it may not be generally available.

When counseling patients regarding a low-fat diet, one should take into consideration the numerous components that affect a person's ability to enact these changes. Additionally, socioeconomic factors such as access to affordable fresh fruits and vegetables should be considered and prioritized when forming public health policy. Once patients have been informed of the mortality reduction, it would benefit both the clinician and the patient to partner with dieticians (who likely in turn should be educated about the mortality benefit) to consider health coaching and other ongoing encouragement of patients to achieve and maintain their lifestyle goals.

Breast cancer prevention strategies continue to evolve with advances in research resulting in newer polygenic profiles to improve breast cancer prediction. Ongoing studies are exploring the impact of single-nucleotide polymorphisms, also known as single-nucleotide variants, in the clinical setting to estimate the polygenic breast cancer risk and revolutionize personalized risk assessment.[13] We have previously shown that after being informed about their personalized risk on the basis of polygenic risk score, women at increased risk for breast cancer were more likely to use endocrine preventive medication.[14] Future trials may demonstrate that polygenic risk scores may not only improve adherence to pharmacologic risk-reduction strategies but potentially improve compliance with a risk-free, low-cost intervention that saves lives, a low-fat diet.

The time has come to pivot and make an impact, but there is much work to be done. Development and validation of practical risk assessment tools for the busy primary care clinicians should not only incorporate risk factor input for reduction in breast cancer risk of both favorable and unfavorable tumor types but also, given the evolving knowledge, emphasize reduction in breast cancer mortality as an important end point. Updating agency breast cancer prevention guidelines with a comprehensive approach that incorporates healthy lifestyle modifications with low-fat dietary recommendations and interventions and pharmacologic options including preventive endocrine therapy or CEE in the research setting can not only reduce breast cancer incidence but also most importantly reduce breast cancer–related mortality. Further research is needed to determine, in addition to low-fat diet and other lifestyle modifications, which pharmacologic option (selective estrogen receptor modulators, AI, or CEE) would provide a net benefit to the patient.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/op.21.00551.

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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Leadership: Abbott
Stock and Other Ownership Interests: Abbott, Abbvie, Becton Dickinson, Illumina
Research Funding: Mytonomy-partnership

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No other potential conflicts of interest were reported.