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Current controversies in breast cancer screening

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ABSTRACT

Multiple large-scale, randomized controlled trials throughout the world have demonstrated screening mammography significantly reduces a woman's risk of dying from breast cancer. Despite the known mortality reduction, the perceived harms of mammography are weighed against the known value. Multiple national guidelines have moved away from recommending all women have annual screening mammograms beginning at age 40. Instead, many now encourage women at average risk for developing breast cancer to engage in shared decision-making with their providers, carefully weighing the perceived harms against the known benefits of mammography. These factors should be incorporated into the decision about when to begin and how often to screen. This paradigm shift has been particularly controversial as it relates to women in the 40–49-year age group, considering their incidence of breast cancer and therefore derived benefit of screening is lower, yet the breast cancers that do occur tend to be more aggressive and often require intensive therapy. Thus, debates ensue over the appropriate age at which to begin screening for breast cancer, how often screening should occur, and when to stop.

Introduction

Breast cancer remains the most prevalent nonskin cancer affecting American women. In 2019, an estimated 268,600 women will be diagnosed with invasive cancer, and 41,760 will succumb to their disease [1]. Since the implementation of widespread breast cancer screening programs in the early 1980s, multiple studies have reported a decrease in breast cancer mortality rates [2-8]. Such decreases are largely attributed to early detection and advances in breast cancer therapies [9,10]. As with any screening program, the primary goal of screening mammography is to detect preclinical disease, thereby decreasing need for more invasive treatments, and ultimately improve survival. Multiple key organizations in the United States, including the US Preventive Services Task Force (USPSTF) [10], American Cancer Society (ACS) [11], National Comprehensive Cancer Network (NCCN) [12], American College of Obstetricians and Gynecologists (ACOG) [13], and American College of Radiology (ACR) [14] all fundamentally acknowledge the life-saving benefits of routine screening mammography. In recent years, however, we have seen a divergence in breast cancer screening recommendations for average risk women. Although there is little question about how screening mammograms benefit women, much discussion centers around whether or not such frequent screening outweighs the perceived harms associated with mammography. Considering most recommendations now encourage women to engage in shared decision-making with their providers and to make decisions based on individual patient preferences and values, the expectation is that providers will have a clear understanding of those benefits and harms, and will be able to reference current recommendations to guide their discussions. The purpose of this paper is to clearly outline the benefits and harms of screening mammography for women at average risk of developing breast cancer, and summarize the discrepancies in current guidelines.

Determination of risk

This commentary specifically addresses the screening recommendations for patients considered to be at average risk (lifetime risk for breast cancer is 20% or less), particularly since a majority of women who ultimately develop invasive breast cancer fall into this average risk category. Screening recommendations for high-risk patients are more stringent and beyond the scope of this paper. As outlined in the NCCN breast cancer screening guidelines [12], the specific factors which increase a patient's risk include (1) known genetic predisposition, especially genetic carriers of BRCA1/2; (2) strong family history even in absence of known genetic mutation (particularly affecting a mother, sister, or daughter); (3) personal history of breast cancer; 4) lifetime risk greater than 20% based on biopsy showing lobular carcinoma in situ or atypia (includ-

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ing atypical ductal and/or atypical lobular hyperplasia); (4) lifetime risk 20% or higher as defined by risk assessment models that are largely dependent on family history; and (5) prior history of chest or mantle radiation at or before age 30. For average risk women, age is the most important risk factor as breast cancer incidence increases steadily with age [11], explaining why age to initiate screening is often at the center of screening debates. An assessment of a woman's breast cancer risk should be initiated prior to age 40, in order to ensure she follows a screening regimen that is appropriate for her risk stratification. [11].

Benefits

The single most important benefit of screening mammography is the reduction in rates of breast cancer mortality, which vary depending on the study type and the population studied (ie, those invited to screen vs actually screened.) Three separate meta-analyses of randomized clinical trials demonstrated a statistically significant 18%–20% reduction in mortality, among those women who were invited to screen [2-4]. Similarly, in meta-analyses of both cohort and case-control studies, the EUROSCREEN Working Group reported reductions in mortality ranging from 25-31% in 50–59-year-old women invited to screen, and 38%–48% in those who were actually screened [5]. The EUROSCREEN Working Group also showed estimates of mortality reduction ranging from 28 to 36% in trend studies [5-8]. Finally, the Cancer Intervention and Surveillance Modeling Network has developed detailed models predicting the benefits and risks of breast cancer screening depending on when screening starts and how often it occurs [15-17]. The mean reduction in mortality across all models is 15%, with the greatest reduction (39.6%) realized in the model initiating annual screening at age 40 [15-18].

Although not discussed as often, it is important to consider several additional benefits of screening mammography beyond the reduction in mortality. First, studies have shown patients who have regular screening mammograms are more likely than women who do not screen to have breast conservation, and are less likely to need chemotherapy [19-24]. This has important implications for the patient's physical health in that treatments are far less intensive, resulting in less toxicity, faster recovery, and fewer overall long-term comorbidities. Second, it is also important to consider the benefit of screening as it relates to asymptomatic patients who have high-risk lesions (eg, atypical ductal hyperplasia) detected at screen. Knowing this element of their breast history allows women to engage in meaningful conversation with their providers about risk reduction and future management of their breast health [25-28].

Harms of screening

Most societies making recommendations about breast cancer screening consider overdiagnosis one of the most important harms related to screening mammograms. Overdiagnosis refers to the potential for over detection of disease in asymptomatic women who are screened, which ultimately leads to overtreatment; in other words diagnosing and treating breast cancer that would otherwise not threaten a woman's health or longevity. Unfortunately, our ability to precisely predict which cancers remain indolent and which will progress and become potentially lethal is limited at best. Until we are able to do so, the appropriate course of action is to detect and treat all breast cancers as early as possible. Overdiagnosis largely describes diagnoses of ductal carcinoma in situ (DCIS), as there is little evidence to suggest that overdiagnosis exists in cases of invasive breast carcinoma [4,29]. Research has shown that 20%–50% of patients with untreated DCIS later advance to invasive disease [30-32], leaving room to speculate that overdiagnosis likely applies to only certain subsets of DCIS [4,29]. True rate of over detection is multifactorial and therefore varying rates are reported in the literature, ranging from less than 5% to more than 50% [4,11,29,33-48]. This is often dependent on study design, whether or not DCIS is included in the estimate, background incidence, length of follow-up, and patient age.

A second harm of screening mammography is the risk of recall for additional imaging of a finding that is otherwise normal or benign tissue. These screening results, also known as "false positives," are considered harmful because they result in additional diagnostic imaging, and possible benign breast biopsies, all potentially at increased cost to the patient. Many argue such false positive results can also lead to short-term patient anxiety. However, studies have shown women who had false positive results generally continue to support screening mammography, with no long term adverse health effects [49-60]. Women also considered false positive results an acceptable consequence of screening mammograms if it meant earlier detection of disease [61-62].

Estimates of recall rates for a woman of any age after a single screening mammogram range from 9.6% to 11.6% [63-66]. A number of factors contribute to elevated recall rates, most notably increased breast density which occurs more frequently in the 40–49 age group [10,67]. Other factors include lack of comparison imaging (or baseline mammograms), use of postmenopausal hormone therapy (which in turn increases density), longer duration between screening exams, and use of digital versus screen film techniques [68-69].

Radiologists are well aware of the potential for false positives at screening mammography, and screening recall rates as well as cancer detection rates for each radiologist are routinely monitored as a requirement of the Mammography Quality and Standards Act [70]. High-quality screening should therefore be emphasized, with attention to appropriate levels of sensitivity and specificity such that women without cancer are less frequently recalled from a screening exam. This concept is addressed through improvements in screening techniques. Digital breast tomosynthesis (DBT), a 3-dimensional mammogram image acquisition, is an advancement in breast imaging technology that has revolutionized the approach to screening.

In DBT, the mammogram unit obtains multiple sequential images of a woman's compressed breast over an arc of acquisition, allowing improved visualization of cancers and lessening the impact of overlapping breast structures [71]. With increased utilization of DBT the impacts of this technology are 2-fold. First, minimized overlapping breast tissue decreases the likelihood of a false positive exam. Large scale screening studies with DBT have shown decreased recall rates of 15%–17%, compared to 2D mammography alone [72]. Second, incremental cancer detection rate is improved by 1.2–2.7 per 1,000 women with DBT [72]. In fact, a 40%–41% increase in invasive cancer detection was reported in the U. S. Multicenter and Oslo trials [73]; importantly, this was without increased detection of DCIS thus respecting increasing concerns of overdiagnosis at screening. DBT therefore successfully addresses two primary criticisms of mammography, by simultaneously decreasing false positive exams while increasing cancer detection rates. These benefits have been shown in women of all breast densities, not exclusively those in a dense tissue category [71].

Role of breast density in the screening controversy

While the topic of breast density is vast and continues to gain public awareness, a conversation about the breast cancer screening controversy would be incomplete without briefly discussing its impact. Dense breast tissue is not uncommon. In fact, approximately 50% of American women who undergo screening are de-

scribed as having either heterogeneously or extremely dense breast tissue [15]. Dense breast tissue is problematic because it can obscure a cancer on mammograms, and therefore decrease cancer detection rates and exam sensitivity. The sensitivity of mammography is 85.7%-88.8% in fatty tissue, dropping to 62.2%–68.1% in extremely dense tissue [75]. Advancements such as replacement of film screen with digital mammography and the implementation of DBT, have improved cancer detection overall, particularly in patients with dense breast tissue [72]. This is increasingly important as there is now evidence to suggest that dense breast tissue in and of itself is a relative risk factor for developing breast cancer [74]. Compared to women with fatty or scattered fibroglandular tissue, women are 1.2 times likely to develop breast cancer if they have heterogeneously dense tissue, and 2.1 times likely if their tissue is extremely dense [75].

Contributing to the screening controversy are competing opinions about the implications of breast density and what, if any, supplemental screening should be offered to women with dense tissue. There are currently no specific separate screening recommendations for women classified as having dense tissue. For women considered to be at average risk of breast cancer, supplemental screening with alternative modalities such as whole breast ultrasonography, contrast enhanced breast MRI, and molecular breast imaging, is not currently recommended by any of the major organizations. Incremental cancer detection with these supplemental modalities comes at a cost of increased false positive exams, and to date there is a lack of randomized trial data to show that adding supplemental testing to mammography saves more lives.

When to start and how frequently: The center of the controversy

There has been increasing support for patients and their providers to engage in shared decision making when determining the best time to initiate screening, and how often it should occur. Such conversations between a patient and her provider should include discussion about her individual risk for breast cancer, the likelihood a mammogram will detect a cancer in her breast, her risk of false positive results and its related impacts, and the delicate balance between benefits and harms in the context of her preferences, experiences, and priorities. This shared decision making between providers and patients is now a fundamental theme among most societies' guidelines.

Historically, national guidelines were unanimous in their recommendations for women at average risk of breast cancer to initiate screening at age 40, essentially supporting the premise that ***any*** reduction in mortality was worth the harms associated with screening. Key organizations in the United States including the USPSTF [10], ACS [11], NCCN [12], ACOG [13], and ACR [14] all still fundamentally acknowledge the life-saving benefits (ie, mortality reduction) of routine screening mammography. Despite intrinsic differences between their screening guidelines, these organizations all agree there is plenty of evidence showing maximum mortality reduction and years of life gained are achieved when mammographic screening begins at age 40 [10-14]. The Pan-Canadian Mammography Study, one of the largest studies of mammography screening to date, found a 40% reduction in mortality, which was similar across all age groups, including those in their 40s [76]. Hendrick and Helvie also published data showing that annual screening starting at age 40 saves approximately 6,500 more lives each year than those who recommend initiating screening at age 50 and screening every other year [77]. Recommendations to begin screening at age 40 are further supported by the Cancer Intervention and Surveillance Modeling Network models which show there is greater reduction in mortality when screening starts at age 40 rather than 45 or 50 and most lives lost due to a breast cancer diagnosis occur in women in their 40s [16,17]. Webb et al showed that 70% of the women who died from breast cancer after being diagnosed in their 40s were among the 20% who were not getting screened [78]. Finally, research has repeatedly shown breast cancer diagnosed in younger patients tends to be more aggressive suggesting more deaths could be avoided with more frequent screening of this population [79-82]. This clearly underscores the overall goal of mammography—to diminish morbidity and mortality through early detection of disease.

Differences between the various organizations' recommendations are largely driven by the perceived harms of mammography, which as a screening tool is not without its documented limitations, as are detailed in the above paragraphs. Controversy surrounding breast cancer screening notably arose in November 2009, when the USPSTF withdrew its unconditional support for mammographic screening in women ages 40–49 [10], inciting a media frenzy and spawning a plethora of both new research and retrospective reviews of screening data. Instead of recommending all women begin screening at age 40, the USPSTF now urged women and providers to weigh the relatively rare but clearly important benefits (if considering only mortality reduction) against the more common, but seemingly less significant harms (eg, false positives) of screening in the context of individual patient preferences. They also changed from annual to biennial screening for those in the 50–74 age group [10]. Other national societies soon followed suit. The ACS conducted a systematic review in 2015, now recommending annual screening for those between 45 and 55 years. Women younger than 45 and older than 55 are encouraged to use shared decision making when deciding when to start and how often to screen [11]. ACOG updated their guidelines in 2017, now recommending providers offer their patients the opportunity to begin screening mammography at age 40. They also recommend women have screening mammograms every 1–2 years, until they are at least age 75. As with other national guidelines, they too strongly endorse shared decision making when deciding when to start screening and how often to screen [13]. In contrast, the NCCN [12] and ACR [14] seek to maximize the benefits afforded by routine screening, as both continue to support annual mammography beginning at age 40.

Conclusion

Navigation of the current breast cancer screening guidelines requires synthesis of varying recommendations and bodies of evidence. The determination of when to begin screening, how frequently it should occur, and when to stop screening, should be based on a patient's overall risk assessment as well as her personal health care goals. While the number of breast cancer deaths is certainly an important metric in the screening debate, it has been proposed that the toll experienced by women and their families also be incorporated into the overall calculus of when, and how frequently, screening should occur [83]. Factors such as life-years lost and quality adjusted life-years have been described to quantify those societal impacts. With intentions of incorporating these important aspects of the breast cancer burden, several organizations including the USPSTF, ACS, and ACOG support shared decision making between women and their health care providers. In order to allow women to make informed decisions about their health, these conversations should include a dedicated breast cancer risk assessment, highlight the goals and benefits of screening, and also summarize the perceived harms. Collective discussions of when to stop screening should also be conducted, accounting for a patient's overall health status and life expectancy.

Declaration of Competing Interest

The authors have no conflict of interest disclosures.

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