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To screen or not to screen older women for breast cancer: a conundrum

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More than 50% of new invasive breast cancer cases diagnosed each year in the USA occur among women aged 65 years and older (hereafter referred to as ‘older’ women), and rates rise dramatically with advancing age [101]. With the increasing life expectancy and aging of women in the USA and worldwide, the absolute number of breast cancer cases among older women is expected to increase substantially over the coming decades. These dual demographic and epidemiologic forces, coupled with heterogeneity in health and the lack of direct evidence for screening effectiveness among older women, create a clinical and policy conundrum: what is the optimal upper age limit and screening frequency for which the balance of benefits and harms continues to favor ongoing screening? [1,2]. Apparent age-related differences in tumor biology, variations in women’s preferences for health outcomes associated with breast cancer screening, and increasing healthcare costs add to the challenge in answering this question [2,3].

The uncertainty regarding the frequency and the upper age limit to stop offering screening mammography is reflected in breast cancer screening guidelines. The US Preventive Service Task Force updated its guidelines in 2009 to extend biennial screening mammography for women from 69 to 74 years of age, but concluded that there was insufficient evidence for or against screening after the age of 74 years [4]. By contrast, the American Cancer Society

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recommends annual screening mammography and does not define an upper age limit except for indicating the importance of considering women's 5-year life expectancy [5]. Guidelines in the majority of European countries set an upper age limit at 70 or 74 years [6].

There is no direct evidence to suggest an improvement in life expectancy or deaths averted from breast cancer among screened women aged 70 years and older. Robust evidence regarding the efficacy of screening mammography from randomized controlled trials in older women is lacking [7]. The results of the Swedish Two-Country trial, the only mammography screening trial that included women up to 74 years of age, did not show a significant reduction in breast cancer mortality (relative risk: 1.12; 95% CI: 0.73–1.72) in a subgroup analysis of women aged 70–74 years screened every 24–33 months, compared with those not offered screening mammography [8]. Although observational data suggest that regular screening mammography may be associated with lower 5-year breast cancer-specific and overall mortality among older women, these results must be interpreted with caution since observational data are prone to lead-time and length biases [9,10]. Results from collaborative modeling of screening in the USA that incorporate population-based breast cancer incidence and mortality information from the SEER program, and US population-based mammography outcomes from the Breast Cancer Surveillance Consortium estimate approximately two additional breast cancer deaths are averted and 22 life years gained per 1000 women screened by continuing biennial screening mammography from 70 to 74 years of age [11]. Continuing screening another 10 years from 74 until 84 years of age could yield a similar magnitude of benefits, although the underlying data upon which these results are based are more uncertain [11].

Important potential, immediate harms of mammography at any age include false-positive mammography and biopsy results, and over-diagnosis and treatment. False-positive mammography rates decrease slightly with age [12]. Still, the risk of false-positive tests is primarily influenced by the frequency of mammography, with almost double the risk of false-positive tests with annual versus biennial screening [11,13]. Specifically, the cumulative probability of a false-positive mammogram after 10 years of screening is higher among annual than biennial screeners: 48.0% (95% CI: 46.1–49.9) of annual screeners aged 66–74 years compared with 29.0% (95% CI: 28.1–29.9) among biennial screeners [13]. When extrapolating this result to the estimated 19.2 million US women aged 66–89 years, annual instead of biennial mammography could result in approximately 3.86 million additional false-positive examinations and 1.15 million additional unnecessary biopsy recommendations [14]. Results from a Markov microsimulation model has demonstrated that risk-based screening could potentially improve the balance of benefits versus harms among older (as well as younger) women, where low-risk women could stop screening or continue to be screened at longer intervals, thereby reducing false-positive results [15,16]. That such an approach could be safely adopted is suggested by the results of a recent US study demonstrating that biennial versus annual mammography does not appear to increase the risk of advanced tumors and lowers the rates of false-positive results among women aged 66–89 years [13]. Risk-based screening that incorporates longer screening intervals may be a more effective approach to improving the balance of benefits versus harms than switching from plain-film to digital mammography, which has not benefited the older population in terms of reducing false positives or downstaging disease, but added costs to the Medicare program [3].

Overdiagnosis and treatment is a major harm of screening at all ages [17]. Overdiagnosis is defined as detection of invasive cancer or ductal carcinoma *in situ* by screening that would not become clinically apparent during a woman's life or would not affect overall survival. Given the steep rise in competing causes of mortality in women older than 74 years, rates of over-diagnosis are probably greater for older women [11,18]. For example, ductal carcinoma

in situ incidence per 10,000 screened women aged 69–74 and 75 years and older is 14.0 and 15.4 and among nonscreened women is 3.8 and 2.3, respectively, indicating the potential for overdiagnosis is much greater in screened women [18]. Evidence regarding the impact of competing mortality, health status and functional limitations on screening mammography outcomes is largely derived from observational and modeling studies. Mandelblatt *et al.* used modeling to examine hypothetical cohorts and demonstrated that benefits of biennial screening in terms of life years saved were important for older women with mild hypertension, but were substantially lower for those with congestive heart failure [19]. For women aged 85 years and older with or without comorbidities, the short-term anxiety and discomfort associated with screening and false-positive tests outweighed any potential benefits [19]. A recent analysis of Medicare claims data defined comorbidities as either 'unstable' (life-threatening or difficult to control) or 'stable' (potential to affect daily activity) for breast cancer patients in the 2 years before mammography. The results indicate that overall rates of advanced-stage breast cancer are lower among women with no comorbidities than among those with stable or unstable comorbidities [20]. A better understanding of the extent to which comorbidity serves as a marker for healthcare contact and which specific comorbid conditions increase risk of more (or less) aggressive disease via biological pathways would inform screening strategies for older women. For example, conditions such as diabetes may increase the risk of more aggressive tumors, but may also increase the risk of death from nonbreast cancer causes. On balance, screening might not affect breast cancer-specific mortality among women with diabetes. This is an important area for future investigation.

Communication of potential benefits and harms to older women poses a formidable challenge given the limited state of knowledge. Clinical decisions regarding undergoing mammography in older populations may benefit from adopting life expectancy-based screening strategies. A recent meta-analysis of survival data from population-based, randomized, controlled trials comparing populations screened and not screened for breast cancer demonstrated that it took 10.7 years (range: 4.4–21.6) on average before one death from breast cancer was prevented for 1000 women screened. The authors concluded that screening for breast cancer should be targeted to women with a life expectancy greater than 10 years [21]. If confirmed, primary care providers might consider the use of tools that provide estimates of women's risk of 10-year mortality [22] to facilitate informed decisions regarding screening older women. A prognostic tool developed by Cruz *et al.* based on data from the Health and Retirement Survey, a nationally representative cohort of community-dwelling US adults older than 50 years of age, estimates 10-year mortality based on age, gender, tobacco use, BMI, diabetes, noncutaneous cancer, chronic lung disease, heart failure, difficulty bathing, difficulty managing finances, difficulty walking several blocks and difficulty pushing/pulling objects [22]. For example, 10-year mortality rates ranged from 2.3% (95% CI: 0.7–3.8) among individuals with a risk score of 0 (example: women aged <60 years without diabetes, heart failure or cancer, without functional limitations, no current tobacco use and with a BMI >25 kg/m^2) to 93% (95%CI: 90–96) among those with a risk score of ≥14 (example: a woman aged ≥85 years with diabetes, heart failure or cancer, with functional limitations, current tobacco use and with a BMI <25kg/m^2) [22]. The application of valid mortality indices in primary care settings may identify older women with a low estimated 10-year mortality that would benefit from screening mammography and conversely identify older women with a high estimated 10-year mortality that would not benefit from screening.

In conclusion, the historical lack of systematic investment in obtaining trial evidence on the care of broad, representative older populations leaves policy makers, clinicians and consumers with limited guidance on who, how often and whether to screen older women for breast cancer. Until this evidence void is filled, optimizing and personalizing breast cancer

screening strategies will necessitate a careful examination of the balance of benefits versus harms based on breast cancer risk, preferences for outcomes and the impact of comorbidity, health habits and functional limitations on the life expectancy of the aging population.

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