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REVIEW

Optimal breast cancer screening strategies for older women: current perspectives

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Abstract: Breast cancer is a major cause of cancer-related deaths among older women, aged 65 years or older. Screening mammography has been shown to be effective in reducing breast cancer mortality in women aged 50–74 years but not among those aged 75 years or older. Given the large heterogeneity in comorbidity status and life expectancy among older women, controversy remains over screening mammography in this population. Diminished life expectancy with aging may decrease the potential screening benefit and increase the risk of harms. In this review, we summarize the evidence on screening mammography utilization, performance, and outcomes and highlight evidence gaps. Optimizing the screening strategy will involve separating older women who will benefit from screening from those who will not benefit by using information on comorbidity status and life expectancy. This review has identified areas related to screening mammography in older women that warrant additional research, including the need to evaluate emerging screening technologies, such as tomosynthesis among older women and precision cancer screening. In the absence of randomized controlled trials, the benefits and harms of continued screening mammography in older women need to be estimated using both population-based cohort data and simulation models.

Keywords: aging, breast cancer, precision cancer screening

Introduction

Globally, breast cancer is the most commonly occurring cancer among women, comprising 23% of the ~1.7 million female cancers that are newly diagnosed each year.[1,2] Approximately 6.2 million women were diagnosed with breast cancer in the last 5 years, making breast cancer the single most prevalent cancer around the globe.[1] In the USA, breast cancer is responsible for most new cases of cancer among women with an estimated 29% of new cancer cases and 14% of cancer deaths in 2014.[2] Approximately 41% of all incident breast cancers and 57% of all breast cancer deaths occur among women aged 65 years and older.[3]

The incidence of breast cancer in the USA generally increases until 80 years of age, at which point the incidence begins to decrease, possibly due to lower rates of screening, the mammographic detection of cancers before 80 years of age, or incomplete detection.[4] Screening mammography, the only population-based method for the early detection of breast cancer, has been shown to be effective in reducing breast cancer mortality in women aged 50–74 years.[5,6] Yet, there is no evidence regarding the effectiveness of screening mammography in women aged 74 years and older. Diminished life expectancy that occurs with aging decreases the probability of a screening benefit and likely increases the risk of harms.[7] Because of large heterogeneity in comorbidity status and life expectancy among older women, aged 65 years or older, a continuing controversy exists over screening mammography in this population.[8,9]

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The consequences of screening older women have not been well described, especially in relation to life expectancy. Randomized trials of screening mammography cannot provide the evidence because the trials excluded women older than 75 years and those with significant comorbidity.[10]

The impact of new imaging technologies on screening mammography outcomes in older women is not well understood. Although routine screening with two-dimensional (2D) digital mammography is the primary means of early breast cancer detection, the use of newer imaging technologies, such as digital breast tomosynthesis (DBT, also referred to as 3D mammography) is diffusing rapidly into clinical practice.[11] In recent studies, the addition of DBT to 2D digital mammography resulted in a decrease in recall rates and an increase in cancer detection rates, when compared with 2D digital mammography alone.[12–17] Given that these findings point to significant improvements in breast cancer screening outcomes with DBT, it will be important to include women in older age ranges in future studies of DBT.

In this review, we summarize the evidence and current perspectives regarding the utilization of screening mammography and performance and outcomes in older women and highlight evidence gaps in this field.

Screening mammography utilization in older women

Several guidelines support screening mammography in older women unless a woman's comorbid conditions limit life expectancy (Table 1). In women aged 70 years and older, the World Health Organization recommendation only specifies that well-resourced settings with the infrastructure to create population-based programs should provide screening.[18] The US Preventive Services Task Force (USPSTF) updated their guidelines in 2009 to recommend biennial, rather than yearly screening mammography until 74 years of age but concluded that evidence was insufficient to make recommendations for women aged 75 years and older.[10,18] Recently revised breast cancer screening recommendations from the American Cancer Society (ACS) are for regular screening mammography for women at an average risk of developing breast cancer beginning at 45 years of age and continuing after 70 years of age amongst women who are in good health.[19] The National Cancer Institute is reevaluating its past recommendations in light of the USPSTF recommendations and supporting further research.[10] Both the ACS and the USPSTF guidelines state that screening in older women should be considered on an individual basis through the evaluation of potential benefits and risks posed by the mammogram in relation to their current health conditions and predicted life expectancy.

In the USA, screening mammography attendance rates among older women are generally high. For example, ~73% of US women aged 75 years or older reported having undergone screening mammography in the 2010 US Behavioral Risk Factor Surveillance System in the last 2 years.[20] According to data from the 2013 National Health Interview Survey, 75.3% of women aged 65–74 years and 56.5% of women aged 75 years and older self-reported screening mammography use in the last 2 years.[21] Crucially, screening mammography is also commonly reported among older US women in poor health in the National Health Interview Survey[22–24] and in the US Breast Cancer Surveillance Consortium.[25] Thus, many older women undergo screening mammography without evidence of benefits from screening.

Screening mammography utilization by comorbidity and functional status

In older women, comorbid conditions and diminished life expectancy may influence a physician's decision to recommend mammography or a woman's decision to undergo screening.[26,27] Table 2 provides a summary of studies that evaluated the association between comorbidity and screening mammography utilization. Several of the studies evaluating comorbidity and screening utilization reported that a higher

Table 1 Guideline recommendations about screening mammography in older women

USPSTF guidelines	ACS guidelines	ACR guidelines	AGS guidelines
Offer biennial screening to women aged 50–74 years. Evidence is insufficient to recommend for or against screening in women >74 years of age. "I" statement*. The Task Force encourages more research on the topic.	Offer screening to women aged ≥45 years and continue as long as a woman is in good health and has life expectancy of ≥10 years.	Offer annual screening to women aged ≥40 years and continue as long as a woman is in good health.	Offer screening to women aged ≤85 years who have life expectancy of ≥5 years and for healthy women aged ≥85 years who have excellent functional status or who feel strongly about the benefits of screening (no screening frequency specified).

Notes: *Current evidence is insufficient to address benefits and harms of breast cancer screening in women >74 years of age.
Abbreviations: ACR, American College of Radiology; ACS, American Cancer Society; AGS, American Geriatrics Society; USPSTF, US Preventive Services Task Force.

Table 2 Summary of studies assessing comorbidity, cognitive/functional status, and general health effects on mammography utilization in older women

Source (sample size)	Study design	Assessment of comorbidity/ functional status	Assessment of mammography utilization	Key findings	
				Comorbidity	Functional status
Mayer et al[41] (N=995)	Randomized control trial	Questionnaire	Questionnaire: ≥1 screen within 2 years		Perceived general health: Good vs poor/fair OR =0.82 (95% CI: 0.50–1.30) Very good vs poor/fair OR =1.10 (95% CI: 0.70–1.90) Excellent vs poor/fair OR =0.87 (95% CI: 0.50–1.50)
Ives et al[38] (N=2,205)	Prospective cohort study	Outpatient medical record, medicare insurance claims	Medicare insurance claims: ≥1 screen within 2 years	MMSE: MMSE: ≤23 vs ≥24 OR =0.98 (95% CI: 0.62–1.57) Depression: CES-D <16 vs ≥16 OR =0.76 (95% CI: 0.56–1.04)	ADL limitations: Yes vs no OR =0.56 (95% CI: 0.34–0.93) IADL limitations: Yes vs no OR =0.92 (95% CI: 0.75–1.14)
Blustein and Weiss[37] (N=2,352)	Retrospective cohort study	Interview	Medicare claims: ≥1 screen within 2 years	Alzheimer's/mental disorder: OR =0.55 (95% CI: 0.35–0.87)	ADL limitations: Yes vs no OR =0.71 (95% CI: 0.59–0.85) Perceived general health: Poor vs excellent OR =0.41 (95% CI: 0.26–0.56) Fair vs excellent OR =0.81 (95% CI: 0.58–1.13) Good vs excellent OR =0.84 (95% CI: 0.60–1.18) Very good vs excellent OR =1.15 (95% CI: 0.85–1.56)
Kiefe et al[28] (N=1,764)	Cross-sectional study on retrospective defined cohort study	Medical records review	Medical records review: ≥1 screen within 2 years	Charlson comorbidity (1 unit increase): OR =0.83 (95% CI: 0.72–0.94)	
Wright et al[29] (N=683)	Cross-sectional population-based study	Telephone interview and medical records	Chart review/ medical records: ≥1 screen within 2 years	Charlson comorbidity (1 unit increase): OR =0.90 (95% CI: 0.74–1.09)	ADL/IADL limitations (1 unit increase): OR =0.70 (95% CI: 0.53–0.94) Perceived general health (1 unit increase): OR =1.19 (95% CI: 0.99–1.42)
Caplan[22]	Prospective cohort study	Interview	Interview		ADL limitations: (Yes vs no) 36.0% vs 52.7% (*P*-value <0.001)
Scinto et al[39] (N=844)	Prospective cohort study	Interview and self-report	Medicare claims: ≥1 screen within 5 years		ADL limitations: (Yes vs no) 12.5% vs 35.6% (*P*-value =0.001) Life expectancy (5-year mammography proportion): Grade 1 (best) – 47.5% Grade 2 – 27.3% Grade 3 – 18.2% Grade 4 (worst) – 7.0% (*P*-value =0.0001)
Wu et al[35] (N=1,403)	Prospective cohort study	Interview	Interview	Number of conditions: ≥2 vs 0–1 OR =0.70 (95% CI: 0.54–0.90) MMSE: MMSE: ≤23 vs ≥24 OR =0.83 (95% CI: 0.63–1.09)	

(*Continued*)

Table 2 (*Continued*)

Source (sample size)	Study design	Assessment of comorbidity/ functional status	Assessment of mammography utilization	Key findings	
				Comorbidity	**Functional status**
Heflin et al[32] (N=1,481)	Cross-sectional within prospective cohort study	Interview	Self-reported: ≥1 screen within 2 years	Number of conditions: ≥3 vs 0–2 OR =1.35 (95% CI: 1.06–1.71) Cognitive impairment (1 unit increase): OR =0.95 (95% CI: 0.66–1.35) Depression: CES-D <9 vs ≥9 OR =1.22 (95% CI: 0.82–1.81)	IADL limitations (1 unit increase): OR =0.94 (95% CI: 0.87–1.03)
Schootman and Jeffe[40] (N=10,639)	Cross-sectional population-based study	Questionnaire	Self-reported		ADL limitations: Short-term vs none OR =0.74 (95% CI: 0.36–1.51) Long-term vs none OR =0.18 (95% CI: 0.07–0.44) IADL limitations: Short-term vs none OR =0.86 (95% CI: 0.51–1.46) Long-term vs none OR =0.40 (95% CI: 0.22–0.73)
Schonberg et al[34] (N=882)	Cross-sectional population-based study	Self-reported/ questionnaire	Self-reported: ≥1 screen within 2 years	Number of conditions: 1 vs 0 OR =0.84 (95% CI: 0.57–1.22) ≥2 vs 0 OR =0.63 (95% CI: 0.38–1.06)	ADL/IADL limitations: IADL dep vs none OR =0.65 (95% CI: 0.40–1.05) ≥1 ADL vs none OR =0.44 (95% CI: 0.22–0.88)
Walter et al[44] (N=3,988)	Cross-sectional population-based study	Self-reported	Self-reported: ≥1 screen within 2 years		Perceived general health: 1 (best) vs 4 (worst) OR =0.80 (95% CI: 0.60–1.00) 2 vs 4 OR =1.20 (95% CI: 0.90–1.60) 3 vs 4 OR =1.10 (95% CI: 0.90–1.50)
Bynum et al[46] (N=722,310)	Retrospective cohort study	Medicare claims	Medicare claims: ≥1 screen within 2 years		Life expectancy (proportion receiving mammography): Grade 1 (low propensity to die) – 61% Grade 2 – 49% Grade 3 – 33% Grade 4 – 19% Grade 5 (high propensity to die) – 5% ($P<0.001$)
Thorpe et al[49] (N=3,655)	Cross-sectional population-based study	Mental component survey	Self-reported: ≥1 screen within 2 years	Psychological distress: High level vs none OR =0.68 (95% CI: 0.34–1.37)	
McBean and Yu[30] (N=16,394)	Cross-sectional population-based study	Medicare claims	Medicare claims: ≥1 screen within 2 years	Charlson comorbidity: 1 vs 0 OR =0.87 (95% CI: 0.76–0.99) ≥2 vs 0 OR =0.65 (95% CI: 0.58–0.72)	
Schonberg et al[42] (N=4,683)	Cross-sectional population-based study	Self-reported	Self-reported: ≥1 screen within 2 years		Perceived general health: Avg vs above avg OR =0.74 (95% CI: 0.57–0.96) Below avg vs above avg OR =0.51 (95% CI: 0.37–0.70)
Williams et al[47] (N=4,222)	Cohort study	Outpatient medical record	Self-reported: ≥1 screen within 2 years		Life expectancy: Good prognosis: Middle income vs low income RR =1.08 (95% CI: 0.96–1.21) High income vs low income RR =1.18 (95% CI: 1.05–1.32) Limited prognosis: Middle income vs low income RR =1.18 (95% CI: 0.77–1.81) High income vs low income RR =1.92 (95% CI: 1.20–3.09)

Mehta et al[48] (N=2,131)	Cross-sectional population-based study	Outpatient medical record	Medicare claims: ≥1 screen within 2 years	Cognitive impairment: Mild vs none OR =0.82 (95% CI: 0.60–1.10) Severe vs none OR =0.46 (95% CI: 0.30–0.80)	
Reyes-Ortiz and Markides[36] (N=1,272)	Prospective cohort study	Interview	Interview: ≥1 screen within 2 years	MMSE: MMSE: ≤18 vs >18 OR =0.62 (95% CI: 0.45–0.86) Depression: CES-D: <16 vs ≥16 OR =1.42 (95% CI: 1.04–1.94)	IADL limitations: ≥4 vs 0–3 OR =0.65 (95% CI: 0.49–0.86)
Caban et al[33] (N=4,610)	Prospective cohort study	Interview	Self-reported	Number of conditions: 1 vs 0 OR =1.14 (95% CI: 0.97–1.34) 2 vs 0 OR =1.21 (95% CI: 0.98–1.49) ≥3 vs 0 OR =1.56 (95% CI: 1.13–2.10) Cognitive impairment: Yes vs no OR =0.93 (95% CI: 0.75–1.15) Depression (last 12 months): Yes vs no OR =0.99 (95% CI: 0.75–1.34)	ADL/IADL limitations: Moderate vs none OR =0.98 (95% CI: 0.81–1.18) Severe vs none OR =0.67 (95% CI: 0.54–0.83) Perceived general health: Fair/poor vs excellent/very good/good OR =0.80 (95% CI: 0.66–0.96)
Tan et al[31] (N=697,825)	Retrospective cohort study	Outpatient medical record	Medicare claims: ≥1 screen within 2 years	Charlson comorbidity (proportion ranges): Charlson score =0 (13.3%–55.3%) Charlson score =1 (12.6%–55.9%) Charlson score =2 (8.3%–49.9%) Charlson score ≥3 (6.8%–37.9%)	
Schonberg et al[45] (N=2,266)	Cross-sectional population-based study	Self-reported	Self-reported: ≥1 screen within 2 years		Life expectancy: Medium vs low OR =1.40 (95% CI: 1.00–1.90) High vs low OR =2.40 (95% CI: 1.60–3.70)
Koya et al[43] (N=4,836)	Cross-sectional population-based study	Self-reported/ questionnaire	Self-reported: ≥1 screen within 1 year		Perceived general health: Excellent/very good vs fair/poor OR =1.12 (95% CI: 0.85–1.49) Good vs fair/poor OR =1.18 (95% CI: 0.90–1.54) Life expectancy: Intermediate risk vs low risk OR =0.69 (95% CI: 0.53–0.90) High risk vs low risk OR =0.37 (95% CI: 0.27–0.49) Very high risk vs low risk OR =0.22 (95% CI: 0.13–0.36)

Abbreviations: ADL, activities of daily living; avg, average; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; IADL, instrumental activities of daily living; MMSE, mini-mental state examination; OR, odds ratio; RR, relative risk.

Charlson comorbidity score was associated with lower screening utilization.[28–31] For example, women with Charlson scores of ≥2 were found to have a 35% reduction in the odds of mammography utilization (odds ratio [OR]: 0.65, 95% confidence interval [CI]: 0.58–0.72).[30] Conflicting evidence exists regarding the impact of the total number of comorbid conditions on screening use, with two studies finding that higher numbers of comorbid conditions increased screening mammography utilization,[32,33] whereas two other studies reported an inverse association.[34,35] This variance may reflect the use of different sums of comorbid conditions.

Studies evaluating the associations between cognitive impairment, depression, and screening mammography utilization have generally shown inconclusive results (Table 2) In a study of Mexican American women aged 75 years and older that measured cognitive impairment (using the mini-mental state examination [MMSE]), lower MMSE scores were associated with decreased odds of screening utilization (OR: 0.62, 95% CI: 0.45–0.86).[36] Moreover, the same study reported that increased depressive symptoms, as reflected by the Center for Epidemiological Studies-Depression (CES-D) scale, were associated with increased screening mammography utilization.[36] However, other studies measuring cognitive impairment with MMSE and depression with CES-D scale in more diverse populations found equivocal results.[32,33,35,37,38]

Studies of functional limitations have generally found an inverse association with screening utilization (Table 2). Specifically, activities of daily living (ADL) limitations were associated with decreased screening mammography utilization,[22,37–40] with one study in 2003 finding more significant decreases in utilization in women older than 70 years (OR: 0.18, 95% CI: 0.07–0.44).[40] Similar results were found with instrumental activities of daily living (IADL) limitations,[32,36,38,40] since long-term IADL limitations – identified by reporting limitations at both visits – were more strongly associated with decreased mammography utilization (OR: 0.40, 95% CI: 0.22–0.73).[40] When considering scales using both ADL and IADL measurements, having severe limitations led to significant decreases in odds of screening mammography.[29,33,34]

In general, women's perceptions of their general health were not statistically significant predictors of change in screening mammography utilization (Table 2). Of the seven studies measuring perceived general health in older women,[29,33,37,41–44] only two found a significant positive association between declining perceived health status and screening mammography utilization.[33,42] Life expectancy measured by a prognostic index was a strong predictor of screening mammography utilization in older women, with four studies indicating that women with a higher risk of mortality had lower odds of screening mammography.[39,43,45,46] Notably, Koya et al found a nearly 80% decrease in odds of mammography utilization in women in the lowest life expectancy group (OR: 0.22, 95% CI: 0.13–0.36).[43] Moreover, in a study that used a life expectancy index with income as a stratifying covariate, women with higher incomes and longer life expectancy (relative risk [RR]: 1.18, 95% CI: 1.05–1.32) or higher incomes and limited life expectancy (RR: 1.92, 95% CI: 1.20–3.09) had increased utilization of screening mammography than their counterparts with lower incomes.[47]

There is paucity of data examining the association between comorbidity or life expectancy and screening mammography utilization in older women outside of the USA. Of note, many of the aforementioned studies employed as the main outcome claims (or health insurance-derived) data[30,31,37–39,46,48] or self-reported mammography utilization,[32–34,40,42,44,45,47,49] with the latter being more likely to result in potentially biased effect estimates.

In summary, there is compelling evidence that older women with a greater comorbidity burden and poorer functional status are less likely to undergo screening mammography, particularly among studies that employed standardized comorbidity measures.[28–31] Moreover, diminished life expectancy was also found to be inversely associated with mammography utilization.[39,43,45,46] Although perceived general health was found to be an inconclusive predictor of screening utilization,[29,33,37,41–44] further research on the impact of life expectancy indicators may enhance our understanding of screening mammography utilization in older women.

Screening mammography performance in older women

Overall, there is limited evidence regarding screening mammography performance in older women. Hitherto, two studies have explicitly examined screening mammography performance in older US women.[50,51] A 2011 study by Sinclair et al evaluated the accuracy and cancer detection rate among 403,448 mammograms (the majority of which were captured with film-screen mammography) for women aged 50–101 years living in Vermont.[50] Interestingly, screening mammography performance improved with age in this study; when compared to women aged 50–59 years, those aged 70–79 years had an increase in sensitivity (77.3%–80.4%),

specificity (98.7%–99.0%), positive predictive value (22.2%–37.6%), and cancer detection rate (3.7/1,000–6.2/1,000 mammograms).[50] The relationship between age and performance measures was not influenced by potential confounders of body mass index, breast density, education, race, ethnicity, family history of breast or ovarian cancer, personal history of ovarian cancer, current or prior use of hormone therapy, and age at menopause or menarche.

The second study in USA, published in 2015, utilized the national Breast Cancer Surveillance Consortium data from 296,496 full-field digital screening mammograms among women aged 65 years and older to assess performance.[51] Of note, the performance measures in this study were also stratified by the Breast Imaging Reporting and Data Systems' breast density values to determine if breast density rather than age was affecting mammography performance. Similar to the 2011 study, the specificity, positive predictive value, and cancer detection rate of digital screening mammography improved significantly with increasing age. In contrast to the 2011 study,[50] the sensitivity of digital screening mammography did not increase with age and was 88.3% overall. The recall rate, which was not examined in the earlier study,[50] decreased significantly from 8.4% (95% CI: 7.8%–8.0%) in women aged 65–69 years to 7.3% (95% CI: 6.9%–7.8%) in women aged 85 years and older. Adjusted models showed similar improvements with increased age, suggesting that both age and breast density impact the recall rate, specificity, positive predictive value, and cancer detection rate. Of note, this study evaluated digital mammography because of its widespread utilization in the USA and did not consider film mammography; the cost-effectiveness of digital mammography compared to film mammography in older women has not been established.[52]

Because screening mammography programs outside the USA do not typically include women older than 70 years or 74 years, there is limited evidence on the performance of screening mammography at the 5- or 10-year age-groups necessary to evaluate performance in older women. The Ontario Breast Screening Program that includes women aged 50–59 years, 60–69 years, and 70–74 years and reports performance measures for these groups reported significant increases in cancer detection rate (CDR) and positive predictive values with increasing age, and a significant decrease in the recall rate with increasing age.[53]

Results from both US studies[50,51] show that as age increased, the proportion of invasive versus ductal carcinoma in situ (DCIS) cases increased, with the exception of women aged 90–101 years in the Vermont study; approximately 75%–81% of cancers detected in older women were invasive. In both studies,[50,51] the proportion of cases with positive nodes decreased with increasing age. Tumors detected in the era of film-screen mammography showed a positive association of age and estrogen receptor-positive status, with the proportion of estrogen receptor-positive increasing with increasing age.[51] However, in the digital screening era, as age increased, the proportion of lower grade tumors increased.[52] Neither study found a significant association of tumor stage with age.[50,51] Moreover, a study by Smith-Bindman et al in 2000 found that women aged 66–79 years who underwent screening mammography had a decreased risk of detecting metastatic breast cancer.[54] Of note, neither of these aforementioned studies examined screening mammography performance in the context of comorbidity or life expectancy.[50,51]

Screening mammography outcomes in older women

Since rates of clinically indolent tumors and DCIS increase with age, older women are more likely to be harmed from overdiagnosis,[55] defined as detection of tumors by screening that would not become clinically apparent during a woman's lifetime or would not affect overall survival. Given the steeper rise in competing causes of mortality in women older than 74 years, evidence suggests that rates of overdiagnosis are likely to be greater for older women than younger women.[55,56] Screening tests can have immediate harmful consequences and the long-term benefits of screening may not be realized in women with a short life expectancy.[26,27,57–59] The most important benefit of screening mammography in older populations is an improvement in life expectancy, while the harms include false-positive results and overdiagnosis.[7] Given the increasing comorbidity burden and attendant decline in life expectancy, some older women are unlikely to have a favorable benefit/harm ratio.[58,60]

The currently available evidence regarding the impact of comorbidity and health status on screening mammography outcomes consists of four observational[25,61–63] and three decision models[64–66] because no randomized trials included women older than 74 years. It is important to recognize that observational data are subject to selection bias as well as lead-time and length bias. In observational studies evaluating screening mammography, the study populations of older women have self-selected to undergo screening mammography and are likely to be healthier than the general US population.[64–66] Both cohort studies and decision analytic models[25,61–66] found that screening benefits decreased with

increasing age and comorbidity burden. Thus, the balance of benefits versus harms varies according to comorbidity and age, which underscores the need for evidence to develop life expectancy-based screening strategies.

Benefits of screening mammography in older women

Only one cohort study has so far evaluated mortality as a benefit of breast cancer screening.[63] In the study by McPherson et al,[63] which included 5,186 women aged 65 years and older diagnosed with breast cancer between 1986 and 1994 through the Upper Midwest Tumor Registry system, women's comorbidity was assessed via the Charlson score.[67] In this study, women aged 65 years and older with no or moderate comorbidity and mammographically detected tumors were found to be at reduced risk of breast cancer death compared to those with clinically detected tumors (Table 3).[63] In addition, among women with severe comorbidity, as defined by a Charlson score of ≥3, screening mammography was associated with reduced breast cancer mortality among women aged 70–74 years, but not in those younger than 70 years or older than 74 years.[63]

Although detection of early stage disease at diagnosis has been utilized as a marker of screening benefit, this may not necessarily represent a benefit in older women with indolent tumors. Of the three cohort studies that evaluated the risk of early versus advanced tumor stage,[25,61,62] two – Braithwaite et al[61] and Yasmeen et al[25] – used data from the US Breast Cancer Surveillance Consortium linked to Medicare insurance claims data from 1999 to 2006, to evaluate comorbidities in the 2 years before screening mammography. In another cohort study, Fleming et al merged data from the Surveillance, Epidemiology and End Results program with Medicare insurance claims for 17,468 women diagnosed with breast cancer between 1993 and 1995.[62] Heterogeneous measures of comorbidity were utilized in these three studies: Braithwaite et al[61] employed the Charlson comorbidity score while Fleming et al[62] and Yasmeen et al[25] reported on 24 individual conditions, and severity-based categorizations of comorbidity, respectively. Yasmeen et al found that overall rates of advanced breast cancer (per 1,000 mammograms) were lower among women with no comorbidity than among those with stable comorbidity in annually and biennially screened women and for those that received their first screen (Table 3).[25] However, among women who had prior mammography within 4–18 months of cancer diagnosis, the rates of advanced-stage cancer were higher among those with either stable or unstable comorbidities than among those without comorbidities.[25] In contrast, Braithwaite et al[61] reported that adverse tumor characteristics, including advanced stage, did not differ significantly by the Charlson score or screening interval. Moreover, Fleming et al[62] reported that women with cardiovascular disease, musculoskeletal disorders, mild-to-moderate gastrointestinal disease, and nonmalignant benign breast disease had a 13%, 7%, 14%, and 24% lower odds, respectively, of being diagnosed with advanced breast cancer, while those with diabetes, other endocrine disorders, psychiatric disorders, and hematologic disorders had increased odds of advanced stage diagnosis by 19%, 11%, 20%, and 19%, respectively, compared to women without these comorbidities.

Consistent with observational data, decision analyses confirm that women aged 65 years or older are less likely to benefit from screening, particularly if they have severe comorbidity,[68] and propose a comorbidity-dependent cessation age.[65] Moreover, another decision analytic model reported minimal quality-adjusted life expectancy for women aged 85 years and older with average health or mild comorbidity and losses in quality-adjusted life expectancy for women with severe comorbidity.[64] Specifically, two decision analyses, Mandelblatt et al[68] and Lansdorp-Vogelaar et al,[65] employed well-established, independently developed Cancer Intervention and Surveillance Modeling Network models, with each model simulating the life histories of large US cohorts, and assessing the underlying disease in the presence and absence of screening. Relative life expectancy benefits of screening in older women according to comorbidity are shown in Table 3. In particular, Lansdorp et al compared the number needed to screen per life-year gained at different stopping ages and estimated threshold stopping ages according to the level of comorbidity, at which the number needed to screen per life-year gained was the same as that of mammography until 74 years of age for women of average comorbidity.[65] Authors evaluated biennial screening mammography from 50 years of age to a cessation age ranging from 66 years to 90 years by simulating US cohorts of women who were 66–90 years old and alive in 2010, and had no comorbidity, mild comorbidity (a history of myocardial infarction, acute myocardial infarction, ulcer, or rheumatologic disease), moderate comorbidity (the presence of vascular disease, cardiovascular disease, paralysis or, diabetes), or severe comorbidity (the presence of AIDS, mild or severe liver disease, chronic obstructive pulmonary disease, chronic renal failure, dementia, or congestive heart failure), as well as comparison cohorts of average comorbidity aged

Table 3 Summary of findings from studies that evaluated the benefits, harms and the balance of benefits versus harms of screening mammography in older women

Source	Subgroups (years)	Outcomes reported		
Benefits				
McPherson et al[63]		**RR of death and 95% CI**		
Screening groups:	Comorbidity	No comorbidity	Moderate	Severe
Mammographic vs clinical (palpation) diagnosis	Ages: 65–69	0.44 (0.32–0.59)	0.32 (0.15–0.69)	0.41 (0.11–1.48)
	Ages: 70–74	0.32 (0.23–0.44)	0.45 (0.22–0.91)	0.30 (0.11–0.79)
	Ages: 75–79	0.36 (0.26–0.49)	0.47 (0.25–0.88)	0.53 (0.20–1.36)
	Ages: ≥80	0.66 (0.52–0.83)	0.52 (0.33–0.80)	0.64 (0.30–1.87)
Fleming et al[62]		**OR (and *P*-value) of late-stage (regional and distant) vs early stage (in situ and local) disease, under comorbid conditions**		
Screening groups:	Comorbidity	Cardiovascular disease	Pulmonary disease, mild/ moderate	Gastrointestinal disease, severe
All patients were screened	OR (*P*-value)	0.87 ($P<0.01$)	1.08 ($P>0.05$)	0.94 ($P>0.05$)
		Diabetes	Genital-urinary disease	Rheumatologic disease
		1.19 ($P<0.01$)	0.91 ($P>0.05$)	1.02 ($P>0.05$)
		Musculoskeletal disease	Renal disease	Other vascular disease
		0.93 ($P<0.01$)	1.15 ($P>0.05$)	1.04 ($P>0.05$)
		Benign breast disease, nonmalignant	Osteoporosis	Psychiatric disease
		0.76 ($P<0.01$)	1.16 ($P>0.05$)	1.2 ($P<0.01$)
		Cerebrovascular disease	Malignant hypertension	Gastrointestinal disease
		1.03 ($P>0.05$)	1.02 ($P>0.05$)	0.86 ($P<0.01$)
		Osteoarthritis	Neurological disease	AIDS
		0.96 ($P>0.05$)	1 ($P>0.05$)	1.41 ($P>0.05$)
		Benign hypertension	Pulmonary disease, severe	Hematologic disease
		0.98 ($P>0.05$)	0.99 ($P>0.05$)	1.19 ($P<0.01$)
		Endocrine disease	Obesity	Other cancers
		1.11 ($P<0.05$)	1.18 ($P>0.05$)	1.04 ($P>0.05$)
Braithwaite et al[61]		**OR and 95% CI for invasive breast cancer vs DCIS**		
Screening groups:		**2- vs 1-year interval**		
2- vs 1-year interval	Comorbidity	Charlson score =0	Charlson score ≥1	
	Ages: 66–74	0.83 (0.59–1.17)	0.92 (0.54–1.56)	
	Ages: 75–89	1.07 (0.71–1.60)	1.02 (0.51–2.03)	
		OR and 95% CI for advanced stage (stages IIB–IV) vs early stage (stages I–IIA)		
	Comorbidity	Charlson score =0	Charlson score ≥1	
	Ages: 66–74	0.75 (0.46–1.22)	0.99 (0.48–2.04)	
	Ages: 75–89	1.27 (0.72–2.25)	0.37 (0.13–1.04)	
		OR and 95% CI for large size tumors (>20 mm) vs small (≤20 mm)		
	Comorbidity	Charlson score =0	Charlson score ≥1	
	Ages: 66–74	0.83 (0.55–1.24)	0.91 (0.50–1.65)	
	Ages: 75–89	1.30 (0.83–2.05)	1.38 (0.70–2.73)	
		OR and 95% CI for positive lymph node involvement		
	Comorbidity	Charlson score =0	Charlson score ≥1	
	Ages: 66–74	0.84 (0.57–1.23)	0.76 (0.41–1.43)	
	Ages:75–89	0.83 (0.51–1.33)	0.62 (0.29–1.34)	

(*Continued*)

Table 3 (*Continued*)

Source	Subgroups (years)	Outcomes reported			
Mandelblatt et al[64]		**Long-term quality-adjusted marginal savings in life-expectancy (in days) and 95% CI**			
Screening groups:	Comorbidity	Average health	Mild hypertension	Congestive heart failure	Average health (black)
Screening vs no screening	Ages: 65–69	2.19 (1.97, 2.41)	1.97 (1.77, 2.16)	1.17 (1.06, 1.28)	2.17 (1.95, 2.39)
	Ages: 70–74	1.85 (1.67, 2.03)	1.68 (1.51, 1.84)	1.08 (0.98, 1.18)	2.22 (1.99, 2.44)
	Ages: 75–79	1.43 (1.30, 1.57)	1.32 (1.20, 1.44)	0.91 (0.83, 0.98)	1.76 (1.59, 1.94)
	Ages: 80–84	1.08 (0.98, 1.18)	1.01 (0.92, 1.10)	0.76 (0.69, 0.82)	1.65 (1.49, 1.80)
	Ages: ≥85	0.80 (0.73, 0.87)	0.76 (0.69, 0.83)	0.59 (0.54, 0.65)	1.16 (1.05, 1.27)
		Long- and short-term quality-adjusted marginal savings in life-expectancy (in days) and 95% CI			
	Comorbidity	Average health	Mild hypertension	Congestive heart failure	Average health (black)
	Ages: 65–69	1.44 (1.22, 1.66)	1.22 (1.03, 1.42)	0.43 (0.31, 0.54)	1.42 (1.20, 1.64)
	Ages: 70–74	1.10 (0.92, 1.28)	0.93 (0.77, 1.09)	0.33 (0.23, 0.44)	1.47 (1.25, 1.69)
	Ages: 75–79	0.69 (0.55, 0.82)	0.57 (0.45, 0.70)	0.16 (0.08, 0.24)	1.01 (0.84, 1.19)
	Ages: 80–84	0.34 (0.24, 0.44)	0.27 (0.17, 0.36)	0.01 (–0.06, 0.07)	0.90 (0.74, 1.06)
	Ages: ≥85	0.05 (–0.02, 0.12)	0.01 (–0.06, 0.08)	–0.15 (–0.20, –0.10)	0.42 (0.31, 0.56)
Messecar[66]		**Quality-adjusted savings in life-expectancy, quality-adjusted life-years (in days)**			
Screening groups:	**Subgroups**	**Following regular biennial screening**		**No prior screening**	
One additional screening	Comorbidity	Cognitive impairment	Healthy	Cognitive impairment	Healthy
following biennial	Ages: 75–79	0.004 (1.5)	0.009 (3.3)	0.055 (20)	0.119 (43.4)
screening vs no prior	Ages: 80–84	0.002 (0.7)	0.007 (2.5)	0.025 (9.1)	0.089 (32.5)
screening	Ages: ≥85	0.001 (0.4)	0.006 (2.2)	0.015 (5.5)	0.071 (25.9)
Lansdorp-Vogelaar et al[65]	**Incremental LYG per 1,000 individuals screened according to guidelines since 50 years of age in populations with average comorbidity,**				
Screening groups:	**by model, and age of screening cessation**				
Age of screening cessation	Comorbidity	**Average comorbidity**			
	Model	MISCAN-Fadia[a]	SPECTRUM[b]		
	Age of cessation =74 (vs 72)	7.6	5.8		
	Age of cessation =76 (vs 74)	6.9	5.1		
	Deaths prevented per 1,000 individuals screened according to guidelines since 50 years of age in populations with average comorbidity, by model, and age of screening cessation				
	Comorbidity	**Average comorbidity**			
	Model	MISCAN-Fadia[a]	SPECTRUM[b]		
	Age of cessation =74 (vs 72)	0.9	0.7		
	Age of cessation =76 (vs 74)	0.9	0.7		

Harms

Braithwaite et al[61]		**% of false-positive recalls at first mammography**			
Screening Group:	Comorbidity	Charlson score =0	Charlson score ≥1		
First mammography for all	Ages: 66–74	8.6 (8.3–8.8)	8.9 (8.5–9.3)		
	Ages: 75–89	8.0 (7.6–8.4)	8.8 (8.2–9.4)		
Screening groups:		**% of women with at least one false-positive recall after 10 years of subsequent mammography, by screening interval**			
Annual screening vs		**Annual**		**Biennial**	
biennial screening	Comorbidity	Charlson score =0	Charlson score ≥1	Charlson score =0	Charlson score ≥1
	Ages: 66–74	49.7 (47.8–51.5)	48.0 (46.1–49.9)	30.2 (29.4–31.1)	29.0 (28.1–29.9)
	Ages: 75–89	47.2 (44.9–49.5)	48.4 (46.1–50.8)	26.6 (25.7–27.5)	27.4 (26.5–28.4)
Screening group:		**% of false-positive biopsy recommendations at first mammography**			
First mammography for all	Comorbidity	Charlson score =0	Charlson score ≥1		
	Ages: 66–74	1.2 (1.1–1.3)	1.7 (1.5–1.9)		
	Ages: 75–89	1.2 (1.1–1.4)	1.7 (1.4–2.0)		
Screening groups:		**% of women with at least one false-positive biopsy recommendation after 10 years of subsequent mammography, by screening interval**			
Annual screening vs		**Annual**		**Biennial**	
biennial screening	Comorbidity	Charlson score =0	Charlson score ≥1	Charlson score =0	Charlson score ≥1
	Ages: 66–74	9.8 (8.4–11.3)	11.8 (10.1–13.8)	4.6 (4.2–5.1)	5.6 (5.1–6.2)
	Ages: 75–89	9.2 (7.5–11.2)	11.3 (9.3–13.6)	4.1 (3.7–4.6)	5.1 (4.5–5.7)
Lansdorp-Vogelaar et al[65]	**False-positive tests per 1,000 individuals screened according to guidelines since 50 years of age in populations with average comorbidity, by model, and age of screening cessation**				
Screening groups:					
Age of screening cessation	Comorbidity	**Average comorbidity**			
	Model	MISCAN-Fadia[a]	SPECTRUM[b]		
	Age of cessation 74 (vs 72)	79	96		
	Age of cessation 76 (vs 74)	77	96		
	Overdiagnosed cases per 1,000 individuals screened according to guidelines since 50 years of age in populations with average comorbidity, by model, and age of screening cessation				
	Comorbidity	**Average comorbidity**			
	Model	MISCAN-Fadia[a]	SPECTRUM[b]		
	Age of cessation 74 (vs 72)	0.8	0.5		
	Age of cessation 76 (vs 74)	1	0.6		

(*Continued*)

Table 3 (*Continued*)

Source	Subgroups (years)	Outcomes reported
Balance of benefits vs harms		
Landsdorp-Vogelaar et al[65]	**Number needed to screen to gain 1 life-year (NNS/LYG), by model and age of screening cessation**	
Screening groups:	Comorbidity	**Average comorbidity**
Age of screening cessation	Model	MISCAN-Fadia[a] SPECTRUM[b]
	Age of cessation =74 (vs 72)	132 173
	Age of cessation =76 (vs 74)	146 198

Notes: [a]MISCAN-Fadia: the MISCAN-Fadia model is a computer simulation program which incorporates information on the natural history of the disease as described by tumor stages and fatal tumor diameter (the size at which cancer becomes fatal) to construct models that compare the (cost-) effectiveness of different screening policies. It consists of four major components that simulate the demography and breast cancer incidence in the population, the natural history of a breast cancer tumor, the dissemination of screening mammography and its effects, and the dissemination of adjuvant treatment and its effects. [b]SPECTRUM: SPECTRUM is an event-driven continuous-time state model, which uses population-based estimates of breast cancer incidence and distribution of stage and other breast cancer characteristics (such as estrogen receptor status, response to treatment, and mortality) to estimate the efficacy of screening programs.

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; LYG, life-years gained; NNS, number needed to screen; OR, odds ratio; RR, relative risk.

74 years and 76 years. In this study, Lansdorp et al found that breast cancer screening through 74 years of age resulted in a number needed to screen to gain 1 life-year among women with no comorbidity of 117–149 across models, which was lower than that in the entire population with average comorbidity; cessation of screening at 76–78 years of age among women with no comorbidities was estimated to yield the same number needed to screen to gain 1 life-year as cessation at 74 years of age in the entire population.[65] Finally, this study points to the benefits of biennial mammography across models until median ages of 76–78 years, 74 years, 70–72 years, and 64–68 years for women with no comorbidity, mild comorbidity, moderate comorbidity, and severe comorbidity, respectively.[65] In hypothetical cohorts examining benefits of biennial screening in terms of life-years, Mandelblatt et al[64] found that long- and short-term quality-adjusted savings in life expectancy from screening compared to a nonscreening strategy were greater for older women with mild hypertension than for those with heart disease, and the benefit in both groups decreased with increasing age (Table 3). Finally, in another decision analysis examining three hypothetical cohorts of women aged 75–79 years, 80–84 years, and ≥85 years with and without cognitive impairment, Messecar tested the gain in quality-adjusted life-years in two models for each group assuming no prior screening versus continued biennial screening. In this study,[66] all older women benefited from biennial screening mammography, although among women with no prior screening, the gain in quality-adjusted life-years was lower among cognitively impaired women (20 days, 9.1 days, and 5.5 days for age-groups 75–79 years, 80–84 years, and ≥85 years, respectively) than their healthy counterparts (43.4 days, 32.5 days, and 25.9 days for age-groups 75–79 years, 80–84 years, and ≥85 years, respectively).[66]

The aforementioned benefits should be considered in conjunction with reported harms of screening in older women.

Harms of screening mammography in older women

There are evidence gaps regarding the harms of screening mammography in older women according to comorbidity and life expectancy;[61,65] a summary of studies that have hitherto addressed this question is shown in Table 3. In the US Breast Cancer Surveillance Consortium cohort study that evaluated the harms of screening mammography, Braithwaite et al reported that the 10-year cumulative probability of a false-positive mammography result was higher among annual screeners than biennial screeners irrespective of comorbidity: 48.0% (95% CI: 46.1%–49.9%) of annual screeners aged 66–74 years

had a false-positive result compared with 29.0% (95% CI: 28.1%–29.9%) of biennial screeners.[61] In a decision-analytic study evaluating the harms of screening, Lansdorp-Vogelaar et al[65] showed that ending screening at 74 years versus 72 years of age resulted in 96 more false-positive tests and 0.5 more overdiagnoses per 1,000 screening tests (Table 3). In examining the balance of benefits versus harms from screening mammography, Lansdorp-Vogelaar et al[65] also assessed numbers needed to screen in relation to life-years gained and estimated that extending breast cancer screening from the age of 72 years until 74 years of age among individuals with average comorbidity, required screening 132–174 women to gain 1 life-year; continuing screening until 76 years of age required an additional 146–198 women to be screened to gain 1 life-year.[65]

Another simulation model indicated that personalized screening based on individual risk that is measured as a function of age, breast density, history of breast biopsy, family history of breast cancer, and screening interval could potentially improve the balance of benefits versus harms among not only older but also younger women, where low-risk women could stop screening or continue to be screened at longer intervals, thereby reducing false-positive results.[69]

Decision-making regarding screening mammography among older women

Communication about potential benefits and harms to older women in their 70s and 80s also poses a challenge, given the limited available evidence.[7,60,70–72] In light of this uncertainty, clinical decisions about undergoing mammography in older populations would likely benefit from adopting life expectancy-based screening. A recent meta-analysis of survival data from population-based, randomized controlled trials comparing populations screened and not screened for breast cancer reported that it took 10.7 years (4.4–21.6 years) on average across included studies, before one death from breast cancer was prevented for 1,000 women screened; hence, this study concluded that screening for breast cancer should be targeted to women with a life expectancy >10 years.[57] To this end, it will be important for primary care physicians to adopt prognostic tools that provide estimates of women's risk of 10-year mortality,[73] since such tools may facilitate informed decisions about screening.

A prognostic tool developed by Cruz et al[73] based on data from the Health and Retirement Survey, a nationally representative cohort of community-dwelling US adults >50 years, is a 12-item mortality index that calculates an estimate of 10-year mortality based on age, sex, tobacco use, body mass index, diabetes, nonskin cancer, chronic lung disease, heart failure, and ADL (difficulty bathing, difficulty managing finances, difficulty walking several blocks, and difficulty pushing/pulling objects, etc). Application of valid prognostic tools in primary care settings may identify women with a low versus high risk of 10-year mortality that would and would not benefit from screening mammography, respectively. Recently developed decision aids show promise for counseling older women about the benefits and harms of screening mammography[74] and may help overcome the challenges of implementing life expectancy-based screening strategies in clinical practice.

Conclusion and future directions

In summary, screening mammography may be beneficial to older women if they have life expectancy of at least 10 years. Optimizing the screening strategy will involve a careful balance of benefits versus harms and life expectancy-based screening strategies. While the balance of benefits versus harms may be favorable for women up to 69 years of age and perhaps even up to 74 years of age with biennial screening, there is little evidence to support annual screening in older populations. Consistent with this, the updated USPSTF guidelines recommend biennial screening for women aged 66–74 years, but there are no explicit recommendations for women aged 75 years and older because of insufficient evidence. To better target populations who will benefit from screening, the National Cancer Institute has launched a new precision-based cancer screening initiative.[75] With the aging of the population, it will be increasingly important to evaluate life expectancy-based screening by identifying women with sufficient life expectancies to benefit from screening, while minimizing harms associated with false-positive results and overdiagnosis among women who will not live long enough to benefit.

This review has identified many areas related to screening mammography in older women that need additional research. For example, there is a paucity of research evaluating emerging screening technologies such as tomosynthesis among older women. Without randomized controlled trials, the benefits and harms of continued screening mammography in older women will need to be estimated using a combination of cohort data and simulation models.

As pointed out in the recent *JNCI* editorial,[76] direct application of simulation models to the breast cancer screening policy and clinical practice remains a challenge. To address this gap and eschew the pseudoprecision that modeling can portray,[76] it will be important to combine empirical evidence with modeling. Moreover, moving the field forward will necessitate modeling screening performance and mortality as a function of comorbidity, cognitive/physical functioning,

and life expectancy as well as cost-effectiveness of different screening strategies according to these factors.

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