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Benefits and Harms of Screening Mammography by Comorbidity and Age: A Qualitative Synthesis of Observational Studies and Decision Analyses

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OBJECTIVE: We conducted a systematic review to assess the quality and limitations of published studies examining benefits and harms of screening mammography in relation to comorbidity and age.

METHODS: We searched MEDLINE and EMBASE from January 1980 through June 2013 for studies that examined benefits or harms of screening mammography in women aged 65 years or older in relation to comorbidity. For each study, we extracted data regarding setting, design, quality, screening schedule, measure of comorbidity, and estimates of benefits and/or harms. We reviewed 1760 titles, identifying 7 articles that met the inclusion criteria: prospective cohort (two studies), retrospective cohort (two studies), and decision analyses (three studies). No randomized controlled trials were identified.

RESULTS: At least one measure of life expectancy or reduction in the risk of breast cancer death as a marker of benefit was examined in four studies, whereas three studies addressed the harms of screening mammography, including false-positive results. Both cohort studies and decision analyses showed that screening benefits decreased with increasing age and comorbidity burden.

CONCLUSIONS: The limited evidence currently available suggests that, apart from older women with severe comorbidity, women 65 and older may experience improvements in life expectancy from screening. Given the potential for harm, it is unclear whether the magnitude of the benefit is sufficient to warrant regular screening. Women, clinicians and policymakers should consider these factors in deciding whether continue screening.

KEY WORDS: breast cancer screening; comorbidity; aging.
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INTRODUCTION

Almost half of new invasive breast cancer cases diagnosed each year in the United Sates occur among women aged 65 years and older (hereafter referred to as older women), and rates rise with advancing age.[1] With the increasing life expectancy and aging of women in the U.S. and globally, the absolute number of breast cancer cases among older women is expected to increase over the coming decades. These dual demographic and epidemiologic forces, coupled with heterogeneity in health and the lack of direct evidence for screening efficacy among women aged 70 and older, create a clinical and policy conundrum: is there a combination of comorbidity and age when women should stop screening because the harms outweigh the benefits?[2,3] Age-related differences in comorbidity and tumor biology, variance in women's preferences for health outcomes associated with breast cancer screening, and increasing health care costs add to the challenge in answering this question.[2–8]

Numerous factors including tumor size, involvement of regional lymph nodes, histologic grade, expression of hormone receptors (estrogen and progesterone), and human epidermal growth factor receptor 2 (HER2) amplification are used to determine which women with early-stage breast cancer should be treated with adjuvant systemic therapy, including endocrine therapy, chemotherapy, and HER2-directed treatments.[9] Importantly, older patients with comorbidities often experience complications from virtually all treatment modalities.[10–12] Although one of the advantages of early diagnosis includes identifying tumors with favorable prognostic markers and risk assessment scores,[9] such benefits may not be realized in older women with substantial comorbidity due to their short life expectancy.[4] The harms of screening are often immediate, and include false-positive results and overdiagnosis.[13–17] Given the increasing comorbidity burden and attendant decline in life expectancy, many older women are unlikely to have a favorable ratio of benefits and harms. Additionally, rates of clinically indolent invasive tumors and *ductal carcinoma in situ* (DCIS) increase with age, raising the concern that older women are likely to be harmed from overdiagnosis and unnecessary treatment.[16] Robust evidence regarding the efficacy of screening mammography in older women is lacking because randomized controlled trials have not included women over age 74 years and those with substantial comorbidity.[18]

The extent to which benefits and harms of breast cancer screening in older women vary according to comorbidity and

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age is not well established. To better target health services to those who may benefit, it is important that screening mammography practices in older women incorporate patient factors such as comorbidity and age, which are important predictors of life expectancy. Our purpose here is to report the results of a systematic review of the literature examining the impact of comorbidity and age on screening mammography outcomes in older women. Limitations of previous studies and future directions are also discussed.

METHODS

Search Strategy and Selection Criteria

Our research question was: Do the benefits and harms of screening mammography in older women vary according to comorbidity and age? We performed a systematic search of the literature using PubMed and EMBASE (January 1, 1980, to July 1, 2013) to identify relevant studies in all languages. The term "breast neoplasms" was combined with the permutations, variations, and abbreviations of the relevant MeSH keywords and non-MeSH key terms for mammography, age, and comorbidity, including specific conditions (e.g., cardiovascular diseases, cognition disorders, diabetes mellitus, health status, heart diseases, hypertension, myocardial infarction, stroke) or comorbidity summary scores. Severe comorbidity was defined as a Charlson score of ≥ 3 and the presence of AIDS, mild or severe liver disease, chronic obstructive pulmonary disease, chronic renal failure, dementia, or congestive heart failure. A Charlson score of 3 or higher also represents severe comorbidity.

Additional studies were obtained through citations of review articles or by contacting experts in the field regarding any unpublished articles that might be suitable for inclusion in the systematic review.

For each study, two authors (MI and DB) independently abstracted data regarding study eligibility and outcomes to determine relevance. We set a priori broad inclusion criteria permitting any study design, including decision analyses that (i) included women aged 65 and older, (ii) assessed women's comorbidity (either as a specific condition or a summary score), and (iii) reported at least one of the following outcomes: (a) tumor stage at diagnosis, (b) reassurance about negative results, (c) life expectancy and/or quality-adjusted life expectancy, (d) mortality, and (e) number needed to screen to gain one life-year. We also evaluated studies that assessed harms as outcomes, specifically (a) false-positive results, (b) false-positive biopsy, and (c) overdiagnosis. We excluded studies of women with a history of breast cancer.

To evaluate the quality of observational studies, we used the Newcastle-Ottawa Scale (NOS),[19] in which a study is judged within three broad perspectives: (i) the selection of the study groups (representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of the exposure and demonstration that the outcome of interest was present); (ii) the comparability of the groups (comparability of cohorts on the basis of the design or analysis); and (iii) the ascertainment of either the exposure or outcome of interest (assessment of outcome, whether follow-up was long enough for outcomes to occur, and adequacy of follow-up of cohorts). Whereas a study can receive one star for meeting each criterion (*), the exception is comparability, for which a study receives one star if the study controlled for age, and two stars if the study also controlled for other important factors. Studies with a score of 5 and above (of a total of 9) are considered of moderate to high quality.

The included decision analyses were critically appraised according to criteria outlined by Richardson and Detsky[20] and Justice et al.,[21] with modification to include the suggestion of Justice et al.[21]—that models should be assessed for their transportability between populations, and that if valid, they should accurately predict events in populations other than the one in which the model was developed. This appraisal method was previously used in a systematic review of benefits and harms of screening mammography in older women.[22]

RESULTS

We identified 1760 potentially relevant abstracts through EMBASE and 398 through MEDLINE (see PRISMA flowchart in Fig. 1). After excluding studies with participants whose average age was less than 65 years, those that did not evaluate breast cancer or mammography screening, those that evaluated outcomes other than benefits or harms of screening, and those that did not report on comorbidity, there were 21 remaining studies published between 1980 and 2013,[3,15,17,23–39] with one article in the process of publication at the time of the literature search, which has since been published.[40] Reviews of the full texts of these studies resulted in the exclusion of 14 studies,[3,17,23–34] leaving 7 studies[15,35–40] (Fig. 1). Characteristics of the included studies are shown in Table 1. All four cohort studies[15,35–37] involved U.S. study populations, and all three decision analyses[38–40] employed U.S.-based population estimates. None of the studies were clinical trials.

Quality Assessment

All four cohort studies scored 5 points or more based on the NOS criteria, indicating moderate to good study quality.[19] A summary of the quality scoring criteria for cohort studies is provided in Table 2. In all cohort studies, downgrading of the evidence was due to a lack of adjustment for important confounding factors. Table 3 presents a critical appraisal of the decision analyses estimating life expectancy gains from screening mammography in older U.S. women. All decision-analytic studies conducted sensitivity analyses, and used U.S. estimates of prior probabilities, utilities, and other parameters in models, and were considered of good quality.

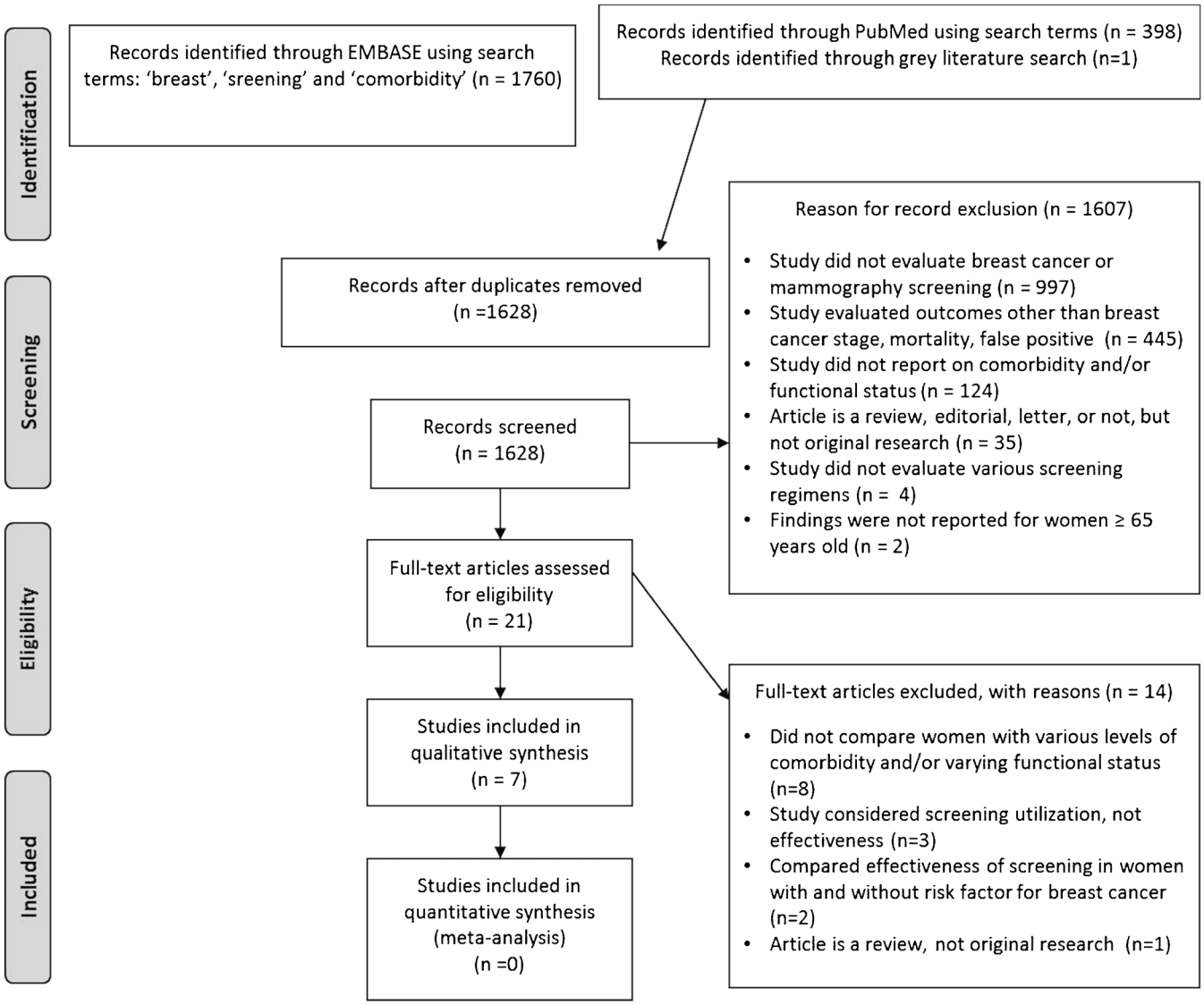

Figure 1 PRISMA flow diagram: description of the literature search.

Estimates of Screening Mammography Benefits from Cohort Studies

Benefit Estimates by Breast Cancer Mortality (Table 4).

In a study by McPherson et al.[37] reporting on 5186 women aged 65 years and older who were diagnosed with breast cancer between 1986 and 1994 through the Upper Midwest Tumor Registry system, women's comorbidity was assessed via the Charlson Comorbidity Score (CCS).[41] In this study, women aged ≥ 65 with no or moderate comorbidity and mammography-detected tumors were found to be at reduced risk of breast cancer death compared to those with clinically detected (palpable) tumors.[37] Furthermore, among women with severe comorbidity, as defined by a CCS score of≥3, mammography screening was associated with reduced breast cancer mortality among women aged 70–74 years, but not in those aged <70 or >74 years.[37]

Benefit Estimates by Tumor Stage. Of the three studies that evaluated the risk of early versus advanced tumor stage,[15,35,36] two—Braithwaite et al. and Yasmeen et al.—used data from the Breast Cancer Surveillance Consortium (BCSC) mammography registries that participated in a linkage with Medicare claims between 1999 and 2006,[15,36] where information on comorbidities was obtained from Medicare claims in the 2 years before screening mammography. In another cohort study, Flemming et al. merged data from the Surveillance, Epidemiology and End Results (SEER) program with Medicare claims for 17,468 women diagnosed with breast cancer between 1993 and 1995.[35] Heterogeneous measures of comorbidity were utilized: Braithwaite et al. employed the CCS,[15,37,41] while Flemming et al.[35] and Yasmeen et al.[36] reported on 24 individual conditions and severity-based categorizations of comorbidity, respectively.

Table 1 Characteristics of Studies Identified in Literature Search

Source	Setting	No. enrolled	Study design	Years of accrual	Age range, years	Length of follow-up	Measures of comorbidity	Screening regimens compared	Outcome(s) of interest reported
Cohort studies									
McPherson, 2002	USA	5186	Retrospective cohort	1986–1994	65–101	1 month to 10.9 years	Charlson Comorbidity Score	Mammographic vs. clinical (palpation) diagnosis	Risk of death
Fleming, 2005	USA	17,468	Retrospective cohort	1993–1995	≥67	–	24 conditions (listed in Table 4)	Diagnostic mammography vs. screening mammography	Late-stage (regional and distant) vs. early-stage (in situ and local) breast cancer
Yasmeen, 2012	USA	149,045	Prospective cohort	1998–2006	≥67	1–6 years	Unstable (life-threatening conditions such as severe heart failure, cardiac arrhythmias, end-stage liver disease), stable (conditions that could affect daily function such as diabetes, depression, arthritis, osteoporosis), or none	1-year interval vs. 2-year interval vs. 3-year interval vs. >3 years or first screening mammography vs. >3 years or first diagnostic mammography	Advanced- (stages IIB–IV) vs. early-stage (stages I–IIA) breast cancer
Braithwaite, 2013	USA	140,942	Prospective cohort	1999–2006	66–89	1–10 years	Charlson Comorbidity Score	1-year interval vs. 2-year interval	1. Invasive breast cancer vs. ductal carcinoma in situ (DCIS) 2. Advanced- (stages IIB–IV) vs. early-stage (stages I–IIA) breast cancer 3. Large (>20 mm) vs. small (≤20 mm) tumors 4. Lymph node involvement vs. no 5. False-positive recall 6. False-positive biopsy recommendation
Decision-analytic models									
Mandelblatt, 1992	USA	–	Decision-analytic model	1975–1984	≥65	–	Average comorbidity (mortality equal to that of the general population), mild hypertension (mild comorbidity), congestive heart failure (major comorbidity)	Screening vs. no screening	1. Marginal savings in life expectancy 2. Long-term quality-adjusted marginal savings in life expectancy 3. Long- and short-term adjusted marginal savings in life expectancy
Messecar, 2000	USA	–	Decision-analytic model	–	≥75	10 years	Cognitive impairment vs. no cognitive impairment	One additional screening following regular biennial screening vs. no prior screening	Quality-adjusted savings in life expectancy

(continued on next page)

Table 1. (continued)

Source	Setting	No. enrolled	Study design	Years of accrual	Age range, years	Length of follow-up	Measures of comorbidity	Screening regimens compared	Outcome(s) of interest reported
Lansdorp-Vogelaar, 2014	USA	–	Decision-analytic models	–	50–90	–	None, mild (history of myocardial infarction [MI], acute MI, ulcer or rheumatologic disease), moderate (cardiovascular disease, paralysis, diabetes), or severe comorbidity (AIDS, chronic obstructive pulmonary disease, mild/severe liver disease, renal failure, dementia, congestive heart failure)	Biennial screening from age 50 to cessation age ranging from 66 to 90	1. Incremental life-years gained (LYG) 2. Cancer deaths prevented 3. Incremental number of screening tests 4. False-positive screens 5. Over-diagnosed cases 6. Number needed to screen to gain one life-year (NNS/LYG) in the population

Yasmeen et al. found that overall rates (per 1000 mammograms) of advanced breast cancer were lower among women with no comorbidity than among those with stable comorbidity in annually and biennially screened women and those that received their first screen.[36] However, among women who had previously undergone mammography within 4 to 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.[36] In contrast, in another BCSC study, Braithwaite et al.[15] reported that adverse tumor characteristics, including advanced stage, did not differ significantly by CCS or screening interval.[15]

Finally, Fleming et al.[35] reported that women with cardiovascular disease, musculoskeletal disorders, mild-to-moderate gastrointestinal disease, and non-malignant benign breast disease had 13, 7, 14, and 24 % lower odds, respectively, of being diagnosed with advanced breast cancer, while those with diabetes, other endocrine disorders, psychiatric disorders, or hematologic disorders had higher odds of advanced-stage diagnosis by 19, 11, 20, and 19 %, respectively, compared to women without these comorbidities.

Estimates of Screening Mammography Benefits from Decision Analyses

Benefit Estimates by Life Expectancy (Table 4). Two decision analyses in this systematic review, Mandelblatt et al.[39] and Lansdorp-Vogelaar et al.,[40] employed well-established, independently developed models that are part of the Cancer Intervention and Surveillance Modeling Network (CISNET), with each model simulating the life histories of large U.S. cohorts, and assessing the underlying disease in the presence and absence of screening.

In the only contemporary study examining the harms and benefits of stopping mammography according to comorbidity, Lansdorp-Vogelaar et al. compared the number needed to screen per life-year gained at different stopping ages and

Table 2 Critical Evaluation of the Quality and Limitations of the *Cohort* Studies Evaluating Benefits and Harms of Screening Mammography According to Comorbidity

	Selection				Comparability of cohorts	Outcome			NOS†
Source	Exposed cohort representative	Non-exposed cohort representative	Exposure ascertainment	Demonstration that outcome of interest was not present at start		Assessment	Follow-up length	Follow-up adequacy	
McPherson, 2002	*	*	*		*	*	*	*	7
Fleming, 2005	*	*	*	*	*	*	*	*	8
Yasmeen, 2012	*	*	*	*	*	*	*	*	8
Braithwaite, 2013	*	*	*	*	*	*	*	*	8

†*Newcastle-Ottawa Quality Assessment Scale: study can have one star (*) for meeting each criterion in the selection and outcome categories. Comparability has a maximum of two stars. In this review, one star was given if a study controlled for age and two stars if it controlled for other important factors*

Table 3 Critical Evaluation of the Quality and Limitations of the *Decision-Analytic* Models Evaluating Benefits and Harms of Screening Mammography According to Comorbidity

Source	Were important strategies included?	Was the potential impact of uncertainty in the evidence determined?	How strong is the evidence?	Do the probabilities fit the U.S. population?	Do the utilities* reflect the values of older women in the U.S.?
Mandelblatt, 1992	Yes - compared screening for women ≥65 years with no screening	Conducted sensitivity analyses by varying quality of life, breast cancer incidence rates, perioperative death rate, sensitivity and specificity of mammography test, stage distribution of detected breast cancer	The evidence is strong, as the model assumes U.S. breast cancer stage distribution and stage-specific survival data	All measures used in models were based on U.S. population estimates	Yes
Messecar, 2000	Yes - compared 1 mammography screening in women ≥75 years with and without cognitive impairment, who (a) underwent regular screening, or (b) had no prior screening	Conducted sensitivity analyses by varying prior probabilities, quality of life, costs of recurrence, sensitivity and specificity of mammography test	The evidence is strong, as the model assumes U.S. breast cancer stage distribution and stage-specific survival data	All measures used in models were based on U.S. population estimates	Yes
Lansdorp-Vogelaar, 2014	Yes - compared biennial mammography screening from age 50 to a range of cessation ages from 66 to 90	Assessed the robustness of choice of metric by considering other harms (false-positive tests, over-diagnosed cancers) and benefits (cancer deaths prevented). Also varied method of extrapolating comorbidity-specific life tables	The evidence is strong, as the models assume U.S. breast cancer stage distribution and stage-specific survival data	All measures used in models were based on U.S. population estimates	Yes

* *Weights used to adjust life expectancy gains for impact on quality of life*

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 mammography until age 74 for women of average comorbidity.[40] The authors evaluated biennial mammography screening from age 50 to a cessation age ranging from 66 to 90 by simulating U.S. cohorts of women who were 66–90 years of age 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 women aged 74 and 76 years with average comorbidity. The authors found that, with breast cancer screening through age 74, the number needed to screen to gain one life-year among women with no comorbidity was 117–149 across models, which was lower than in the entire population with average comorbidity; cessation of screening at age 76–78 years among women with no comorbidities was estimated to yield the same number needed to screen to gain one life-year as cessation at age 74 years in the entire population.[40] Finally, this study pointed to the benefits of biennial mammography across models until median ages of 76–78, 74, 70–72, and 64–68 years for women with no comorbidity, mild comorbidity, moderate comorbidity, and severe comorbidity, respectively.[40]

In hypothetical cohorts examining the benefits of biennial screening in terms of life-years, Mandelblatt et al.[39] found that long- and short-term quality-adjusted savings in life expectancy from screening compared to a non-screening 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.

In another decision analysis examining three hypothetical cohorts of women aged 75–79, 80–84, and ≥ 85 years, with and without cognitive impairment, Messecar et al. tested two models for each group, assuming no prior screening versus continued biennial screening. Whereas all older women benefited from biennial mammography screening, among women with no prior screening, the gain in quality-adjusted life-years was lower for cognitively impaired women (20, 9.1, and 5.5 days for ages 75–79, 80–84, and ≥ 80 years, respectively) than their healthy counterparts (43.4, 32.5, and 25.9 days for ages 75–79, 80–84, and ≥ 80 years, respectively).[38]

Estimates of Screening Mammography Harms from Cohort Studies

Harm Estimates by False-Positive Results (Table 4). In the only cohort study to evaluate 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 than biennial screeners, irrespective of comorbidity: 48.0 % (95 % CI 46.1–49.9 %) of annual screeners aged 66 to 74 years had a false-positive result, compared with 29.0 % (95 % CI 28.1–29.9 %) of biennial screeners.[15]

Table 4 Summary of Findings from Studies Evaluating the Benefits, Harms and the Balance of Benefits Versus Harms of Screening Mammography

Source	Subgroups	Outcomes Reported			
Benefits					
McPherson, 2002		Relative risk (RR) of death and 95 % confidence interval (CI)			
	Screening groups	Mammographic vs. clinical (palpation) diagnosis			
	Comorbidity	No comorbidity	Moderate	Severe	
	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, 2005		Odds ratio (and *p* value) of late-stage (regional and distant) vs. early-stage (in situ and local) disease, by comorbid condition			
	Screening groups	All patients were screened			
	Comorbidity	Cardiovascular disease	Benign hypertension	Malignant hypertension	Other vascular disease
		0.87 ($P<0.01$)	0.98 ($P<0.05$)	1.02 ($P>0.05$)	1.04 ($P>0.05$)
		Diabetes	Endocrine disease	Neurological disease	Psychiatric disease
		1.19 ($P<0.01$)	1.11 ($P<0.05$)	1 ($P>0.05$)	1.2 ($P<0.01$)
		Musculoskeletal disease	Pulmonary disease, mild/moderate	Pulmonary disease, severe	Gastrointestinal disease
		0.93 ($P<0.01$)	1.08 ($P>0.05$)	0.99 ($P>0.05$)	0.86 ($P<0.01$)
		Benign breast disease, nonmalignant	Genital-urinary disease	Obesity	AIDS
		0.76 ($P<0.01$)	0.91 ($P>0.05$)	1.18 ($P>0.05$)	1.41 ($P>0.05$)
		Cerebrovascular disease	Renal disease	Gastrointestinal disease, severe	Hematologic disease
		1.03 ($P>0.05$)	1.15 ($P>0.05$)	0.94 ($P>0.05$)	1.19 ($P<0.01$)
		Osteoarthritis	Osteoporosis	Rheumatologic disease	Other cancers
		0.96 ($P>0.05$)	1.16 ($P>0.05$)	1.02 ($P>0.05$)	1.04 ($P>0.05$)
Yasmeen, 2012		Rates (per 1000 mammograms) and 95 % confidence intervals for advanced (stages IIB–IV) vs. early-stage (stages I–IIA) breast cancer			
	Screening groups	One additional screening			
	Comorbidity	All	No comorbidities	Stable comorbidities	Unstable comorbidities
	Time since prior screening				
	4–18 months (1 year)	0.7 (0.6–0.8)	0.3 (0.2–0.6)	0.7 (0.6–0.8)	0.9 (0.7–1.2)
	19–30 months (2 years)	0.9 (0.7–1.2)	0.4 (0.1–1.5)	0.9 (0.6–1.3)	1.0 (0.6–1.6)
	31–42 months (3 years)	1.6 (1.1–2.4)	2.2 (0.8–5.9)	1.0 (0.5–1.9)	2.7 (1.6–4.7)
	>42 months/first screen	1.7 (1.2–2.4)	1.3 (0.4–3.9)	1.5 (0.9–2.5)	2.2 (1.3–3.9)
Braithwaite, 2013		Odds ratio (OR) and 95 % confidence interval (CI) for invasive breast cancer vs. ductal carcinoma in situ (DCIS)			
	Screening groups	2-year vs. 1-year interval			
	Comorbidity	CCS = 0	CCS ≥ 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)		
		Odds ratio (OR) and 95 % confidence interval (CI) for advanced-stage (stages IIB–IV) vs. early-stage (stages I–IIA) breast cancer			
	Screening groups	2-year vs. 1-year interval			
	Comorbidity	CCS = 0	CCS ≥ 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)		
		Odds ratio (OR) and 95 % confidence interval (CI) for large tumors (>20 mm) vs. small (≤20 mm)			
	Screening groups	2-year vs. 1-year interval			
	Comorbidity	CCS = 0	CCS ≥ 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)		
		Odds ratio (OR) and 95 % confidence interval (CI) for positive lymph node involvement			
	Screening groups	2-year vs. 1-year interval			
	Comorbidity	CCS = 0	CCS ≥ 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)		
Mandelblatt, 1992		Long-term quality-adjusted marginal savings in life expectancy (in days) and 95 % confidence intervals (CI)			
	Screening groups	Screening vs. no screening			
	Comorbidity	Average health	Mild hypertension	Congestive heart failure	Average health (black)
	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)

(*continued on next page*)

Table 4. (continued)

Source	Subgroups	Outcomes Reported			
	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 and 95 % confidence intervals (CI)			
	Screening groups	Screening vs. no screening			
	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, 2000		Quality-adjusted savings in life expectancy, quality-adjusted life-years (days)			
	Screening groups	One additional screening in women following regular biennial screening vs. no prior screening			
	Subgroups	*Following regular biennial screening*		*No prior screening*	
	Comorbidity	Cognitive impairment	Healthy	Cognitive impairment	Healthy
	Ages: 75–79	0.004 (1.5)	0.009 (3.3)	0.055 (20)	0.119 (43.4)
	Ages: 80–84	0.002 (0.7)	0.007 (2.5)	0.025 (9.1)	0.089 (32.5)
	Ages: ≥85	0.001 (0.4)	0.006 (2.2)	0.015 (5.5)	0.071 (25.9)
Lansdorp-Vogelaar 2015		Incremental life-years gained (LYG) per 1000 individuals screened according to guidelines since age 50 in populations with average comorbidity, by model and age of screening cessation			
	Screening groups	Age of screening cessation			
	Comorbidity	Average comorbidity			
	Model	*MISCAN-Fadia**	*SPECTRUM*†		
	Age of cessation 74 (vs. 72)	7.6	5.8		
	Age of cessation 76 (vs. 74)	6.9	5.1		
		Deaths prevented per 1000 individuals screened according to guidelines since age 50 in populations with average comorbidity, by model and age of screening cessation			
	Screening groups	Age of screening cessation			
	Comorbidity	Average comorbidity			
	Model	*MISCAN-Fadia**	*SPECTRUM*†		
	Age of cessation 74 (vs. 72)	0.9	0.7		
	Age of cessation 76 (vs. 74)	0.9	0.7		
Harms					
Braithwaite, 2013		% of false-positive recalls at first mammography			
	Screening groups	First mammography for all women			
	Comorbidity	CCS = 0	CCS ≥ 1		
	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)		
		% of women with at least one false-positive recall after 10 years of subsequent mammography, by screening interval			
	Screening groups	*All women were screened annually*		*All women were screened biennially*	
	Comorbidity	CCS = 0	CCS ≥ 1	CCS = 0	CCS ≥ 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)
		% of false-positive biopsy recommendations at first mammography			
	Screening groups	First mammography for all women			
	Comorbidity	CCS = 0	CCS ≥ 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)		
		% of women with at least one false-positive biopsy recommendation after 10 years of subsequent mammography, by screening interval			
	Screening groups	*All women were screened annually*		*All women were screened biennially*	
	Comorbidity	CCS = 0	CCS ≥ 1	CCS = 0	CCS ≥ 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 (in press)		False-positive tests per 1000 individuals screened according to guidelines since age 50 in populations with average comorbidity, by model and age of screening cessation			
	Screening groups	Age of screening cessation			
	Comorbidity	Average comorbidity			
	Model	*MISCAN-Fadia**	*SPECTRUM*†		
	Age of cessation 74 (vs. 72)	79	96		
	Age of cessation 76 (vs. 74)	77	96		

(continued on next page)

Table 4. (continued)

Source	Subgroups	Outcomes Reported	
		Over-diagnosed cases per 1000 individuals screened according to guidelines since age 50 in populations with average comorbidity, by model and age of screening cessation	
	Screening groups	Age of screening cessation	
	Comorbidity	Average comorbidity	
	Model	*MISCAN-Fadia**	*SPECTRUM*†
	Age of cessation 74 (vs. 72)	0.8	0.5
	Age of cessation 76 (vs. 74)	1	0.6
Balance of benefits versus harms			
Landsdorp-Vogelaar (2014)		Number needed to screen to gain one life-year (NNS/LYG), by model and age of screening cessation	
	Screening groups	Age of screening cessation	
	Comorbidity	Average comorbidity	
	Model	*MISCAN-Fadia**	*SPECTRUM*†
	Age of cessation 74 (vs. 72)	132	173
	Age of cessation 76 (vs. 74)	146	198

* *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 stage 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 mammography screening and its effects, and the dissemination of adjuvant treatment and its effects*

†*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 characteristic (such as estrogen receptor status, response to treatment, and mortality) to estimate the efficacy of screening programs*[53]

Estimates of the Harms of Screening Mammography from Decision Analyses

Harm Estimates by False-Positive Results (Table 4). In the only decision-analytic study to evaluate the harms of screening, Lansdorp-Vogelaar et al.[40] showed that ending screening at age 74 versus 72 years resulted in 96 more false positive tests and 0.5 more over-diagnoses per 1000 screening tests.

Balance of Benefits Versus Harms from Decision Analyses

Lansdorp-Vogelaar et al.[40] also estimated that extending breast cancer screening from age 72 to 74 years among individuals with average comorbidity required screening 132 to 174 women to gain one life-year; continuing screening until age 76 years required an additional 146–198 women screened to gain one life-year.[40]

DISCUSSION

As life expectancy continues to rise, it becomes increasingly important to determine the harms and benefits of preventive services such as screening mammography in older populations. The continuing controversy of whether to extend screening mammography to older women indicates a need to evaluate the extent to which benefits and harms of screening vary according to the extent and severity of comorbidity and age. The evidence currently available from both cohort studies and decision-analytic models[19,57–62] indicates that, apart from older women with severe comorbidity, women 65 and older may experience improved life expectancy from screening. Because studies in this synthesis were conducted over a long period of time, ranging from the mid-1970s to today, it is possible that outcomes may have been affected by the screening modality used, specifically film-screen versus digital mammography. However, the evidence has shown similar cancer detection rates with digital versus film-screen mammography among U.S. women aged 50–79 in the Breast Cancer Surveillance Consortium cohort.[42]

Comorbidity and Benefits of Screening in Older Women

Evidence points to a complex relationship between comorbidity and screening outcomes such as tumor stage at diagnosis and mortality, with variation linked to multiple patient factors including heterogeneous comorbidity measures, age, and screening intervals. Whereas Yasmeen et al. found that overall rates of advanced breast cancer were generally lower among women with no comorbidity versus those with stable comorbidity, Braithwaite et al.[57] reported that adverse tumor characteristics, including advanced stage, did not differ significantly based on Charlson score or screening interval in the population-based BCSC cohort[57]. Moreover, Fleming et al.[58] reported that the odds of early versus advanced tumor stage varied across individual comorbid conditions, with diabetes and hematologic disorders showing the highest (19 % increased) odds of advanced-stage disease at diagnosis. Finally,

in women with severe comorbidity, as defined by a Charlson score ≥ 3, mammography screening was associated with reduced breast cancer mortality among women aged 70–74 years, but not in those aged < 70 or > 74 years[59]. Consistent with observational data, decision-analytic models indicate that benefits were unlikely among women aged 65 years or older with severe comorbidity[60–62]. Specifically, in a decision-analytic model, Lansdorp-Vogelaar et al. showed that the benefits of biennial mammography existed 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.[61]

Comorbidity and Harms of Screening in Older Women

Overall, there is a dearth of evidence on the harms of screening mammography in older women: only one cohort study[15] and one decision model[40] in this systematic review assessed screening harms according to comorbidity. Braithwaite et al. demonstrated that the cumulative 10-year probability of a false-positive mammography result was approximately twice as high in biennially screened as in annually screened women aged 66 to 74 years, irrespective of comorbidity.[15] While examining one of the hypothetical cohorts, Lansdorp-Vogelaar et al.[40] demonstrated that ending screening at age 74 versus 72 years resulted in 96 more false-positive tests and 0.5 more cases of overdiagnosis per 1000 screening tests. Because rates of clinically indolent tumors and *ductal carcinoma in situ* (DCIS) increase with age, older women are more likely to be harmed from overdiagnosis,[16] defined as detection of tumors by screening that would not become clinically apparent during a woman's life or would not affect overall survival. Given the steeper rise in competing causes of mortality in women older than 74, evidence suggests that rates of overdiagnosis are likely to be greater for older than for younger women.[16,43]

Decision Making Regarding Benefits and Harms of Screening in Older Women

Given the limited available evidence, the communication of potential benefits and harms to women in their 70s and 80s also poses a challenge.[4,17,44–46] Clinical decisions among older populations about whether to undergo mammography may benefit from life expectancy-based screening strategies, especially given the evidence showing that screening mammography may not be targeted to the women who are most likely to benefit.[47] One meta-analysis demonstrated that 10.7 years (4.4 to 21.6) on average was required before one death from breast cancer was prevented per 1000 women screened, which supports the notion that screening should be targeted to women with a life expectancy greater than 10 years.[48] If these findings are replicated and confirmed with large-scale cohort data, women and their providers might consider the use of decision aids that accurately predict life expectancy in order to estimate a woman's risk of 10-year mortality and facilitate informed decisions about screening mammography.[49–51]

Evidence Gaps

This review has identified many areas related to screening mammography outcomes in older women that require additional research. Without randomized controlled trials, the benefits of continued screening mammography in women aged 75 and older will need to be ascertained from cohort data and simulation models. As noted in the recent *Journal of the National Cancer Institute* (*JNCI*) editorial,[52] it will be important to eschew the pseudo-precision that direct application of microsimulation models can offer by combining empirical evidence with modeling. Moreover, moving the field forward will necessitate modeling screening performance (false-positive rates, detection rates) and breast cancer survival as a function of comorbidity status and life expectancy, as well as the cost-effectiveness of various screening strategies according to comorbidity.

Strengths and Limitations

An important strength of this systematic review is that, to our knowledge, this is the first synthesis evaluating the extent to which benefits and harms of screening mammography vary according to comorbidity and age. It is important to recognize that observational data on screening mammography in older populations are subject to selection bias as well as lead-time and length bias.[5] In observational studies evaluating screening mammography, the study populations of older women have self-selected to undergo mammography screening, and are thus likely healthier than the general U.S. population. Moreover, this systematic review identified heterogeneous studies with differing endpoints, which precluded us from synthesizing our results and estimating effects and bias quantitatively.

Conclusions

In summary, the limited evidence currently available suggests that, apart from the oldest women and those with severe comorbidity, women aged 65 and older may experience a slight increase in life expectancy from screening. Given the potential for harm, it is unclear whether the magnitude of the benefit is sufficient to warrant regular screening. Women, clinicians, and policymakers should consider these factors in deciding whether to continue screening. Because Medicare is required under the Affordable Care Act to pay for yearly mammography screening at no cost to women age ≥ 40, with no upper age limit,[1,2] screening harms may increase among older women with multiple comorbid conditions as a result of inappropriate screening utilization. Given that a randomized controlled trial of mammography in older women is unlikely, more high-quality observational research examining innovative measures of life expectancy and contextual factors may facilitate an improved understanding of the benefits and harms of different screening mammography cessation ages and frequencies among older women and,

ultimately, inform clinical and policy decisions about the appropriate use of screening in this growing population.

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Compliance with ethical standards:

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