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Benefits and Harms of Mammography Screening After Age 74 Years: Model Estimates of Overdiagnosis

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Abstract

Background: The aim of this study was to quantify the benefits and harms of mammography screening after age 74 years, focusing on the amount of overdiagnosis of invasive breast cancer and ductal carcinoma in situ (DCIS).

Methods: Three well-established microsimulation models were used to simulate a cohort of American women born in 1960. All women received biennial screening starting at age 50 years with cessation ages varying from 74 up to 96 years. We estimated the number of life-years gained (LYG), quality-adjusted life-years, breast cancer deaths averted, false-positives, and overdiagnosed women per 1000 screens.

Results: The models predicted that there were 7.8 to 11.4 LYG per 1000 screens at age 74 years (range across models), decreasing to 4.8 to 7.8 LYG per 1000 screens at age 80 years, and 1.4 to 2.4 LYG per 1000 screens at age 90 years. When adjusted for quality-of-life decrements, the LYG decreased by 5% to 13% at age 74 years and 11% to 22% at age 80 years. At age 90 to 92 years, all LYG were counterbalanced by a loss in quality-of-life, mainly because of the increasing number of overdiagnosed breast cancers per 1000 screens: 1.2 to 5.0 at age 74 years, 1.8 to 6.0 at age 80 years, and 3.7 to 7.5 at age 90 years. The age at which harms began to outweigh benefits shifted to a younger age when larger or longer utility losses because of a breast cancer diagnosis were assumed.

Conclusion: The balance between screening benefits and harms becomes less favorable after age 74 years. At age 90 years, harms outweigh benefits, largely as a consequence of overdiagnosis. This age was the same across the three models, despite important model differences in assumptions on DCIS.

Mammography screening has been shown to be effective in reducing breast cancer mortality in randomized trials and nationwide screening programs in women age 50 to 74 years (1–4). Benefits and harms of screening mammography in women age 74 years and older are less well established and surrounded by uncertainty, because none of the randomized controlled trials designed to evaluate screening mammography included sufficient numbers of women age 74 years and older.

There are several factors that might influence the balance between benefits and harms of screening women older than 74 years. Because breast cancer incidence increases with age (5,6) and sensitivity is higher in the older age groups (7), the benefits of screening may be larger for older than for younger women. On the other hand, the benefits of screening might be limited because of the higher death rate from competing causes with advancing age. With regard to the harms of screening, the false-positive rates

have been found to decrease or remain stable after age 74 years (7), while the amount of overdiagnosis may on average increase with age because of the shorter remaining life-expectancy.

The extent to which overdiagnosis occurs is uncertain and widely debated, reflected in the wide range of estimates of up to 54% that have been published (8–15). Overdiagnosis is generally defined as "the detection of tumors that would not have been detected in a woman's lifetime in the absence of screening" (4,16). The difficulties associated with estimating the amount of over-diagnosis are reflected in this definition; once a screening pro-gram has been initiated it is impossible to know what would have happened in the absence of screening. The Independent UK Panel on Breast Cancer Screening stated that the results from observa-tional studies support the occurrence of overdiagnosis, but esti-mates of its magnitude are unreliable (4). An alternative effective method to address this issue is to use microsimulation models, which represent tumor growth and/or transitions among cancer states, incorporating age-related difference in tumor biology, and evaluate screening effects based on the synthesis of detailed data.

Despite the uncertainty around the benefits and harms, many women age 75 years and older are being screened in the United States. A recent study found that 62% of women age 75 to 79 years and 50% of women over age 80 years reported receiving a mammogram in the past two years (17). A physician recom-mendation is a strong determinant of mammography screening (17–19), and 70% to 86% of primary care physicians would re-commend mammography for a healthy woman age 80 years (20).

There is, however, no consensus in the United States on whether or not to recommend screening for women beyond age 74 years. For example, the American Cancer Society recommends mammography screening as long as women are in good health (21), while the US Preventive Services Task Force (USPSTF) recommends screening from age 50 to 74 years and concluded that "the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older" (22).

Previous modeling studies have assessed the benefits and harms of screening mammography, some of which have included older women. However, most of these studies focused on a subset of outcomes, without focusing on overdiagnosis explicitly (23), were based on the results of one model only (24,25), and/or looked at extending screening using large age ranges (eg, stopping at age 79 vs 70 years) (26).

In the present study, we therefore quantified the additional benefits (deaths averted and life-years gained) and harms (over-diagnosis and false-positives) of continuing mammography screening after age 74 years using three well-established micro-simulation models. Furthermore, we aimed to provide informa-tion about the harms and benefits of screening in a meaningful way, as previous studies have found that women as well as primary care physicians may have difficulties in understand-ing cancer screening statistics (27,28). Therefore, we presented the outcomes in two ways, as previously recommended (29): Benefits and harms were presented on the same scale (ie, as absolute numbers per 1000 screens) and combined in a single metric, quality-adjusted life-years (QALYs). We also estimated the age at which mammography screening no longer resulted in a positive number of QALYs, as a proxy for the age at which the harms began to outweigh the benefits of screening.

Methods

Model Overview

We used three microsimulation models developed as part of the Cancer Intervention and Surveillance Modeling Network

(CISNET): model E (Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands), model G-E (Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, NY), and model W (University of Wisconsin, Madison, WI, and Harvard Medical School, Boston, MA). The models have been described in detail elsewhere (30–32), and information about the models can be found online (http://cisnet.cancer.gov/). Briefly, the models simulated life histories for individual women. After estimating breast cancer incidence and mortality in the absence of screening and treatment, the models overlaid screening use and improvements in survival associated with treatment advances. A schematic representa-tion of the influence of breast cancer screening on (simulated) life histories is shown in Figure 1.

All three models incorporated age-related difference in tumor biology. Models E and W explicitly modeled tumor growth, and model G-E incorporated age-specific sojourn times and stage. At higher ages, the chance that a slow-growing tumor is detected increases. In addition, all three models included ductal carci-noma in situ (DCIS) with three different types of preclinical DCIS: regressive DCIS, DCIS that is diagnosed clinically, and DCIS that progresses to invasive disease. Model W also assumed that some cases of small invasive cancer are nonprogressive and have limited malignant potential (LMP). The models used incidence and mortal-ity data by age and calendar year (1975–1999) from the Surveillance, Epidemiology, and End Results (SEER) Program to estimate natural history parameters, including the transition rates of DCIS becoming invasive or clinically diagnosed and DCIS regression rates (model E) and the proportion of DCIS with LMP (model G-E and model W). All models have been previously validated and adequately reproduced SEER breast cancer incidence in women age 70 to 79 years (Figure 2) and age-adjusted mortality rates over time (30–33).

Model Parameters

We used a common set of age-specific model inputs (23) for the natural history of disease (incorporating age-related difference in tumor biology), breast cancer incidence (34), breast cancer–specific survival (35), and competing non–breast cancer causes of death (36). A cohort of women born in 1960 was simulated and followed throughout their entire lifetime. We assumed 100% adherence with screening and adjuvant treatment guidelines. In addition, we applied quality-of-life decrements by attaching weights to specific health states for women undergoing a mam-mogram and diagnostics (37) and life-years with breast cancer by stage of disease at diagnosis (38) (Table 1) to estimate QALYs.

Analysis

Biennial screening with 100% adherence started at age 50 years with varying cessation ages of screening. First, we simulated the screening policy currently recommended by the USPSTF (bien-nial screening from age 50–74 years) and assessed the benefits and harms per 1000 women alive at age 50 years, followed until death. We then determined the benefits and harms of the last screen (at age 74 years), and the additional benefits and harms of adding one more screen after the last screening test were estimated for increasing stopping ages of up to 96 years. We estimated the number of life-years gained (LYG), QALYs, breast cancer deaths averted, false-positive exams, and overdiagnosed women for each screening scenario per 1000 screens. The num-ber of overdiagnosed women was calculated as the difference in the predicted number of diagnosed women in the presence of screening and the predicted number of diagnosed women in the absence of screening.
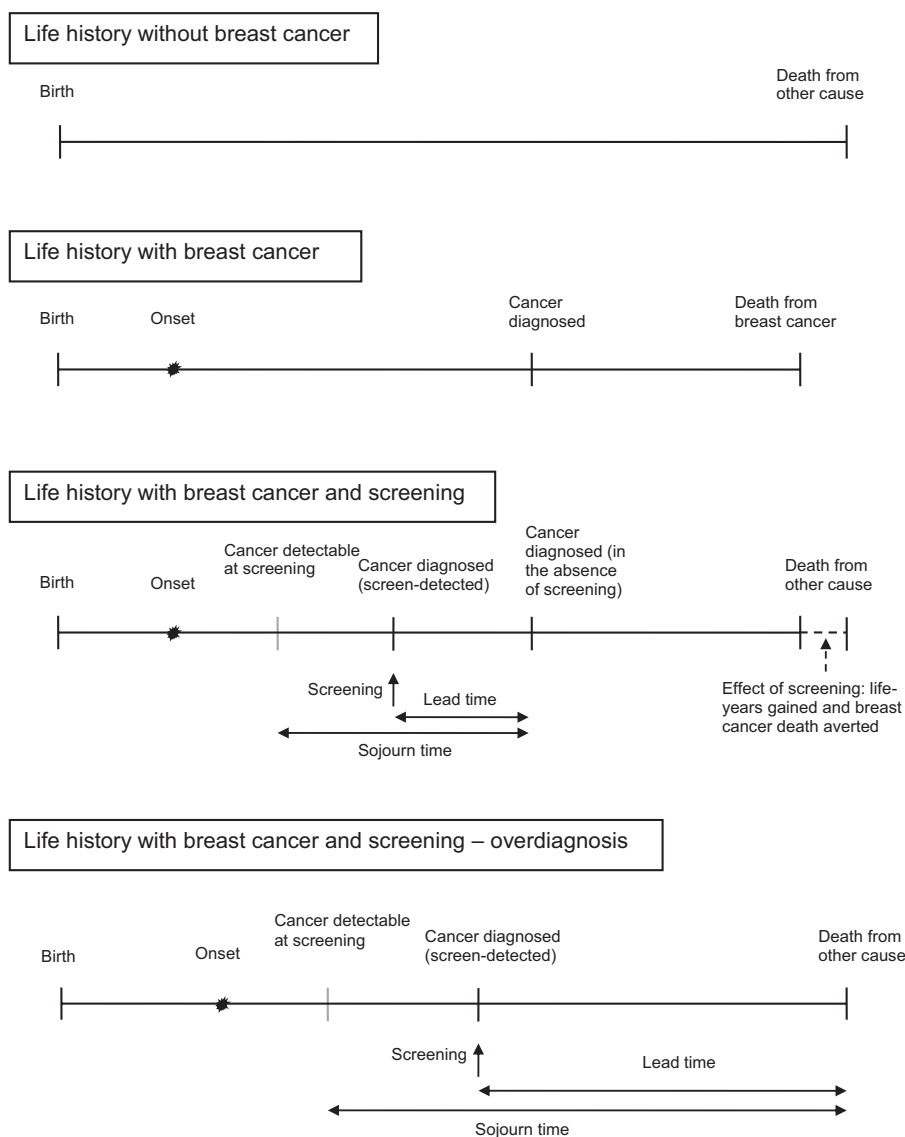
Figure 1. Schematic overview of simulated life histories and effect of screening. Sojourn time is the duration of the preclinical, screen-detectable phase of the tumor, and lead time is the interval from screen detection to the time of clinical diagnosis, when the tumor would have been diagnosed without screening. If the tumor is screen-detected without a clinical diagnosis in the absence of screening, the detection represents overdiagnosis. Lead time represents additional years that are lived with breast cancer because of screening.

Sensitivity Analysis

To evaluate how the results were influenced by certain assumptions and parameter values, we performed several sensitivity analyses. In particular, we assessed the effect of using different utility decrements associated with a breast cancer diagnosis for DCIS and local disease as used in previous studies (0.05, 0.15, and 0.20, instead of 0.10) (39,40). In addition, we assessed the effect of different durations for the utility decrements (5 years instead of 2 years for the effect of diagnosis in the DCIS, local or regional state).

Results

The models estimated that if 1000 women age 50 years underwent biennial screening from age 50 to 74 years (thus, undergoing a total of 11 117–11 337 mammograms), between 8.0 and 8.9 breast cancer deaths were prevented, depending on the model, and there were 132 to 142 LYG (Table 2). The models predicted that in the absence of screening there would be 137 to 154 breast cancers diagnosed. In the presence of screening this increased to 151 to 170 diagnoses. Thus, among these 1000 women, 5.9 to 33.0 women (0.5–3.0 per 1000 screens) were diagnosed in the presence of screening but would not have been diagnosed in the absence of screening, and were thus overdiagnosed.

Extending screening beyond age 74 years resulted in a steep increase in the number of overdiagnosed women (Figure 3, A-C). The number of overdiagnosed breast cancers (DCIS + invasive) increased from 1.2 to 5.0 per 1000 screens at age 74 years, 1.8 to 6.0 at age 80 years, and 3.7 to 7.5 at age 90 years.

If overdiagnosis is expressed as a percentage of screen-detected cancers, it also increased steeply in all three models (Table 3). Screening women from ages 50 to 74 results in 5% to 32% (range between the models) of the invasive breast cancers that were screen-detected being overdiagnosed, increasing to 14% to 36% for a screen at age 80 years and 28% to 41% for a
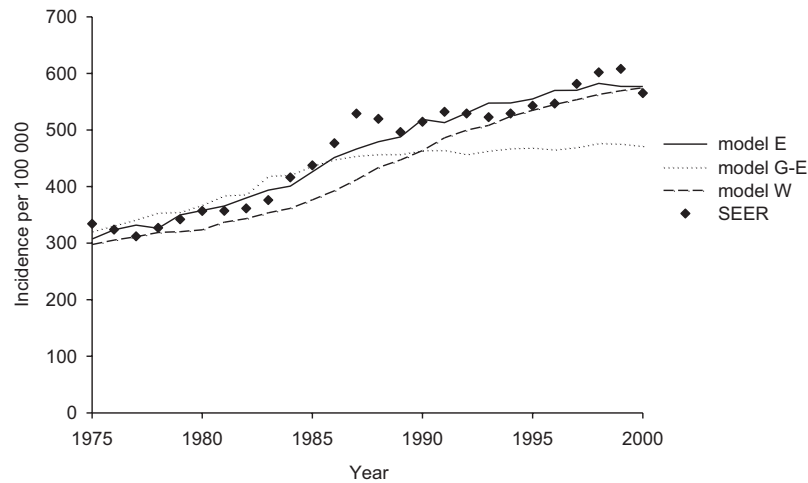
Figure 2. Age-adjusted breast cancer incidence rates from 1975 to 2000 predicted by the models vs reported to SEER for women age 70 to 79 years. SEER = Surveillance, Epidemiology, and End Results.

Table 1. Utility values and durations of different health states used in the simulation models of breast cancer

State	Utility	1-utility	Duration	Source
Screening attendance	0.994	0.006	1 wk	de Haes (37)
Diagnostic phase	0.895	0.105	5 wk	de Haes (37)
Breast cancer by stage of disease at diagnosis				
Local or DCIS*	0.90	0.10	2 y	Stout (38)
Regional	0.75	0.25	2 y	Stout (38)
Distant	0.60	0.40	Until death	Stout (38)

*DCIS = ductal carcinoma in situ.

Table 2. Benefits and harms of biennial mammography screening age 50–74 y, assuming 100% attendance

Outcomes per 1000 women alive at age 50 y	Model E	Model G-E	Model W
Number of mammograms	11 151	11 337	11 117
Number of breast cancers in the absence of screening	139	154	137
Number of breast cancers	151	159	170
Screen detected BCs (% DCIS)	84 (26)	81 (19)	95 (30)
Life-years gained (per 1000 screens)	136 (12.2)	142 (12.6)	132 (11.8)
QALYs (per 1000 screens)*	132 (12)	135 (12)	119 (11)
Reduction in LYG after adjustment for QoL, %	3	6	9
BC deaths in the absence of screening	31.3	36.0	35.3
BC deaths	22.4	28.0	27.2
BC deaths averted (per 1000 screens)	8.9 (0.8)	8.0 (0.7)	8.1 (0.7)
False-positives (per 1000 screens)	865 (78)	1030 (91)	915 (82)
Overdiagnosis DCIS (per 1000 screens)	9.2 (0.8)	2.7 (0.2)	11.4 (1.0)
Overdiagnosis invasive BCs (per 1000 screens)	3.0 (0.3)	3.2 (0.3)	21.7 (2.0)
Overdiagnosis Total (per 1000 screens)	12.2 (1.1)	5.9 (0.5)	33.0 (3.0)
% of all BCs detected at ages 50+†	8	4	19
% of BCs detected during screening‡	11	6	27
% of screen-detected BCs§	14	7	35

* Example calculation of quality-adjusted life-years (QALYs): Model G-E predicts that screening biennially from age 50 to 74 years results in 142 life-years gained (LYG). These LYG are reduced when correcting for quality-of-life in different phases: undergoing screening results in a utility loss of 1.31 (11 337 screens x 0.006 [1-utility] x 7/365 [duration 1 week]) and undergoing testing because of additional positive tests results in a utility loss of 10.43 ([1030+6] x 0.105 [1-utility] x 35/365 [duration 5 weeks]). In addition, the number of life-years after breast cancer (BC) diagnosis in different stages is estimated in a situation with and without screening, which results in an increase in life-years after diagnosis in local stage and ductal carcinoma in situ (DCIS) of 44.47, resulting in a utility loss of 4.5 (44.47 x 0.10). Because of earlier diagnosis a reduction in life-years after diagnosis in the regional and distant stage is predicted, resulting in utility losses of -5.35 (-21.44 LY x 0.25 [1-utility]) and -2.97 (-7.44 x 0.40 [1-utility]), respectively. Taken together, this results in a total reduction in LYG of 7.8 (1.31+10.43+4.5-5.35-2.97), and thus 142.4 LYG - 7.8 = 134.6 QALYs. The corresponding reduction in LYG after adjustment for quality of life is 7.8/134.6 = 6%. BC = breast cancer; DCIS = ductal carcinoma in situ; LYG = life-years gained; QALY = quality-adjusted life-year; QoL = quality of life.
† Number of excess cancers as a proportion of cancers diagnosed from age 50 years to death.
‡ Number of excess cancers as a proportion of cancers diagnosed during the screening period (between age 50 and 74 years).
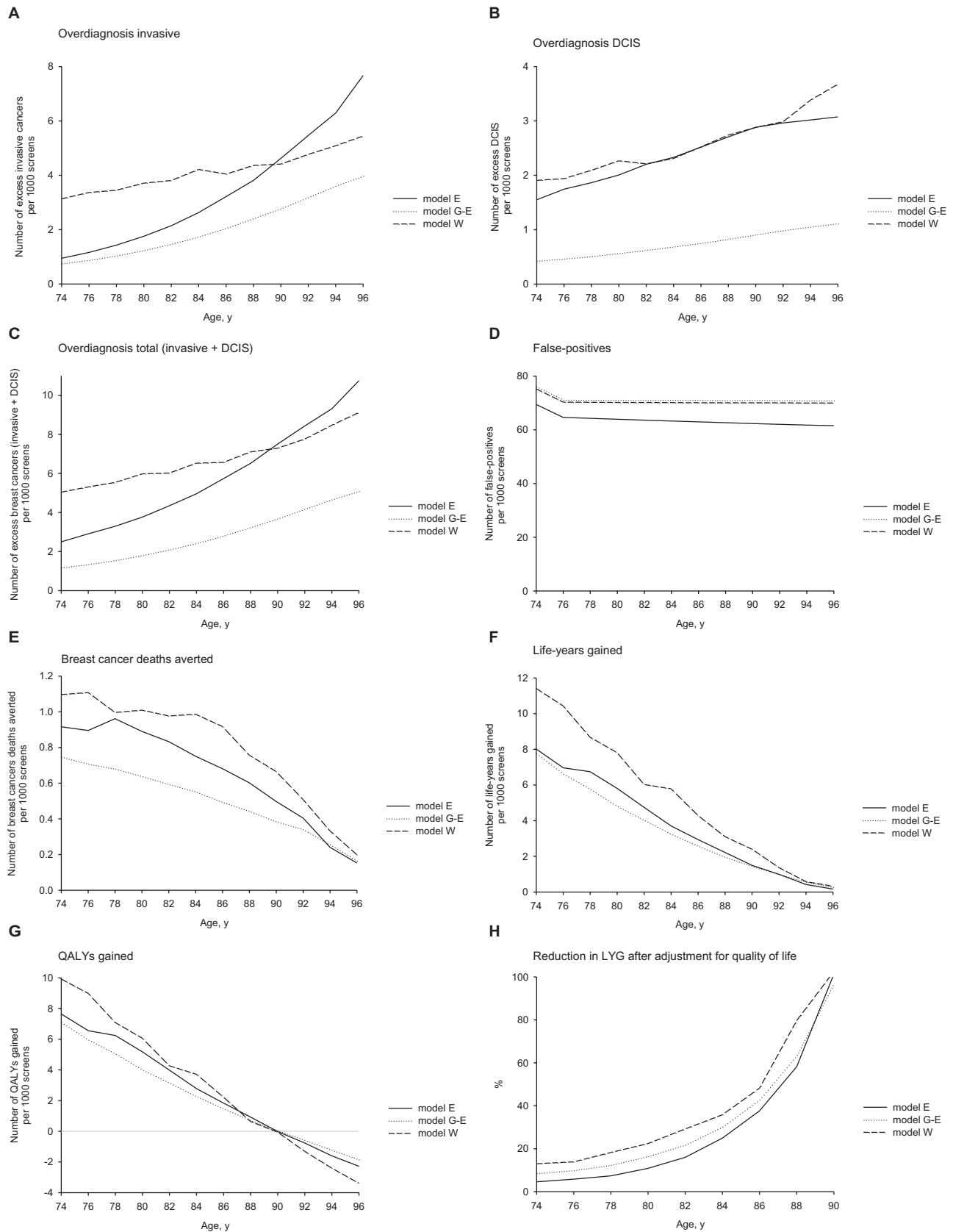§ Number of excess cancers as a proportion of screen-detected cancers.

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Figure 3. Benefits and harms of continuing screening after age 74 years (outcomes per 1000 screens at increasing ages). **A)** Number of excess invasive cancers per 1000 screens. **B)** Number of excess ductal carcinomas in situ (DCIS) per 1000 screens. **C)** Number of excess total breast cancers per 1000 screens (invasive + DCIS). **D)** Number of false-positives. **E)** Number of breast cancer deaths averted per 1000 screens. **F)** Number of life-years gained per 1000 screens. **G)** Number of quality-adjusted life-years gained per 1000 screens. **H)** Relative reduction in LYG after adjustment for quality of life (%). DCIS = ductal carcinoma in situ; LYG = life-years gained; QALY = quality-adjusted life-years.

Table 3. Percentage of screen-detected breast cancers (invasive and DCIS) that are overdiagnosed* by screening age and model

Stage at diagnosis	Screening age, y†	Model E, %	Model G-E, %	Model W, %
Invasive	50–74	5	5	32
	74	11	9	35
	80	17	14	36
	90	37	28	41
DCIS	50–74	41	18	40
	74	61	27	47
	80	72	35	52
	90	91	53	60
Total	50–74	14	7	35
	74	22	12	39
	80	29	17	41
	90	48	32	47

* Number of excess cancers as a proportion of cancers detected at screening. DCIS = ductal carcinoma in situ.
† All screens with 100% attendance. Screening age 50–74 years: biennial screening starting at age 50 years and ending at age 74 years. The percentage includes all excess breast cancers detected at screening between age 50 and 74 years divided by all screen-detected breast cancers between age 50 and 74 years. Screening age 74, 80, 90 years: all women have been screened biennially up to the screening age. The percentage includes all excess breast cancers detected at screening at age 74, 80, and 90 years divided by all screen-detected breast cancers at age 74, 80, and 90 years, respectively.
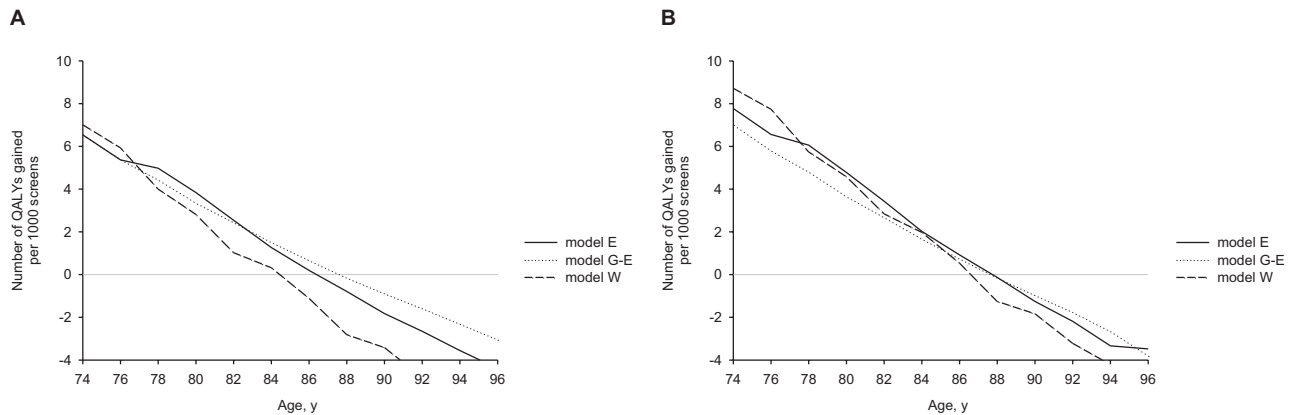

Figure 4. The number of quality-adjusted life-years (QALYs) gained of continuing screening after age 74 years (outcomes per 1000 screens at increasing ages). **A)** QALYs gained per 1000 screens assuming a utility decrement of 0.2 instead of 0.1 for ductal carcinoma in situ (DCIS) and local disease. **B)** Assuming utility decrements for a breast cancer diagnosis of DCIS, local and regional disease for a duration of five years instead of two years. DCIS = ductal carcinoma in situ; LYG = life-years gained; QALY = quality-adjusted life-years.

screen at age 90 years (Table 3). For DCIS, the percentages were higher in all three models, and increased from 18% to 41% for screening from age 50 to 74 years to 35% to 72% for a screen at age 80 years and 53% to 91% for a screen at age 90 years.

The models predicted that the numbers of false-positives were relatively stable after age 74 years (Figure 3D) and that screening beyond age 74 years resulted in benefits in terms of breast cancer deaths averted and LYG with no upper age limit, although the number of breast cancer deaths averted and LYG per 1000 screens steadily declined with increasing age (Figure 3, E and F); screening women at age 74 years results in 7.8 to 11.4 LYG per 1000 screens, which decreased to 4.8 to 7.8 for a screen at age 80 years and 1.4 to 2.4 for a screen at age 90 years. Thus, a breast cancer death averted at age 74 years saves 15.4 to 17.9 life-years, while at age 80 years this is 6.5 to 7.7 life-years, and the amount of LYG per death averted decreases to 3.0 to 3.7 at age 90 years.

The number of QALYs gained per 1000 screens decreased steadily with increasing age from 7.1 to 9.9 at age 74 years to 4.0 to 6.1 at age 80 years, and 2.4 to 3.7 at age 84 years. QALYs were still positive for screening up to age 90 years (Figure 3G). The number of QALYs gained became negative at age 90 years in models E and W and at age 92 years in model G-E. In other words, at age 90 to 92 years, all LYG were counterbalanced by a loss in quality of life because of undergoing a screening test and

diagnostics and additional life-years with disease that would have been spent in a healthy state in the absence of screening. The percentages of LYG that were counterbalanced by losses in quality of life increased steeply with increasing age at screening: when adjusted for quality-of-life decrements, the LYG decreased by 5% to 13% at age 74 years and 11% to 22% at age 80 years (Figure 3H).

Sensitivity Analysis

If a larger utility loss because of a breast cancer diagnosis was assumed for DCIS and local disease, the age at which QALYs became negative shifted to a younger age in all three models. For instance, when the utility loss is 0.2 instead of 0.1, the age at which the number of QALYs gained became negative shifted to age 86 years in model W and to age 88 years in models E and G-E (Figure 4A). If instead of a two-year duration, a five-year duration for the utility decrements was assumed, the age shifted to age 88 years in all three models (Figure 4B).

Discussion

The model results were very consistent in estimating the age at which the harms began to outweigh the benefits of mammography screening. At age 90 to 92 years, all LYG were

counterbalanced by a loss in quality of life, mainly because of the increasing amount of overdiagnosis. The consistency between models was remarkable, because the models included different assumptions on the natural history of DCIS.

Despite the consistency of our results, some limitations have to be considered. We estimated the benefits and harms for a cohort of women born in 1960, who on average have a remaining life expectancy at age 74 of 13 to 14 years. If life expectancy for older women continues to increase in the future, then we might have underestimated the benefits and overestimated the harms of screening. In addition, life expectancy varies by health status. Recently, two studies focused on more individualized decision-making about mammography in older women. A recently published review reported that observational studies favor extending screening mammography to older women who have a life expectancy of more than 10 years (41). However, tools to accurately estimate remaining life expectancy are still limited. Another recently published study showed that when screening at a certain age, for healthy women the balance between benefits and harms is more favorable than for women with severe comorbidity. For women with no, mild, moderate, and severe comorbid conditions, screening until ages 76, 74, 72, and 66 years, respectively, resulted in harms and benefits similar to screening average health persons until age 74 years (42).

To calculate QALYs we used utility values; ie, we attached weights to certain health states. We found that adjusting for quality of life (thus using QALYs instead of LYG) has only a small effect for ages 50 to 74 years, but an increasing effect at older ages because of the increasing amount of overdiagnosis, and hence additional life-years with disease. In addition, we found that the age at which harms began to outweigh benefits was sensitive to the utility values and shifted to a younger age when a larger disutility of the disease state or a longer duration for the utility decrements was assumed. This emphasizes the need for validated data on patient's utilities and durations for specific breast cancer disease states and a better understanding of utilities for different breast cancer disease states among older women. The advantages and disadvantages of using utilities and QALYs have been widely discussed (43,44). For the present study, the most important drawback is that individual preferences might diverge from the assumed values. For those women, looking at the benefits and harms per 1000 screens might be more informative than looking at the number of QALYs.

Our results on QALYs gained are largely in line with what has been previously reported. For example, a previous study found no reduction in the number of QALYs gained, as the upper age of screening increases when optimistic assumptions about the preclinical durations were made. However, when pessimistic assumptions were made, the QALYs gained became negative when screening was continued beyond age 80 years (45). The estimates from the present study are in between those from the optimistic and pessimistic scenarios (45).

The amount of overdiagnosis has been the topic of intense debate, partly because of methodological issues. Overdiagnosis is overestimated when calculations are derived from the implementation period of a screening program and when there is insufficient follow-up to observe a reduction in breast cancer incidence (9). Similarly, the range of overdiagnosis estimates is considerably smaller and estimates are lower (1% to 10%) when only studies that adequately adjust for lead time and changes in breast cancer risk are included (46).

The models estimated that 4% to 19% of all breast cancers detected in women age 50 years and over who undergo biennial screening from age 50 to 74 years are overdiagnosed. This range is consistent with the overdiagnosis estimate of 11% of cancers in women invited for screening from the Independent UK Panel on Breast Cancer Screening. A recent study on overdiagnosis in the United States estimated that 31% of breast cancers diagnosed in 2008 were overdiagnosed (15). This estimate cannot be directly compared with the estimates presented here, as we estimated overdiagnosis for specific screening scenarios and not for the screening as observed in the United States. The estimates from the models will, however, likely be lower, mainly because the models incorporate an age-period-cohort model, which incorporates a stronger increase in background incidence over time (34).

The model results showed a large range in overdiagnosis estimates. For invasive disease, one model (model W) estimated markedly higher overdiagnosis than the other two models up to age 86 years. This difference between models is because of the fact that model W includes a subset of small invasive cancers with limited malignant potential, which are assumed to grow only to a limited size and then disappear.

There was also a large difference in the predicted amount of overdiagnosis of DCIS between models, which likely reflects the continued uncertainty about DCIS natural history (47). Little is known on the natural history of DCIS, because DCIS is usually removed as soon as it is detected. There is evidence for progression of DCIS from studies in women with low-grade DCIS that is initially mistakenly diagnosed as benign, reporting that 14% to 60% of those women develop invasive cancer within 10 to 20 years (48–50). There is, however, also evidence that not all DCIS become invasive, for example from autopsy studies that found a prevalence of DCIS of 0% to 15% in women not known to have had breast cancer (51). Our results do not provide additional information on the natural history of DCIS, because all three models adequately replicated incidence trends, despite differences in the assumed natural history of DCIS. This finding is in line with a previous modeling study that found that two alternative models with extreme assumptions on progression and regression rates of DCIS fit the observed breast cancer incidence in the Netherlands equally well (52).

The models estimated that at age 90 years, 53% to 91% of the screen-detected DCIS are overdiagnosed, indicating that for every 1000 screens performed at age 90 years, one to three women are overdiagnosed with DCIS. The majority of those women will undergo treatment for their disease; almost all women (97.5%) diagnosed with DCIS undergo a surgical procedure (53), 61% of women diagnosed with DCIS receive radiotherapy (54), and 47% receive adjuvant hormonal therapy (55). Although older women tend to receive less aggressive treatment than younger women (56), older women undergoing treatment may be exposed to more toxicity than younger women (57). Future research on the biological behavior of DCIS and predictors of risk for developing invasive disease is needed in order to prevent harm from treating nonprogressive disease (58,59).

In summary, the balance between benefits and harms of mammography becomes less favorable beyond age 74 years because of the increasing amount of overdiagnosis. For women with average life expectancy, beyond age 90 years screening harms outweigh benefits. An upper age limit of breast cancer screening, therefore, seems appropriate. The appropriate upper age for an individual woman depends on the weight she attaches to specific benefits and harms. From a societal perspective, the willingness to pay for a QALY may also need to be taken into account. If we were better able to distinguish between subtypes of DCIS that progress and those that do not, harm from treating nonprogressive disease could be prevented.

Funding

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