Annals of Internal Medicine | ORIGINAL RESEARCH

Tipping the Balance of Benefits and Harms to Favor Screening Mammography Starting at Age 40 Years

A Comparative Modeling Study of Risk

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Background: Timing of initiation of screening for breast cancer is controversial in the United States.

Objective: To determine the threshold relative risk (RR) at which the harm–benefit ratio of screening women aged 40 to 49 years equals that of biennial screening for women aged 50 to 74 years.

Design: Comparative modeling study.

Data Sources: Surveillance, Epidemiology, and End Results program, Breast Cancer Surveillance Consortium, and medical literature.

Target Population: A contemporary cohort of women eligible for routine screening.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Mammography screening starting at age 40 versus 50 years with different screening methods (film, digital) and screening intervals (annual, biennial).

Outcome Measures: Benefits: life-years gained, breast cancer deaths averted; harms: false-positive mammography findings; harm–benefit ratios: false-positive findings/life-years gained, false-positive findings/deaths averted.

Results of Base-Case Analysis: Screening average-risk women aged 50 to 74 years biennially yields the same false-positive findings/life-years gained as biennial screening with digital mammography starting at age 40 years for women with a 2-fold increased risk above average (median threshold RR, 1.9 [range across models, 1.5 to 4.4]). The threshold RRs are higher for annual screening with digital mammography (median, 4.3 [range, 3.3 to 10]) and when false-positive findings/deaths averted is used as an outcome measure instead of false-positive findings/life-years gained. The harm–benefit ratio for film mammography is more favorable than for digital mammography because film has a lower false-positive rate.

Results of Sensitivity Analysis: The threshold RRs changed slightly when a more comprehensive measure of harm was used and were relatively insensitive to lower adherence assumptions.

Limitation: Risk was assumed to influence onset of disease without influencing screening performance.

Conclusion: Women aged 40 to 49 years with a 2-fold increased risk have similar harm–benefit ratios for biennial screening mammography as average-risk women aged 50 to 74 years. Threshold RRs required for favorable harm–benefit ratios vary by screening method, interval, and outcome measure.

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Breast cancer is the most frequently diagnosed noncutaneous cancer among women in the United States, where it is second only to lung cancer as a cause of cancer deaths. Mammography screening has been shown to reduce breast cancer mortality rates in randomized trials (1, 2) and nationwide screening programs (3).

The U.S. Preventive Services Task Force (USPSTF) recommends biennial breast cancer mammography screening for women aged 50 to 74 years on the basis of a comprehensive evaluation of current research indicating a favorable balance of benefits and harms (4, 5). Individual trials have not demonstrated significant breast cancer mortality reductions from screening women in their 40s (6, 7), but a meta-analysis of 8 trials found a 15% mortality reduction (8). The absolute benefits (for example, number of deaths prevented) are smaller than for older women because of the lower incidence of breast cancer and lower sensitivity of mammography in women aged 40 to 49 years. At the same time, screening in this age group is accompanied by more harm (false-positive results and unnecessary biopsies) as a result of lower screening specificity. As a result, the USPSTF concluded that the "decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into

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Context

Do the benefits and harms of breast cancer screening for younger women ever equal those for women aged 50 to 74 years?

Contribution

This modeling study found that starting biennial screening with digital mammography at age 40 years for high-risk women (those with a 2-fold increased risk above average) yields the same ratio of false-positive results to life-years gained as biennial screening of average-risk women aged 50 to 74 years.

Caution

Factors associated with risk were assumed not to influence screening performance.

Implication

Women aged 40 to 49 years with a 2-fold increased risk have harm–benefit ratios for biennial screening mammography similar to those of average-risk women aged 50 to 74 years.

—The Editors

account patient context, including the patient's values regarding specific benefits and harms" (4, 9).

Technology that improves screening test performance might influence the balance of benefits and harms of screening in younger women. Digital mammography has rapidly replaced film mammography in most areas of the United States (10). Younger women are more likely than older women to have dense breasts, and screening regimens using digital mammography in women aged 40 to 49 years might have a different balance of benefits and harms than strategies that use film mammography. Digital has a higher test sensitivity than film mammography in women younger than 50 years (11), detects more cases of ductal carcinoma in situ, and leads to more false-positive results (12). Thus, it is uncertain whether initiating screening at age 40 years with digital mammography would yield a more favorable balance of benefits and harms.

Another factor that changes the balance of benefits and harms is risk for breast cancer. Clearly, the absolute benefits of screening before age 50 years will be larger for women with an increased risk for breast cancer than for average-risk women. A more risk-based screening approach might therefore be appropriate (13–17). To implement a risk-based screening approach, it is crucial to know the magnitude of the relative risk (RR) that would tip the balance of benefits and harms to recommend screening for women aged 40 to 49 years (that is, threshold RR) and which risk factors lead to that elevated risk.

This study sought to determine the threshold risk at which the harm–benefit ratio of starting screening at age 40 years equals the harm–benefit ratio of currently recommended biennial screening for average-risk women starting at age 50 years. It also evaluates the effect of screening method (film, digital) and screening interval (annual, biennial) on the threshold RR by using 4 simulation models (18–21).

METHODS

Model Overview

We used 4 microsimulation models developed as part of the Cancer Intervention and Surveillance Modeling Network (CISNET), which is an international collaborative modeling consortium funded by the National Cancer Institute (22, 23). The 4 models were model D (Dana-Farber Cancer Institute, Boston, Massachusetts), model E (Erasmus University Medical Center, Rotterdam, the Netherlands), model G-E (Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York), and model W (University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts). The models have been described in detail elsewhere (18–21), 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 (22). The **Appendix Figure** (available at www.annals.org) shows the influence of breast cancer screening on (simulated) life histories. **Supplement 1** (available at www.annals.org) outlines the main model differences and assumptions.

Model Parameters

The model inputs and assumptions were based on assumptions previously used in a supporting article for the most recent USPSTF recommendation (23). We used a common set of age-specific variables for breast cancer incidence, survival, and competing non–breast cancer causes of death (**Supplement 2**, available at www.annals.org). A cohort of women born in 1960 was simulated and followed throughout their entire lifetime. We assumed 100% adherence to screening and adjuvant treatment guidelines.

The Breast Cancer Surveillance Consortium (BCSC) provided data on recent performance (between 2001 and 2007) of film and digital mammography (**Table 1**). The BCSC collects prospective data on breast imaging in community practice in 5 mammography registries and 2 affiliated sites in the United States (http://breastscreening.cancer.gov). Each registry obtains annual approval from its institutional review board for consenting processes or a waiver of consent, enrollment of participants, and ongoing data linkages for research purposes. All registries have received Federal Certificates of Confidentiality that protect the identities of research participants. The 4 models used BCSC data inputs for sensitivity; specificity; and stage distribution by age, screening method (film, digital), and

screening interval (annual, biennial) (http://breastscreening.cancer.gov/data/elements.html).

Screening Strategies

The effects of 5 screening scenarios were estimated per 1000 average-risk women aged 40 years followed over their lifetimes. These scenarios included biennial screening for women aged 50 to 74 years extended with 4 screening scenarios for women aged 40 to 49 years varying by screening interval (annual and biennial) and screening method (film and digital): 1) biennial film screening at age 50 to 74 years; 2a) biennial film screening at age 50 to 74 years and biennial film screening at age 40 to 49 years; 2b) biennial film screening at age 50 to 74 years and biennial digital screening at age 40 to 49 years; 3a) biennial film screening at age 50 to 74 years and annual film screening at age 40 to 49 years; and 3b) biennial film screening at age 50 to 74 years and annual digital screening at age 40 to 49 years.

The incremental effects of each scenario were determined by comparing it with the previous, less intensive scenario. To determine the effects of adding biennial screening for women in their 40s, scenarios 2a and 2b were compared with scenario 1; for annual screening, scenarios 3a and 3b were compared with scenarios 2a and 2b, respectively.

Benefits, Harms, and Harm–Benefit Ratios

We estimated the effect of each screening strategy on the number of breast cancer cases detected, the number of breast cancer deaths averted, the number of life-years gained, and the number of false-positive results on mammography screening. The time horizon for calculating effects was from age 40 years until death of all simulated women.

First, the effects (benefits and harms) of biennial screening between ages 50 and 74 years were determined. We defined harm as the number of false-positive results and benefits as the number of breast cancer deaths averted and number of life-years gained. Then, the additional effects of screening between ages 40 and 49 years were assessed for 2 screening intervals (annual and biennial) and 2 screening methods (film and digital). For each screening strategy, we determined the harm–benefit ratios by dividing the incremental harm by the incremental benefits.

We then implemented different RRs in the models. The higher risk was modeled over the entire lifetime of the simulated women. We calculated the incremental harms, benefits, and harm–benefit ratios of the 5 screening scenarios for women at increased risk. We used the harm–benefit ratio of biennial screening for average-risk women between ages 50 and 74 years (scenario 1) as a threshold value. Then, we determined how high the RR needed to be to have the same harm–benefit ratio as the threshold value for the 4 screening scenarios (scenarios 2a, 2b, 3a, and 3b) that started at age 40 years.

Sensitivity Analysis

To evaluate how the harm–benefit ratios and threshold RRs were influenced by certain assumptions and parameter values, we performed several sensitivity analyses. First, we explored the effect of reduced adherence (70%). Second, we considered alternative screening test characteristics of digital mammography (best-case scenario) by using an improved sensitivity and specificity (using the upper limit of the 95% CI). Third, we assessed the influence of a broader measure of harm on the threshold RRs by calculating quality-adjusted life-years (QALYs) lost. We applied quality-of-life decrements due to undergoing mammography and diagnostics (24) and life-years with breast cancer by stage of disease at diagnosis (25) (**Supplement 3**, available at www.annals.org). The number of QALYs lost incorporates harm from mammography, having a false-positive screening test result, and harm from overdiagnosis because with more overdiagnosis, more life-years are spent in disease stages and, thus, more QALYs are lost when

Table 1. **Sensitivity and Specificity of Screening Mammography (Digital and Film) by Age and Screening Interval Used in the Cancer Intervention and Surveillance Modeling Network Models Based on Data From the Breast Cancer Surveillance Consortium, 2001–2007***

Test Characteristic According to Age	Film Mammography		Digital Mammography	
	Annual	Biennial	Annual	Biennial
Sensitivity				
Age 40–44 y	69.5 (62.6–75.9)	68.0 (57.8–77.1)	78.4 (64.4–90.9)†	90.7 (76.8–100)†
Age 45–49 y	73.8 (69.6–77.7)	80.6 (75.1–85.3)	79.8 (67.6–87.7)†	91.6 (73.0–99.0)†
Specificity				
Age 40–44 y	91.0 (90.8–91.2)	90.1 (89.8–90.3)	87.5 (87.0–88.0)	87.7 (86.8–88.6)
Age 45–49 y	90.9 (90.7–91.0)	89.8 (89.6–90.0)	87.9 (87.5–88.3)	87.4 (86.6–88.2)

* Values in parentheses are 95% CIs.

† The models used extrapolated values for the sensitivity of digital mammography because the 95% CIs of the sensitivity of digital mammography were wide. The extrapolated values were derived by using regression models based on the sensitivity values in other age groups (data not shown). The 4 extrapolated numbers are shown and were very close to the Breast Cancer Surveillance Consortium data (80.0 and 78.9 for annual screening at ages 40 to 44 and 45 to 49 y, respectively, and 91.7 for biennial screening at age 45 to 49 y), except for the sensitivity of biennial screening with digital mammography for the 40- to 44-y age group, for whom the Breast Cancer Surveillance Consortium data indicated a sensitivity of 100.

Table 2. **Effects of Biennial Screening Between Ages 50 and 74 Years per 1000 Women***

Model†	Mammography Screenings, *n*	Breast Cancer Cases Detected, *n*	Benefits		Harms (False-Positive Findings), *n*	Harm–Benefit Ratios	
			Breast Cancer Deaths Averted, *n*	Life-Years Gained		False-Positive Findings/Breast Cancer Deaths Averted	False-Positive Findings/Life-Years Gained
D	10 529	156	6.9	113	877	128	7.8
E	10 655	164	5.3	93	795	151	8.5
G-E	10 566	163	6.6	108	939	142	8.7
W	10 660	232	5.9	111	890	151	8.0
Median	10 610	163	6.3	109	883	146	8.3

* Screening equivalent to 12.5 screening rounds in 25 y.
† Model D: Dana-Farber Cancer Institute, Boston, Massachusetts; model E: Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E: Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W: University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts.

there is a large amount of overdiagnosis. All 4 models incorporate overdiagnosis because in all models breast cancer may be detected in the presence of screening but would not have become symptomatic and would not have caused death during a woman's lifetime if no screening had taken place. Overdiagnosis estimates vary across models because of different underlying assumptions (for example, on the rates of progression from ductal carcinoma in situ to invasive disease and on the possibility of limited malignant potential of invasive disease). We used the harm–benefit ratio QALYs lost/life-years gained to re-estimate the threshold RRs.

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RESULTS

Average Risk

In the absence of screening, the models estimate that a median of 153 cases of breast cancer would be diagnosed (range across models, 152 to 158) and 25 deaths from breast cancer would occur (range, 19 to 35) among 1000 women 40 years of age followed over their lifetimes (data not shown).

If these women underwent biennial film mammography between the ages of 50 and 74 years, the models predict that 10 610 (range, 10 529 to 10 660) mammograms would be obtained over 12.5 screening rounds; 6.3 (range, 5.3 to 6.9) breast cancer deaths would be avoided; 109 (range, 93 to 113) life-years would be gained; and 883 (range, 795 to 939) mammography results would be read as false-positive. The harm–benefit ratios are estimated as 8.3 (range, 7.8 to 8.7) false-positive findings/life-years gained and 146 (range, 128 to 151) false-positive findings/deaths averted (**Table 2**).

In all models, the harm–benefit ratios for adding screening between ages 40 and 49 years are less favorable than those for biennial screening starting at age 50 years (**Table 3**). In all models, adding annual to biennial screening leads to slight increases in additional life-years gained and breast cancer deaths averted, but at the expense of greater increases in incremental harm. Adding annual screening to biennial screening starting at age 40 years therefore has a less favorable harm–benefit ratio than adding biennial screening starting at age 40 years to biennial screening from ages 50 to 74 years in all 4 models (**Table 3**).

With digital mammography screening, more life-years are gained and more breast cancer deaths averted than with film mammography, but because of the lower specificity of digital mammography for women in their 40s, it also yields more false-positive results. In all 4 models, there is greater harm relative to benefit from digital than from film mammography in women aged 40 to 49 years (**Table 3**).

Increased Risk

In all models, screening women with increased risk for breast cancer leads to a more favorable harm–benefit ratio. Screening women with increased risk results in more life-years gained and more breast cancer deaths averted with approximately the same number of false-positive results (see **Supplements 4** and **5**, available at www.annals.org, for data on women with a 2-fold increased risk for cancer). The models predict that annual screening with digital mammography for women aged 40 to 49 years with a 4-fold increased risk above average (median threshold RR, 4.3 [range across models, 3.3 to 10]) would yield similar estimates of false-positive findings/life-years gained as biennial screening for average-risk women aged 50 to 74 years. To find similar estimates of false-positive findings/life-years gained for biennial screening with digital mammography for women aged 40 to 49 years, the threshold RRs are lower in all models (median threshold RR, 1.9 [range across models, 1.5 to 4.4]).

For screening with film mammography, the threshold RRs are predicted to be somewhat lower in all models than

those estimated for digital mammography (median threshold RR for biennial screening, 1.6 [range, 1.5 to 3.7]) (**Table 4**). When deaths averted was considered as an outcome measure instead of life-years gained, all models estimated higher threshold RRs of 3.3 (range, 2.3 to 5.7) for biennial screening and even higher threshold RRs for annual screening (**Table 4**). The incremental changes in the benefits and harms of starting screening at age 40 years instead of at age 50 years per 1000 women for the threshold RRs are listed in **Supplement 6** (available at www.annals.org).

Sensitivity Analysis

When 70% adherence was assumed instead of 100%, the harms diminished by 30%, whereas the benefits diminished less (by 26% for biennial and 5% for annual screening). Therefore, more favorable harm–benefit ratios were found for biennial screening (for example, for film mammography in model E: 12.2 false-positive findings/life-years gained vs. 12.7 when 100% attendance was assumed) and for annual screening (in model E: 14.9 false-positive findings/life-years gained vs. 20.4 when 100% attendance was assumed). However, adding annual screening to biennial screening starting at age 40 years still had a less favorable harm–benefit ratio than adding biennial screening.

Changing screening test characteristics of digital mammography had only a very small influence on the harm-benefit ratios. The best-case scenario resulted in somewhat more benefits and fewer harms, but the differences in harm–benefit ratios were very small (<8%).

Use of the more comprehensive measure of harm (QALYs lost) led to somewhat higher predicted median threshold RRs (for example, 2.1 [range, 1.4 to 2.9] for biennial screening with digital mammography [vs. 1.9 when false-positive findings were used]).

Discussion

For women with approximately 2-fold increased risk for breast cancer, the balance of benefits and harms (life-years gained vs. false-positive results) of starting biennial screening at age 40 years approximates that of biennial screening for average-risk women starting at age 50 years. The models consistently showed that the additional benefits of adding annual screening are small and that there is greater harm relative to benefit from digital than from film mammography in women aged 40 to 49 years. To obtain harm–benefit ratios similar to those that result from currently recommended screening, the false-positive rates for biennial screening with digital mammography would have to decrease substantially among women in their 40s.

The model results on the difference between annual and biennial screening are largely in line with previous work. A retrospective study found that women screened annually versus biennially had similar distributions of prognostic factors (such as tumor size, lymph node status, and histologic grade) (26). However, another study found that specifically among women age 40 to 49 years, those undergoing biennial screening were more likely to have late-stage disease at diagnosis than those undergoing annual screening (27). It has been suggested that annual screening for younger women would be more beneficial than biennial screening because of the faster tumor growth

Table 3. **Incremental Changes in the Benefits and Harms of Starting Screening at Age 40 Years Instead of at Age 50 Years per 1000 Women**

Model*	Benefits				Harms (Additional False-Positive Findings), *n*		Harm–Benefit Ratios			
	Additional Breast Cancer Deaths Averted, *n*		Additional Life-Years Gained				False-Positive Findings/Breast Cancer Deaths Averted		False-Positive Findings/Life-Years Gained	
	Film	Digital	Film	Digital	Film	Digital	Film	Digital	Film	Digital
Biennial screening for women starting at age 40 y†										
D	0.5	0.5	17	16	490	607	896	1166	29	39
E	1.2	1.3	37	39	470	582	381	450	13	15
G-E	1.0	1.1	29	32	406	579	406	526	14	18
W	1.3	1.6	41	49	486	603	363	370	12	12
Median	1.1	1.2	33	36	478	592	393	488	13	16
Annual screening for women starting at age 40 y‡										
D	0.2	0.3	8	11	393	593	1579	1732	50	54
E	0.6	0.6	18	19	376	568	641	940	20	30
G-E	0.3	0.2	7	7	426	577	1420	2884	60	84
W	0.7	0.7	21	21	390	589	565	841	18	28
Median	0.4	0.5	13	15	391	583	1030	1336	35	42

* Model D: Dana-Farber Cancer Institute, Boston, Massachusetts; model E: Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E: Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W: University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts.
† Incremental to biennial screening for women starting at age 50 y.
‡ Incremental to biennial screening for women starting at age 40 y.

Table 4. **Threshold Relative Risks Estimated by the Cancer Intervention and Surveillance Modeling Network Models for the Different Screening Strategies***

Model†	Relative Risks Estimated by Using False-Positive Findings/Breast Cancer Deaths Averted				Relative Risks Estimated by Using False-Positive Findings/Life-Years Gained			
	Biennial		Annual		Biennial		Annual	
	Film	Digital	Film	Digital	Film	Digital	Film	Digital
D	5.1	5.7	6.4	6.6	3.7	4.4	4.9	5.1
E	2.4	2.8	3.8	5.6	1.5	1.7	2.3	3.3
G-E	2.9	3.7	>10	>10	1.6	2.1	7.0	10
W	2.2	2.3	3.4	5.1	1.5	1.5	2.2	3.4
Median	2.7	3.3	5.1	6.1	1.6	1.9	3.6	4.3

* The threshold relative risks represent the risk at which the harm–benefit ratio of starting biennial or annual screening at age 40 y would equal that of currently recommended biennial screening starting at age 50 y.
† Model D: Dana-Farber Cancer Institute, Boston, Massachusetts; model E: Erasmus University Medical Center, Rotterdam, the Netherlands; model G-E: Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, Bronx, New York; model W: University of Wisconsin, Madison, Wisconsin, and Harvard Medical School, Boston, Massachusetts.

rates in this age group (28–30). This is reflected in the model outcomes showing that adding annual screening to biennial screening in the 40- to 49-year age group is somewhat more beneficial than in older age groups. For example, a previous study showed that 72% to 89% of the mortality benefit is maintained in these 4 models when women aged 50 to 74 years move from annual to biennial screening scenarios (23). The present study shows that in the 40- to 49-year age group, the percentage of mortality benefit maintained is somewhat lower (66% to 77%).

All 4 models found only small differences between film and digital mammography with regard to the benefits of screening, which is in line with results of a study reporting that improvements in sensitivity did not markedly affect breast cancer mortality (31). However, digital mammography did result in substantially more false-positive results than did film mammography. This translated into greater harm relative to benefits for digital than for film mammography in younger women. Therefore, it seems unlikely that data on the performance of digital mammography, if they had been available, would have led the USPSTF to recommend screening women starting at age 40 years. A recent study in the Netherlands found that referral and false-positive rates first increased after the implementation of digital mammography but started to decrease over time and stabilized at a somewhat higher level than film mammography after a little more than 1 year (32). However, in a recent U.S. study comparing the screening performance of digital and film mammography, excluding the first year after the transition to digital mammography did not influence results (33). Another recent study found that the availability of comparison mammography halved the false-positive recall probability (34). It remains to be investigated whether false-positive rates in the United States can be reduced without also decreasing sensitivity or detection rates.

The results of the models are consistent regarding differences between outcome measures, predicting considerably higher threshold RRs when breast cancer deaths averted are used instead of life-years gained, because there are more life-years to gain by averting a death in the 40- to 49-year age group than in older age groups. Life-years gained may be considered preferable because, as a summary measure, it incorporates both the number of lives saved and the number of life-years gained per life saved. Our results indicate that the outcome measure used is a main determinant of the screening strategy that will be chosen for women aged 40 to 49 years, highlighting the importance of taking into account preferences of individual women for specific benefits and harms.

Several limitations of this study should be mentioned. Of note, we calculated the harm–benefit ratios for women aged 50 to 74 years who were screened biennially, and we used these as threshold values for younger women. However, younger women may have different concerns and preferences than do older women and these preferences may vary between individual women. In calculating the harm–benefit ratio, we included only false-positive screening mammography results as the harm. Ideally, all harms and all benefits are taken into account in determining optimal screening scenarios. In addition to false-positive results, harms of screening mammography include unnecessary biopsies, radiation exposure, false reassurance, pain related to the procedure, overdiagnosis (the detection of lesions that would not have become clinically apparent without screening), overtreatment, and the burden of performing medical tests on healthy individuals. Several studies have shown that the risk of radiation is minimal (35, 36), and false reassurance has been found to play only a minor role in breast cancer screening (37). Although many women experience pain during the procedure (range, 1% to 77%), very few consider this a deterrent from future screening (8, 38). Estimates of overdiagnosis vary widely, ranging up to 54% (39). Although a proportion of invasive cancer diagnosed by mammography may never have presented clinically, the proportion is probably small for

women aged 40 to 49 years, ranging up to 7% (39). For ductal carcinoma in situ, this proportion might be larger but is surrounded by uncertainty. For these reasons, we chose to focus on false-positive examinations as the main harm for women in their 40s. We did, however, perform a sensitivity analysis in which we considered a more comprehensive measure of harm: QALYs lost. Although this measure is more comprehensive, capturing disutility of false-positive results and the effect of overdiagnosis, it is less transparent than the number of false-positive results, and the preferences of individual women might diverge from the assumed societal utilities.

Another limitation is that the models differed for some outcomes. For biennial film screening, 3 models (E, G-E, and W) found similar threshold RRs (1.5 to 1.6), whereas 1 model (D) estimated a threshold RR of 3.7. This discrepancy relates to differences in the estimated benefits, reflecting differences in model structures. In model D (19), the stage distribution data are directly incorporated in constructing breast cancer–specific survival. Thus, small incremental changes in stage shifts between annual/biennial or between film/digital led to smaller incremental benefits. The other models used a combination of sensitivity values and stage distribution to calibrate parameters and show larger benefits. In addition, the models differed regarding the predicted incremental benefit of adding annual to biennial screening (range of life-years gained, 7 to 21) because the models make different assumptions for unobservable variables, such as sojourn time, which is the duration of the preclinical, screen-detectable phase of the tumor. To our knowledge, no randomized, controlled trials have directly compared annual and biennial screening. The range in model outcomes thus reflects uncertainties in current knowledge of the incremental benefits of screening women aged 40 to 49 years and about shortening the screening interval.

Finally, model outcomes largely depended on the inputs and assumptions. One assumption was that the higher risk influenced only the incidence (onset of disease) and not the screening performance (sensitivity, specificity) or natural history of disease (such as the tumor growth rate and breast cancer survival). However, at least some risk factors, including breast density and family history, influence both breast cancer risk and screening performance (40, 41). If this is taken into account, the harm–benefit ratio could change for women with risk factors that influence performance. The psychological effect of false-positive results might also differ by risk group. For example, the amount of anxiety or distress might be higher for younger women and for women with a family history of breast cancer than for average-risk women (42).

Our finding that women with increased risks for breast cancer have similar harm–benefit ratios from starting biennial screening mammography at age 40 years is in line with studies finding that breast cancer risk or detection for women with a first-degree relative is similar to that for women a decade older without such a history (40). Several other countries have risk-based screening guidelines. For example, guidelines in the Netherlands state that women with a moderately increased risk, defined as an RR of 2 to 3, should be offered annual screening starting at age 40 years. Similarly, in Australia, guidelines specify that a starting age younger than 50 years or more frequent examinations should be considered individually for women with moderately increased risk, defined as an RR of 1.5 to 3.

A systematic review and meta-analysis of risk factors and their prevalence rates in women aged 40 to 49 years in the United States was conducted jointly with the present study (43). Two risk factors were associated with a 2-fold or higher RR: having a first-degree relative with breast cancer (9% of women in the United States) and extremely dense breasts on mammography (13% of women with Breast Imaging Reporting and Data System category 4 breast density). Results of these 2 studies imply that women with these characteristics could benefit from biennial screening starting at age 40 years and that the balance of benefits and harms of screening for these women would be similar to the balance of benefits and harms for average-risk women starting screening at age 50 years. In addition to these single risk factors, combinations of risk factors could potentially reach this risk threshold (16, 17). A potential difficulty with including breast density in screening recommendations is that breast density is not uniformly reported and requires baseline mammography examinations to determine breast density, introducing additional potential screening harms.

Our results provide important information toward more individualized, risk-based screening, suggesting that starting biennial screening at age 40 years for women with an increased risk for breast cancer (RR $\geq$1.9) has a balance of benefits and harms similar to that of biennial screening for average-risk women aged 50 to 74 years. For women below this level of risk, the harm–benefit ratio of starting screening at age 40 years is less favorable than that of biennial screening between ages 50 and 74 years. Reducing the false-positive rate is crucial to improving the balance of benefits and harms for screening regimens for women of all ages.

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Reproducible Research Statement: *Study protocol:* Available from Ms. van Ravesteyn (e-mail, n.vanravesteyn@erasmusmc.nl). *Statistical code:* Not available; model profiles are available at http://cisnet.cancer.gov/breast/profiles.html. *Data set*: Procedures for requesting BCSC data for research purposes are provided at http://breastscreening.cancer.gov/work/proposal_data.html.

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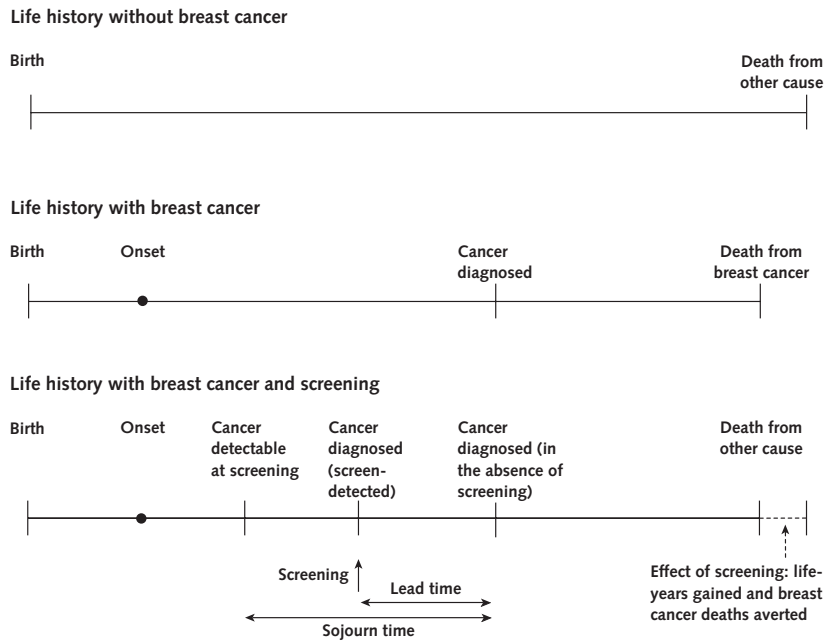
Appendix Figure. **Schematic overview of simulated life histories and effect of screening.**



The italicized words in the descriptions below refer to the words outlined in the figure. *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 surfaced without screening. **Model D** is a state transition model where potential benefit from early detection arises because of a stage shift. The natural history of breast cancer is modeled analytically by using stochastic models. The model assumes that breast cancer (invasive) progresses from a no-disease (S0) state to preclinical (Sp) state and to clinical (Sc) state. Some cases will continue to the disease-specific death (Sd) state. Death due to other causes is treated as a competing risk. The Sp state begins when *cancer is detectable at screening,* and Sc begins *when cancer is diagnosed in absence of screening*. For a given birth cohort, age-specific invasive breast cancer incidence rate and age-dependent *sojourn time* in Sp (published values) are used to estimate the transition probabilities from S0 to Sp. The transition probabilities from Sp to Sc are estimated on the basis of the age-specific breast cancer incidence rate. The other basic assumption is that any reduction in mortality associated with screening is from the stage-shift: that is, *screen-detected cases* have a better stage distribution with a higher proportion of cases in earlier stages. The stage distribution data for *screen-detected* cases are obtained from BCSC and directly incorporated in constructing breast cancer–specific survival. In addition, the *lead time* for screen-detected cases is treated as a random variable and is adjusted in constructing the breast cancer–specific survival *for screen-detected cases*. When cancer is diagnosed, a treatment is applied by age, stage, and estrogen receptor status and treatment reduces the hazard of breast cancer–specific mortality by age, stage, and estrogen receptor status. **Model E** is a microsimulation model based on continuous tumor growth. The natural history of breast cancer is modeled as a continuously growing tumor from *onset* of cancer (starting with a tumor diameter of 0.1 mm). The moments that events happen are determined by tumor sizes. The screening threshold diameter determines the moment that *the cancer is detectable at screening*, and the diameter of clinical detection determines when the *cancer will be diagnosed in the absence of screening*. Each tumor has a size (the fatal diameter, which differs between tumors) at which diagnosis and treatment will no longer result in cure given available treatment options. If the tumor is diagnosed (either on the basis of clinical presentation with symptoms or by screening) and treated before the tumor reaches the fatal diameter, the woman will be cured and will die of non–breast cancer causes (*death from other causes*). Variation between tumors is modeled by probability distributions of parameters. Screening might detect tumors at a smaller tumor size with a larger probability of cure (because the tumor has not yet reached the fatal diameter) than when the cancer is diagnosed in the absence of screening. **Model G-E** is an event-driven continuous time–state transition model. On the basis of birth cohort–specific incidence curves, the date at which progressive *breast cancer will appear clinically* (if ever) is sampled, and the stage, estrogen receptor, and *HER2* are then sampled according to age- and period-specific stage distributions for these parameters. A *sojourn time* is sampled from an age-specific distribution, and the beginning of the sojourn period is defined as the clinical incidence date minus the sojourn time. If a screening event takes place during the sojourn period, it may detect the tumor with probability equal to the age-specific mammography sensitivity. If the tumor is *screen detected*, a stage at detection is sampled from a probability distribution calculated from the observed lead time, the distributions of dwell times in the clinical stages, and the stage at the clinical detection date. Whether clinically detected or screen detected, treatment is sampled from an age-, stage-, estrogen receptor–, and HER2-period–specific distribution of possible treatment regimens. Each particular treatment regimen reduces the hazard of breast cancer mortality by a ratio that depends on age and stage at diagnosis, estrogen receptor, and HER2. The date of *breast cancer death* (which may turn out to be after the date of death from other causes) is then sampled from the corresponding age-, stage-, estrogen receptor–, HER2-treatment regimen–specific survival function. Simulated women who do not have progressive breast cancer may have limited malignant potential (LMP) breast cancer. Breast cancer with LMP cancer is modeled as never being clinically detected and is never fatal. However, it is screen detectable for 5 years and, if screen detected, its stage is always ductal carcinoma in situ (DCIS). These screen-detected LMP DCIS are then treated the same way as progressive breast cancer diagnosed during the DCIS stage, but treatment has no effect on mortality because these LMP tumors are never fatal. **Model W** is a discrete-event, stochastic tumor growth simulation model. It simulates the natural history of breast cancer using a continuous time growth model for tumor size and a Poisson process for tumor extent with a randomly assigned growth rate from a population-level distribution. In the model, breast cancer is assumed to be a progressive disease arising in the in situ stage. Model W further assumes that a fraction of all tumors have LMP. This subtype is nonfatal, is limited in size and stage to in situ and early localized disease, and is predominantly detected by screening mammography. If undetected for a fixed dwell period, such tumors are assumed to regress. Breast cancer can be detected by 1 of 2 methods: breast imaging (*screen detected*), or *by symptoms*, where the likelihoods of detection are functions of a woman's age and tumor size. Upon detection, a woman will receive standard treatment and, depending on calendar year and woman- and tumor-level characteristics, may also receive adjuvant treatment. Treatment effectiveness, a function of treatment type, is independent of the method of detection and is modeled as a "cure/no-cure" process.