ORIGINAL RESEARCH

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The Effect of Treatment Advances on the Mortality Results of Breast Cancer Screening Trials: A Microsimulation Model

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Background: Mammography trials, which are the primary sources of evidence for screening benefit, were conducted decades ago. Whether advances in systemic therapies have rendered previously observed benefits of screening less significant is unknown.

Objective: To compare the outcomes of breast cancer screening trials had they been conducted using contemporary systemic treatments with outcomes of trials conducted with previously used treatments.

Design: Computer simulation model of 3 virtual screening trials with similar reductions in advanced-stage cancer cases but reflecting treatment patterns in 1975 (prechemotherapy era), 1999, or 2015 (treatment according to receptor status).

Data Sources: Meta-analyses of screening and treatment trials; study of dissemination of primary systemic treatments; SEER (Surveillance, Epidemiology, and End Results) registry.

Target Population: U.S. women aged 50 to 74 years.

Time Horizon: 10 and 25 years.

Perspective: Population.

Intervention: Mammography, chemotherapy, tamoxifen, aromatase inhibitors, and trastuzumab.

Outcome Measures: Breast cancer mortality rate ratio (MRR) and absolute risk reduction (ARR) obtained by the difference in cumulative breast cancer mortality between control and screening groups.

Results of Base-Case Analysis: At 10 years, screening in a 1975 trial yielded an MRR of 90% and an ARR of 5 deaths per 10 000 women. A 2015 screening trial yielded a 10-year MRR of 90% and an ARR of 3 deaths per 10 000 women.

Results of Sensitivity Analysis: Greater reductions in advanced-stage disease yielded a greater screening effect, but MRRs remained similar across trials. However, ARRs were consistently lower under contemporary treatments. When contemporary treatments were available only for early-stage cases, the MRR was 88%.

Limitation: Disease models simplify reality and cannot capture all breast cancer subtypes.

Conclusion: Advances in systemic therapies for breast cancer have not substantively reduced the relative benefits of screening but have likely reduced the absolute benefits because of their positive effect on breast cancer survival.

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Academic and public dialogue is polarized about whether the benefits of population screening programs outweigh their harms (1, 2). Policy panels are mandated to prioritize randomized clinical trials when developing guidelines, as indicated by the U.S. Preventive Services Task Force's designation of randomized clinical trials as "level I evidence" in its hierarchy of research designs (3). When results from randomized clinical trials conflict, such as in breast and prostate cancer screening trials (4, 5), creating guidelines becomes controversial.

Recent studies (6–8) have highlighted a particularly intractable issue about screening benefit: The benefit of early detection of cancer is inextricably linked to the effectiveness of treatment in reducing cancer mortality. Recognizing this link between treatment and screening, some researchers (9–11) have hypothesized that contemporary treatments may have decreased the effect of screening mammography. Many of the mammography trials, which were initiated in the 1960s and 1970s (12), predated the advent of adjuvant multiagent chemotherapy and endocrine treatment that entered general use in the 1980s and 1990s and are now standards of care (13). The availability of these therapies is cited as a potential reason that the Canadian National Breast Screening Study, which was conducted in the 1980s, did not find a significant effect of screening on mortality (5, 14, 15), whereas meta-analyses of all trials estimated a 15% to 20% relative reduction in mortality (9, 10, 16). The recent Cochrane review (9) and Swiss Medical Board guideline (11) similarly cite advances in treatment as support for the hypothesis that the true mortality reduction due to mammography is lower than that suggested by meta-analyses.

Jüni and Zwahlen (10) recently proposed that "The only way to know [the effect of mammography screening] for certain is to initiate a new trial in the era of contemporary screening technologies and breast cancer therapies." Unfortunately, the 20 years of follow-up needed to reliably observe mortality reductions attributable to screening (17) presents a problem of timing that no trial can circumvent. Treatments administered in a new trial may be outdated in 20 years (18). Moreover, predicting how treatment advances will affect screen-

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ing is difficult. When treatments improve for tumors detected early in the process of disease progression, the benefit of screening will increase. Conversely, better treatments for more advanced disease will decrease the value of screening.

When empirical studies fall short of providing the evidence needed for policy development, modeling can be valuable. Models have been used to decouple the joint contributions of screening and treatment to trends in breast cancer mortality in the population setting (6, 19), but the effect of treatment advances on screening trial results has not been explicitly investigated. We developed a modeling framework to quantify how screening trial results change when treatments improve. We applied this framework to breast cancer to address the hypothesis that advances in treatment have altered the effect of screening on breast cancer mortality.

EDITORS' NOTES

Context

Whether improved treatments for breast cancer have reduced the mortality benefits previously observed in trials of mammography screening is not known.

Contribution

This simulation found that the relative reduction in mortality with breast cancer screening is similar with current therapies, those available in 1999, and those available before the use of chemotherapy. Treatment advances have probably reduced the absolute benefit of screening because of their positive effect on survival.

Caution

Modeling cannot capture all clinical variables that would influence the results of a clinical trial.

Implication

Advances in therapy for breast cancer have probably not reduced the relative benefit of mammography screening.

METHODS

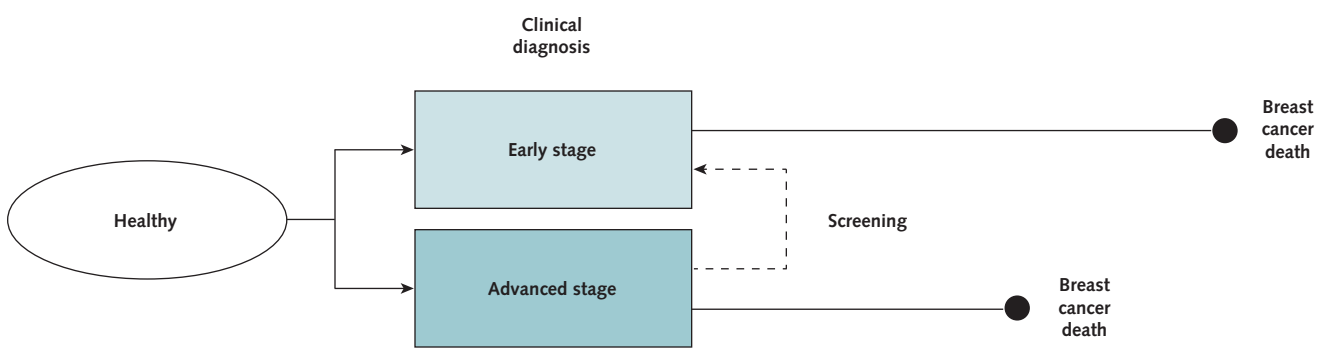
Overview

We used a microsimulation approach to implement a state-transition model, where the states were healthy, screen-detected or clinically detected breast cancer, and death (Figure). Breast cancer may be detected at either an early or an advanced stage; the time from diagnosis to death depends on the stage at detection and the treatments received. The effect of screening is to shift some cases that would have been detected later to an earlier stage at diagnosis, resulting in a decrease in advanced-stage incidence. The effect of treatment is to change the disease-specific survival given the stage at diagnosis.

We used the model to project mortality results corresponding to 3 hypothetical screening trials, which reflected the same effect of screening on disease stage but different treatment distributions. The resulting virtual trials were a 1975 trial with treatments available in the U.S. population at that time, a 1999 trial with treatment frequencies in the U.S. population from that year, and a 2015 trial that reflected optimal use of contemporary treatments for the specific types of breast tumors modeled. For each virtual trial, we simulated a population of 200 000 women aged 50 years who were randomly assigned to screening and control groups. Our objective was to compare the projected effect of screening on disease-specific mortality across the 3 virtual trials.

In the remainder of this section, we describe the data and methods used to generate the dates of diagnosis and death for the control and screening groups in the virtual trials. Additional details are included in Appendix Table 1 (available at www.annals.org). The model was built and deployed using R, version 3.2.0 (R Foundation for Statistical Computing) (20). This study was exempt from institutional review board approval

Figure. Breast cancer states in the state-transition model.



Healthy women are at risk for clinical breast cancer diagnosis in the absence of screening. Patients clinically diagnosed with breast cancer may have either early- or advanced-stage disease at diagnosis, and their survival in the absence of screening was assigned accordingly. The effect of screening is to reduce the chance of diagnosis in the advanced stage; for a fraction of advanced-stage cases, the stage at diagnosis was reclassified as early with a commensurate change in disease-specific survival.

because it used only published or publicly available data.

Disease Incidence and Stage Distribution in the Absence of Screening

The incidence of disease in the absence of screening (clinical incidence) was an anchor point for the model. We focused on clinically incident cases because they are the only cases that lead to disease-specific mortality, which was our primary outcome of interest. For these cases, we generated the following 3 variables.

Age at Clinical Diagnosis of Cancer (Diagnosis in the Absence of Screening)

This was based on age-specific rates of clinical diagnosis (within 5-year age categories) from the SEER (Surveillance, Epidemiology, and End Results) database for 1975 to 1979 (21), which represents the interval directly before the adoption of mammography in the United States. The empirical age-specific incidence was used and was kept constant across the virtual trials.

Stage at Clinical Diagnosis in the Absence of Screening

This was assigned as "early" (in situ or localized) or "advanced" (regional or distant). We used historical SEER breast cancer stage distributions from 1975 to 1979.

Other Stage-Specific Disease Characteristics

We included the breast cancer tumor receptor category because different treatments are used depending on estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status (22). Separately for early and advanced stages, we used SEER data on patients aged 50 to 75 years with breast cancer diagnosed in 2010 and known receptor status to simulate positive or negative/borderline ER and HER2 status.

Disease Incidence and Stage Distribution in the Presence of Screening

We retained the number of patients with incident disease generated in the absence of screening and their simulated age at clinical diagnosis but reduced advanced-stage incidence by reclassifying a fraction of advanced-stage patients as early-stage at diagnosis. We used a fraction of 15% for our main analysis; this reflected the median decrease in the cumulative incidence of advanced-stage disease reported across 8 mammography trials (23). In the model, this "stage shift" under screening improves disease-specific survival.

Disease Mortality

Disease-specific survival was generated from the date of clinical diagnosis and depended on the stage of diagnosis and the treatment received. For baseline survival in the absence of systemic treatments, we used an exponential distribution fit to disease-specific survival from patients in SEER aged 50 to 75 years who were diagnosed between 1975 and 1979. Modern systemic treatments were incorporated by applying hazard ratios (HRs) to the baseline survival to modify the time from clinical diagnosis to cancer death. The age at death was generated as the lower of the age at cancer death and the age at other-cause death based on U.S. cohort life tables for women aged 50 years in 2000 (24).

With screening, a fraction of advanced-stage patients were reclassified as early-stage ("stage-shifted") because of early detection. For these patients, disease-specific survival from clinical diagnosis to cancer death was regenerated from the distribution of early-stage survival times. Although screening leads to early detection, the effect of the earlier diagnosis was modeled as an extension of the survival from the original date of clinical diagnosis in the absence of screening to avoid lead-time bias (25, 26). For these patients, the survival time in the presence of screening was explicitly correlated with their survival time in the absence of screening (both were generated using the same percentile with their respective distributions).

Systemic Treatments and Their Effect on Mortality

Treatment distributions were based on a study of adjuvant treatment dissemination (27), which provided frequencies of treatment with multiagent chemotherapy and tamoxifen for ER-positive tumors between the 1970s and 2000. Therefore, in the 1975 virtual trial, we used treatment patterns from 1975, when chemotherapy was made available to only a fraction of patients with advanced disease (Table 1). The 1999 virtual trial reflected the shift toward using ER status to target adjuvant tamoxifen and greater use of chemotherapy. The 2015 virtual trial approximated a contemporary scenario in which combination chemotherapy and aromatase inhibitor therapy were used for ER-positive patients and chemotherapy alone was used for ER-negative patients. In addition, HER2-positive patients with either ER status received trastuzumab. Within each virtual trial, both the control and screening groups received the same stage-specific distributions of treatment.

Treatment efficacies were based on published meta-analyses. For chemotherapy and tamoxifen, we used results from the Early Breast Cancer Trialists' Collaborative Group (28, 29) (see Appendix Table 1 for more details). For trastuzumab, Cochrane reviews (30, 31) reported HRs for overall survival; we used these HRs as proxies for the effect on disease-specific survival. For aromatase inhibitor therapy, we multiplied the tamoxifen HR by 0.89 based on the reduction in breast cancer mortality after recurrence observed in 2 major trials comparing aromatase inhibitors and tamoxifen (32). Finally, we assumed multiplicative independent effects on the HR scale for combination therapies.

Outcomes

The main outcome of interest was the cumulative number of breast cancer deaths in the control and screening groups of each virtual trial. We assessed the effect of screening by using the mortality rate ratio

Table 1. Treatment Distributions in Each of the 3 Virtual Trials, Conditional on Stage at Diagnosis and ER Status*

Variable	Early-Stage			Advanced-Stage		
	1975	1999	2015	1975	1999	2015
ER-positive						
No treatment	100	24	–	80	2	–
Chemotherapy	–	8	–	20	38	–
Tamoxifen	–	58	–	–	10	–
Tamoxifen plus chemotherapy	–	10	–	–	50	–
AI plus chemotherapy	–	–	100	–	–	100
ER-negative						
No treatment	100	25	–	80	2	–
Chemotherapy	–	50	100	20	85	100
Tamoxifen	–	20	–	–	3	–
Tamoxifen plus chemotherapy	–	5	–	–	10	–
AI plus chemotherapy	–	–	–	–	–	–

ER = estrogen receptor.
* Values are the percentages of women receiving each treatment in each virtual trial within each stage and ER group. The 1975 and 1999 distributions were derived from Mariotto and colleagues' 2006 analysis of treatment dissemination in the U.S. population in 1975 and 1999 (27). The 2015 trial approximated an optimal scenario in which all ER-positive case patients received aromatase inhibitors and chemotherapy and all ER-negative case patients received chemotherapy. In addition, in the 2015 trial, all patients positive for human epidermal growth factor receptor 2 received trastuzumab. See **Appendix Table 1** (available at www.annals.org) for treatment efficacies.

(MRR) (the ratio of cumulative mortality between the screening and control groups) and the absolute risk reduction (ARR) (the absolute amount by which screening reduced cumulative breast cancer mortality). We report these statistics over 10 and 25 years. In addition, we assessed the combined effect of screening and treatment across virtual trials by computing MRRs and ARRs for each group of each trial relative to the control group of the 1975 trial. Along with our "within-trial" results reflecting screening efficacy, we also present these "across-trial" results reflecting the effect of screening and treatment changes.

Validation

To externally validate the model, we used the SEER program's DevCan software, version 6.7.3 (33), which provides estimates of the chance of dying of breast cancer over a specified interval beginning at a specified age. The software does not provide results before 2000. We used the DevCan 25-year mortality estimates based on breast cancer mortality rates for 2000 to 2002 to validate our 1999 trial and the estimates based on mortality rates for 2009 to 2011 to validate the 2015 trial.

Sensitivity Analysis

To investigate the sensitivity of our modeled outcomes to changes in key assumptions, we explored 4 alternatives to our main analysis. First, we assumed Weibull rather than exponential distributions for baseline survival by stage. The 2-parameter Weibull distribution can capture an increasing or decreasing risk for disease-specific death over time, as opposed to the exponential distribution, which assumes a constant mortality risk. Second, treatment efficacies per stage were varied independently, from an HR of 0.25 (very beneficial) to 1 (no benefit), to represent treatment advances that affect the 2 stages in different ways. We assumed that all detected cases were treated and varied the effect of treatment on stage-specific survival. Third, the decrease in advanced-stage incidence was increased from 15% to 50%, which could represent increased early-stage detection due to better technology or more frequent screening or biopsy. Finally, the breast cancer mortality rate among early-stage patients in the screened group was reduced by 30% to reflect improvement in survival corresponding to a within-stage shift. This would allow a benefit for patients detected at an early stage with screening even if they would have been detected at an early stage in the absence of screening. This benefit was not applied to patients shifted by screening from an advanced stage to an early stage.

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RESULTS

Validation

For 2000 to 2002, the DevCan (33) estimate of the cumulative 25-year breast cancer mortality rate for a population of women aged 50 years without breast cancer was 1.4%; our 1999 trial estimate for women aged 50 years having screening was 1.67%. For 2009 to 2011, the DevCan estimate for women aged 50 years without breast cancer was 1.2%; our 2015 trial estimate for women aged 50 years undergoing screening was 1.33% (**Appendix Table 2**, available at www.annals.org).

Main Analysis

Table 1 presents the modeled frequency of systemic treatment by disease stage and ER or HER2 status

Table 2. 10-y Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Induced a 15% Decrease in Advanced-Stage Incidence (15% Stage Shift)*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	48 (46–50)	37 (37–38)	30 (30–31)
Screening	43 (41–45)	34 (33–35)	27 (27–28)
MRRs within trials	0.90 (0.90–0.90)	0.91 (0.90–0.93)	0.90 (0.89–0.91)
MRRs across trials†			
No screening	1.00	0.78 (0.76–0.79)	0.63 (0.62–0.65)
Screening	0.90 (0.90–0.90)	0.71 (0.71–0.71)	0.57 (0.56–0.58)
ARRs within trials	4.7 (4.5–4.8)	3.3 (2.8–3.8)	2.9 (2.6–3.3)
ARRs across trials†			
No screening	0	10.6 (9.5–11.7)	17.6 (16.0–19.1)
Screening	4.7 (4.5–4.8)	13.9 (13.2–14.6)	20.5 (19.3–21.7)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 y of follow-up in a cohort of 100 000 women aged 50 y in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative incidences and ARRs are reported per 10 000 women. MRRs reflect the ratio of cumulative incidences. MRRs and ARRs within trials indicate the effect of screening for that trial.
† Combined effect of screening and treatment compared with the no-screening group of the 1975 trial.

in the 1975, 1999, and 2015 virtual trials. Appendix Table 1 summarizes our remaining input parameters and their sources. We estimated that, in the absence of screening, 49.6% of patients would be detected at an early stage and the remainder would be detected at an advanced stage. Baseline annual breast cancer excess mortality rates for early- and advanced-stage patients were set to 2.0% and 10.7%, respectively, based on observed disease-specific survival for early- and advanced-stage patients diagnosed between 1975 and 1979.

Our main analysis assumed a 15% reduction in advanced-stage incidence associated with screening. Table 2 presents the projected cumulative mortality over 10 years for the 3 virtual trials, by trial group. The MRR for the 1975 trial was 0.90, reflecting a 10% reduction in the disease-specific mortality risk over this follow-up period. Within-trial MRRs for the 1999 and 2015 trials were almost identical (0.91 and 0.90, respectively), showing almost no effect of the improved mortality benefits of systemic therapies on screening efficacy. Corresponding absolute mortality reductions ranged from 5 (1975 trial) to 3 (2015 trial) deaths per 10 000 women. Thus, although changes in treatment across the 3 trial settings affected survival, they did not substantively alter the relative mortality benefit associated with screening but may have been associated with reductions in the absolute mortality benefit.

The survival benefits of treatment advances were readily apparent from mortality comparisons across trials. The 10-year MRR comparing the control groups of the 2015 and 1975 trials was 0.63, reflecting a 37% reduction in the risk for disease-specific death due to treatment advances during this time. The 10-year MRR comparing the screening group of the 2015 trial with the control group of the 1975 trial was 0.57, reflecting a 43% reduction in the risk for disease-specific death due to screening and treatment advances during this time.

Long-term (25-year) results were similar to the 10-year findings with respect to the relative effect of the modeled systemic therapies, but ARRs were substantially higher, as expected with the longer follow-up (Appendix Table 2).

Sensitivity Analyses

Assuming Weibull distributions, as fitted to SEER survival data, yielded a reduced effect of screening on disease-specific mortality, with MRRs ranging from 0.93 to 0.95 across trials (Appendix Table 3, available at www.annals.org). Nevertheless, MRRs comparing screening and control groups were similar across trials, indicating only a minor effect of treatment advances on screening efficacy.

When we allowed treatment advances to benefit the stages differently, we found a greater range of MRRs across trials. Across 16 virtual trials with varying efficacies of early- and advanced-stage treatment (4 levels of efficacy per stage), screening reduced mortality by 2% to 13% (Appendix Figure, available at www.annals.org). The most modest MRRs occurred when advanced treatment was highly effective but early treatment was not, and the lowest MRRs occurred when advanced treatment was ineffective and early treatment was highly beneficial. This is intuitively reasonable because under a given stage shift, screening provides the most benefit when patients with advanced-stage disease fare poorly, but they are amenable to highly curative therapy when they are diagnosed early.

When the reduction in advanced-stage incidence with screening increased to 25%, the projected mortality reductions in each trial increased but still remained similar across trials. Within-trial MRRs over 10 years ranged from 0.83 to 0.85, and ARRs ranged from 5 to 7 deaths per 10 000 women (Appendix Table 4, available at www.annals.org). With a 50% reduction in advanced-stage incidence with screening, within-trial MRRs

ranged from 0.67 to 0.70 and ARRs ranged from 9 to 14 deaths per 10 000 women (**Appendix Table 5**, available at www.annals.org).

Adding a within-stage survival benefit associated with screening with an associated HR of 0.70 (**Appendix Table 6**, available at www.annals.org) improved the within-trial MRRs to 0.85. In this setting, we still projected almost identical within-trial MRRs for the 3 virtual trials, indicating the robustness of our main result to the screening benefit mechanism.

DISCUSSION

In this study, we developed a novel modeling framework to investigate whether screening benefit assessed in historical trials is likely to be preserved in a changing therapeutic landscape. Our modeling framework decoupled the effects of screening on disease stage from the effects of primary systemic treatment. We obtained similar MRRs across the 3 virtual trials, indicating that systemic treatment changes in the United States do not substantively change the relative mortality effect of mammography screening. This result was robust to different assumptions for the extent to which screening affects advanced-stage incidence and suggests that speculation that treatment changes were responsible for the negative results of the Canadian trial and other mammography studies is probably incorrect. However, we did observe differences in the within-trial ARRs, particularly over the long term. The results of our 25-year analysis show that the absolute number of lives saved by screening tends to decrease when more efficacious treatments are available. This is a natural consequence of the decrease in absolute mortality that occurs with improved systemic therapies. A consequence of this effect is that in the presence of effective systemic therapies, the number needed to screen is likely to increase even as the MRR associated with screening remains unchanged.

Our models projected a reduction of about 10% in the risk for breast cancer death when we assumed that screening reduces advanced-stage disease at diagnosis by 15%, which was the median reduction reported across the major breast screening trials. This mortality reduction is consistent with the estimate from the recent Cochrane review (9), which was restricted to trials deemed to have adequate randomization (summary MRR, 0.90 [95% CI, 0.79 to 0.92]), and lies within the range provided by a U.S. modeling study (19). It is more modest than the summary reduction provided by the meta-analyses of the Independent U.K. Panel on Breast Cancer Screening (12) and the Canadian Task Force on Preventive Health Care (34), as well as the overall Cochrane review estimate (9), all of which reflect a 20% reduction in mortality associated with screening. Our more modest results may be a consequence of our assumption that the effect of screening is to reduce the incidence of advanced-stage tumors at diagnosis. When we modeled a within–early-stage benefit on top of the benefit from the reduction in advanced-stage disease, we projected a result that was closer to that obtained in trial meta-analyses.

The stage-shift assumption or mechanism underlying screening benefit is well-established in models of cancer screening. In the U.S. modeling study (19), each of the 7 models of breast cancer screening and treatment that were presented used a version of the stage-shift mechanism. Across the models, screening accounted for a decrease of 7% to 22% (median, 15%) in U.S. breast cancer mortality in 2000, whereas adjuvant systemic therapies accounted for a decrease of 14% to 21% (median, 19%). In our 1999 virtual trial, screening accounted for a decrease in breast cancer mortality of approximately 9% (within-trial MRR, 0.91), whereas systemic therapies accounted for a decrease of approximately 22% (**Table 2**) (10-year across-trial MRR, 0.78 [when the 1999 and 1975 control groups were compared]). Our finding of a relatively higher contribution of treatment to reductions in mortality could be because we modeled the effect of systemic therapies at all stages of disease rather than focusing on systemic therapies used only in the adjuvant setting for local and regional stages, as was done in Berry and colleagues' study (19). When we set the treatment HR to 1 for advanced-stage disease (**Appendix Table 7**, available at www.annals.org), we found that screening accounted for more of the reduction in mortality in our 1999 virtual trial than treatment.

Other changes in the management and diagnosis of breast cancer have occurred since the trials. Examples include the advent of digital mammography and, more recently, tomosynthesis, which may confer improved sensitivity to detect early tumors. In addition, improvements in focal therapies, such as radiation, could affect localized cases of disease. Improvements in supportive therapies might have enhanced the ability of patients to complete systemic treatment regimens and improved the efficacy of these regimens. Our sensitivity analyses were designed to investigate how such changes might affect our main results. We found that with a greater shift from advanced- to early-stage breast cancer at diagnosis, screening efficacy increased but remained relatively unaffected by treatment changes. However, screening efficacy was enhanced when treatment benefit was increased among patients with early-stage disease.

Our study focused on screening benefit in terms of mortality reductions, but personal and policy decisions about mammography screening must also take potential harms into account. In particular, the issue of overdiagnosis has received much attention in recent years (35–37). Because we focused on disease cases that would have been diagnosed only in the absence of screening, we did not address the problem of overdiagnosis. Changes in treatment patterns will not affect overdiagnosis but can affect overtreatment. Changes in screening technologies could affect overdiagnosis, but assessment of overdiagnosis is complex (38) and calls for data and analytics that are beyond the scope of our study.

Because our framework was highly simplified, examining the limitations of the model in light of their potential effect on our main conclusions is important. The most influential simplification was the assumption that the stage-shift mechanism captured the essence of the benefit of early detection. In addition, recent advances have identified features of tumor biology that are highly significant to disease prognosis and therapeutic response (39). Genomic tests have emerged that can effectively classify disease prognosis (40). "Triple-negative" patients with breast cancer seem to have particularly poor survival, and optimal treatment remains undefined (41). Certain tumor types may be more easily detected with existing screening technologies (42). Our tumor subgroups were those for which we could source reliable treatment efficacies; we recognize that the field is evolving and that recent research has identified tumor subgroups within standard classifications, such as by ER status, for which chemotherapy has variable performance (43).

In conclusion, our findings indicate that results from historical breast screening trials are likely to provide reasonable approximations to the relative mortality reductions that would have resulted with contemporary systemic treatments. Our findings may help set realistic expectations about what questions can be answered by the initiation of new screening trials and may inform policymakers and parties responsible for creating screening guidelines.

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Reproducible Research Statement: *Study protocol*: Available from Dr. Etzioni (e-mail, retzioni@fredhutch.org). *Statistical code*: Available at https://github.com/netterie/screentreat. *Data set*: All data are from publicly available sources (see **Appendix Table 1**). The user interface for the model is available at https://emarkowitz.shinyapps.io/screening_trial_updater.

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References

1. **Kolata G.** Considering when it might be best not to know about cancer. The New York Times. 29 October 2011. Accessed at www.nytimes.com/2011/10/30/health/cancer-screening-may-be-more-popular-than-useful.html on 14 August 2015.
2. **Woolf SH, Harris R.** The harms of screening: new attention to an old concern. JAMA. 2012;307:565-6. [PMID: 22318274] doi:10.1001/jama.2012.100
3. **Agency for Healthcare Research and Quality.** U.S. Preventive Services Task Force Procedural Manual. AHRQ publication no. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2008. Accessed at www.uspreventiveservicestaskforce.org/Home/GetFile/6/7/procmanual/pdf on 14 August 2015.
4. **Moyer VA; U.S. Preventive Services Task Force.** Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:120-34. [PMID: 22801674] doi:10.7326/0003-4819-157-2-201207170-00459
5. **Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA.** Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. BMJ. 2014;348:g366. [PMID: 24519768] doi:10.1136/bmj.g366
6. **Berry DA.** Breast cancer screening: controversy of impact. Breast. 2013;22 Suppl 2:S73-6. [PMID: 24074796] doi:10.1016/j.breast.2013.07.013
7. **Etzioni R, Gulati R, Cooperberg MR, Penson DM, Weiss NS, Thompson IM.** Limitations of basing screening policies on screening trials: the US Preventive Services Task Force and prostate cancer screening. Med Care. 2013;51:295-300. [PMID: 23269114] doi:10.1097/MLR.0b013e31827da979
8. **Marmot MG.** Sorting through the arguments on breast screening. JAMA. 2013;309:2553-4. [PMID: 23722915] doi:10.1001/jama.2013.6822
9. **Gøtzsche PC, Jørgensen KJ.** Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2013;6:CD001877. [PMID: 23737396] doi:10.1002/14651858.CD001877.pub5
10. **Jüni P, Zwahlen M.** It is time to initiate another breast cancer screening trial. Ann Intern Med. 2014;160:864-6. [PMID: 24711124] doi:10.7326/M14-0569
11. **Biller-Andorno N, Jüni P.** Abolishing mammography screening programs? A view from the Swiss Medical Board. N Engl J Med. 2014;370:1965-7. [PMID: 24738641] doi:10.1056/NEJMp1401875
12. **Independent UK Panel on Breast Cancer Screening.** The benefits and harms of breast cancer screening: an independent review. Lancet. 2012;380:1778-86. [PMID: 23117178] doi:10.1016/S0140-6736(12)61611-0
13. **Sledge GW, Mamounas EP, Hortobagyi GN, Burstein HJ, Goodwin PJ, Wolff AC.** Past, present, and future challenges in breast cancer treatment. J Clin Oncol. 2014;32:1979-86. [PMID: 24888802] doi:10.1200/JCO.2014.55.4139
14. **Harris R.** Screening is only part of the answer to breast cancer. Ann Intern Med. 2014;160:861-3. [PMID: 24711098] doi:10.7326/M14-0616
15. **Kalager M, Adami HO, Bretthauer M.** Too much mammography [Editorial]. BMJ. 2014;348:g1403. [PMID: 24519765] doi:10.1136/bmj.g1403
16. **U.S. Preventive Services Task Force.** Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151:716-26. [PMID: 19920272] doi:10.7326/0003-4819-151-10-200911170-00008
17. **Smith RA.** The value of modern mammography screening in the control of breast cancer: understanding the underpinnings of the current debates. Cancer Epidemiol Biomarkers Prev. 2014;23:1139-46. [PMID: 24991021] doi:10.1158/1055-9965.EPI-13-0946
18. **Elmore JG, Harris RP.** The harms and benefits of modern screening mammography [Editorial]. BMJ. 2014;348:g3824. [PMID: 24938686] doi:10.1136/bmj.g3824
19. **Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators.** Effect of screening and adjuvant therapy on

mortality from breast cancer. N Engl J Med. 2005;353:1784-92. [PMID: 16251534]
20. **The Comprehensive R Archive Network.** R. Accessed at https://cran.r-project.org on 14 August 2015.
21. **National Cancer Institute.** Surveillance, Epidemiology and End Results Program SEER*Stat software. Accessed at http://seer.cancer.gov/seerstat on 14 August 2015.
22. **Ludwig JA, Weinstein JN.** Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Cancer. 2005;5:845-56. [PMID: 16239904]
23. **Autier P, Héry C, Haukka J, Boniol M, Byrnes G.** Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. J Clin Oncol. 2009;27:5919-23. [PMID: 19884547] doi:10.1200/JCO.2009.22.7041
24. **Wilmoth JR.** The Berkeley Mortality Database. 2005. Accessed at www.demog.berkeley.edu/~bmd/index.html on 14 August 2015.
25. **Wever EM, Draisma G, Heijnsdijk EA, de Koning HJ.** How does early detection by screening affect disease progression? Modeling estimated benefits in prostate cancer screening. Med Decis Making. 2011;31:550-8. [PMID: 21406620] doi:10.1177/0272989X10396717
26. **Feuer EJ, Mariotto A, Merrill R.** Modeling the impact of the decline in distant stage disease on prostate carcinoma mortality rates. Cancer. 2002;95:870-80. [PMID: 12209732]
27. **Mariotto AB, Feuer EJ, Harlan LC, Abrams J.** Dissemination of adjuvant multiagent chemotherapy and tamoxifen for breast cancer in the United States using estrogen receptor information: 1975–1999. J Natl Cancer Inst Monogr. 2006:7-15. [PMID: 17032888]
28. **Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771-84. [PMID: 21802721] doi:10.1016/S0140-6736(11)60993-8
29. **Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379:432-44. [PMID: 22152853] doi:10.1016/S0140-6736(11)61625-5
30. **Balduzzi S, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, et al.** Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2014;6:CD006242. [PMID: 24919460] doi:10.1002/14651858.CD006242.pub2
31. **Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al.** Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4:CD006243. [PMID: 22513938] doi:10.1002/14651858.CD006243.pub2
32. **Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, et al.** Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 2010;28:509-18. [PMID: 19949017] doi:10.1200/JCO.2009.23.1274
33. **National Cancer Institute.** DevCan—Probability of Developing or Dying of Cancer. Bethesda, MD: National Cancer Institute; 2015. Accessed at http://surveillance.cancer.gov/devcan on 14 August 2015.
34. **Fitzpatrick-Lewis D, Hodgson N, Ciliska D, Peirson L, Gauld M, Liu YY; Canadian Task Force on Preventive Health Care.** Breast Cancer—Systematic Review. Accessed at http://canadiantaskforce.ca/ctfphc-guidelines/2011-breast-cancer/systematic-review on 14 August 2015.
35. **Ong MS, Mandl KD.** National expenditure for false-positive mammograms and breast cancer overdiagnoses estimated at $4 billion a year. Health Aff (Millwood). 2015;34:576-83. [PMID: 25847639] doi:10.1377/hlthaff.2014.1087
36. **Bleyer A, Welch HG.** Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med. 2012;367:1998-2005. [PMID: 23171096] doi:10.1056/NEJMoa1206809
37. **Etzioni R, Xia J, Hubbard R, Weiss NS, Gulati R.** A reality check for overdiagnosis estimates associated with breast cancer screening. J Natl Cancer Inst. 2014;106. [PMID: 25362701] doi:10.1093/jnci/dju315
38. **Etzioni R, Gulati R, Mallinger L, Mandelblatt J.** Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. Ann Intern Med. 2013;158:831-8. [PMID: 23732716] doi:10.7326/0003-4819-158-11-201306040-00008
39. **Kalia M.** Personalized oncology: recent advances and future challenges. Metabolism. 2013;62 Suppl 1:S11-4. [PMID: 22999010] doi:10.1016/j.metabol.2012.08.016
40. **Chung C, Christianson M.** Predictive and prognostic biomarkers with therapeutic targets in breast, colorectal, and non-small cell lung cancers: a systemic review of current development, evidence, and recommendation. J Oncol Pharm Pract. 2014;20:11-28. [PMID: 23493335] doi:10.1177/1078155212474047
41. **Ismail-Khan R, Bui MM.** A review of triple-negative breast cancer. Cancer Control. 2010;17:173-6. [PMID: 20664514]
42. **Chuang SL, Chen SL, Yu CP, Chang KJ, Yen AM, Chiu SY, et al.** Using tumor phenotype, histological tumor distribution, and mammographic appearance to explain the survival differences between screen-detected and clinically detected breast cancers. APMIS. 2014;122:699-707. [PMID: 25046200] doi:10.1111/apm.12294
43. **Albain KS, Paik S, van't Veer L.** Prediction of adjuvant chemotherapy benefit in endocrine responsive, early breast cancer using multigene assays. Breast. 2009;18 Suppl 3:S141-5. [PMID: 19914534] doi:10.1016/S0960-9776(09)70290-5

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Appendix Table 1. Input Parameters of the State-Transition Microsimulation Model*

Parameter	Definition	Data Source	Simulation Method	Values
In the absence of screening (control group of each virtual trial)				
1. Age at clinical diagnosis	Age at which cancer would be diagnosed symptomatically, without screening.	5-year age-specific rates of diagnosis, SEER 1975-1979 (SEER 9, 2013 November submission)	Linearly interpolated between 5-year rates to estimate probability of diagnosis for 1-year age groups and derived the corresponding incidence-free survival curve using the product-limit (Kaplan–Meier) method. Simulated exact age at clinical diagnosis from the curve using inverse transform sampling, again using linear interpolation between the 1-year age intervals. To constrain age at clinical diagnosis to be greater than age at entry into virtual trial (age 50), sampling was limited to have an upper bound of S(x) = S(50).	–
2. Stage at clinical diagnosis	Two categories, "early" or "advanced." Early stage corresponds to SEER in-situ and localized tumors and advanced stage corresponds to SEER regional and distant tumors.	Stage distribution of SEER 1975-1979 diagnoses aged 50-79 (SEER 9, 2013 November submission)	Stage distributions were combined with receptor subtypes to yield 8 possible diagnoses categories. See next parameter.	Local: 49.6% Regional/distant: 50.4% Among regional/distant: 82.9% regional, 17.1% distant
3. Breast cancer biologic subtype (receptor status)	ER status (positive or negative) and HER2 status (positive or negative). Receptors determine patient responses to select treatments: ER+ women respond to tamoxifen and AIs, and HER2+ women respond to trastuzumab.	Stage-specific receptor distribution of SEER 2010 diagnoses aged 50-79 (SEER 18, 2013 November submission)	Stage distribution was used to weight receptor distributions conditional on stage to yield stage-receptor distribution over 8 possible categories: early- or advanced-stage, ER+ or ER-, HER2+ or HER2-. Simulated stage-receptor status from corresponding multinomial distribution.	Early stage: ER+HER2+: 4% ER+HER2−: 38% ER−HER2+: 2% ER−HER2−: 6% Advanced stage: ER+HER2+: 6% ER+HER2−: 34% ER−HER2+: 3% ER−HER2−: 7%
4. Age at cancer death, baseline	Age at cancer death in the absence of screening or systemic treatment by stage; 75% of early-stage and 36% of advanced-stage cases survive 10 years.	Stage-specific survival of SEER 1975-1979 diagnoses aged 50-79 (SEER 9, 2013 November submission)	For each of local, regional, and distant stage, averaged the exponential rate corresponding to 5-year cause-specific net survival with the exponential rate corresponding to 10-year cause-specific net survival. Collapsed the averaged regional and distant rates into one advanced-stage rate using frequency-weighting. Used inverse transform sampling to simulate time from clinical diagnosis to breast cancer death from the appropriate stage-specific exponential survival curve. Added this time to age at clinical diagnosis to yield age at cancer death, baseline. We fit Weibull distributions to baseline disease-specific survival by stage by utilizing 5- and 10-year survival probabilities and simultaneously fitting the 2 Weibull parameters to match these 2 probabilities. We did this separately for local and combined regional/distant stage.	Exponential rates Early stage: 0.01992 (mean survival = 50.20 years) Advanced stage: 0.10693 (mean survival = 9.35 years) Weibull shape and scale Early stage: 0.948 and 53.615 Advanced stage: 0.642 and 15.69

Continued on following page

Appendix Table 1—Continued

Parameter	Definition	Data Source	Simulation Method	Values
5. Age at cancer death, treated (age at cancer death in the presence of treatment. Influenced by 2 subcomponents)	A. Availability and distribution of treatment for newly diagnosed cases. B. Efficacy of treatment (specified as HRs on a scale of 0-1; smaller numbers indicate higher efficacy).	Mariotto et al, 2006 (27) (See Table 1) Meta-analyses of breast cancer treatments (28-32). (See main text)	By stage, simulated treatment from multinomial distribution. Raised baseline survival curves to the relevant treatment HR. Used quantile corresponding to the already-simulated baseline survival to simulate a treated time from clinical diagnosis to cancer death from the treated survival curve. Added this time to age at clinical diagnosis to yield age at cancer death, treated.	See Table 1 Treatment HRs Tamoxifen (both stages): 0.70 for ER+, 1.0 for ER− Chemotherapy (both stages): 0.775 for all Tamoxifen + chemotherapy (both stages): 0.5425 for ER+, 0.775 for ER− AI + chemotherapy (both stages): 0.4828 for ER+ Trastuzumab: for HER2+ tumors, multiply HRs by 0.66 for early stage and 0.82 for advanced stage
6. Age at death from other causes	Age at death from non-cancer cause of death.	U.S. life tables for birth cohort aged 50 in 2000 (24)	Empirical survival curve derived from 1-year mortality rates using product-limit (Kaplan–Meier) method. Exact age at other-cause death simulated using inverse transform sampling and linear interpolation between 1-year ages. As with age at clinical incidence, upper bound of sampling was S (50).	–
7. Cause of death and age at death	Taken from event that occurs first, cancer, or other-cause death.	–	–	–
In the presence of screening, additional parameters (screening group of each virtual trial)				
8. New stage at diagnosis	A percentage of advanced-stage cases are shifted to early stage, due to the introduction of screening. For all other cases, same as parameter 2.	Median of reduction in advanced-stage incidence due to screening observed across 8 trials of mammography screening (23)	Among advanced-stage cases, simulated reclassification to early-stage status under screening using binomial distribution.	Main analysis: reduction in advanced-stage incidence (stage-shift) = 15% Sensitivity analyses: 25% and 50% stage-shift in the presence of screening
9. New cause of death and age at death	For the shifted cases, generated after updating parameters 4 and 5 to reflect the new early stage status. For all other cases, same as parameter 7.	–	See parameters 4, 5, and 7.	–

AI = aromatase inhibitor; ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; HR = hazard ratio; SEER = Surveillance, Epidemiology, and End Results.
* Each of the following inputs defines a life event in each virtual trial participant relevant to the natural history of breast cancer and the effect of screening and treatment on that natural history. The entire modeling process (steps 1-9) is repeated 100 times to account for simulation uncertainty, i.e. variation due to random-number generation. Reported results are the means over 100 simulations and 95% uncertainty intervals are defined by the 2.5th and 97.5th percentiles across simulations.

Appendix Table 2. 25-Year Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 15%*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	220 (220–220)	182 (182–182)	147 (147–148)
Screening	202 (199–205)	167 (165–170)	133 (131–135)
MRRs within trials	0.92 (0.90–0.93)	0.92 (0.91–0.94)	0.91 (0.89–0.92)
MRRs across trials†			
No screening	1.0	0.83 (0.83–0.83)	0.67 (0.67–0.67)
Screening	0.92 (0.90–0.93)	0.76 (0.75–0.77)	0.61 (0.60–0.62)
ARRs within trials	18.1 (15.2–21.0)	14.5 (11.6–17.3)	14.0 (11.3–16.6)
ARRs across trials†			
No screening	0.0	37.9 (37.5–38.3)	72.5 (71.9–73.2)
Screening	18.1 (15.2–21.0)	52.3 (49.9–54.8)	86.5 (84.5–88.5)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 25 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs within trials indicate the impact of screening in that trial. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial.
† All comparisons are with the no-screening group of the 1975 trial.

Appendix Table 3. Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 15% and Survival Is Modeled Using a Weibull Distribution*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	36 (32–39)	25 (22–28)	17 (15–19)
Screening	33 (30–37)	23 (21–26)	16 (14–18)
MRRs within trials	0.93 (0.91–0.96)	0.95 (0.92–0.97)	0.94 (0.90–0.97)
MRRs across trials†			
No screening	1.0	0.69 (0.65–0.74)	0.48 (0.43–0.53)
Screening	0.93 (0.91–0.96)	0.66 (0.61–0.70)	0.45 (0.40–0.50)
ARRs within trials	2.4 (1.4–3.5)	1.4 (0.8–2.0)	1.1 (0.5–1.7)
ARRs across trials†			
No screening	0.0	10.9 (9.1–13.0)	18.6 (15.5–21.5)
Screening	2.4 (1.4–3.5)	12.3 (10.4–14.3)	19.7 (16.7–22.6)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial. A Weibull distribution for baseline survival is assumed.
† All comparisons are with no-screening group of the 1975 trial.

Appendix Table 4. Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 25%*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	47 (42–51)	36 (32–40)	28 (25–31)
Screening	40 (25–43)	31 (27–34)	23 (20–27)
MRRs within trials	0.85 (0.81–0.88)	0.85 (0.82–0.89)	0.83 (0.79–0.87)
MRRs across trials†			
No screening	1.0	0.78 (0.73–0.82)	0.60 (0.55–0.65)
Screening	0.85 (0.81–0.88)	0.66 (0.62–0.71)	0.50 (0.46–0.55)
ARRs within trials	7.0 (5.7–8.5)	5.4 (4.0–6.7)	4.6 (3.4–5.8)
ARRs across trials†			
No screening	0.0	10.4 (8.2–12.8)	18.5 (15.8–21.0)
Screening	7.0 (5.7–8.5)	15.8 (13.4–18.7)	23.1 (19.9–26.2)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial.
† All comparisons are with the no-screening group of the 1975 trial.

Appendix Table 5. Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 50%*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	47 (42–51)	36 (32–40)	28 (25–31)
Screening	32 (28–36)	25 (22–28)	19 (16–21)
MRRs within trials	0.70 (0.65–0.74)	0.70 (0.65–0.75)	0.67 (0.61–0.72)
MRRs across trials†			
No screening	1.0	0.78 (0.73–0.82)	0.60 (0.55–0.65)
Screening	0.70 (0.65–0.74)	0.54 (0.49–0.59)	0.40 (0.36–0.45)
ARRs within trials	14.1 (11.9–16.7)	10.8 (8.6–12.7)	9.2 (7.2–11.0)
ARRs across trials†			
No screening	0.0	10.4 (8.2–12.8)	18.5 (15.8–21.0)
Screening	14.1 (11.9–16.7)	21.2 (18.2–24.3)	27.7 (24.1–31.1)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial.
† All comparisons are with the no-screening group of the 1975 trial.

Appendix Table 6. Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 15% and Improves Disease-Specific Survival for Early-Stage Cases by 30% (Within-Stage Benefit)*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	47 (42–51)	36 (32–40)	28 (25–31)
Screening	40 (36–43)	31 (27–34)	24 (21–27)
MRRs within trials	0.85 (0.83–0.88)	0.85 (0.82–0.88)	0.85 (0.81–0.88)
MRRs across trials†			
No screening	1.0	0.78 (0.73–0.82)	0.60 (0.55–0.65)
Screening	0.85 (0.83–0.88)	0.66 (0.61–0.71)	0.51 (0.46–0.56)
ARRs within trials	6.8 (5.2–8.4)	5.4 (4.0–6.8)	4.3 (3.3–5.6)
ARRs across trials†			
No screening	0.0	10.4 (8.2–12.8)	18.5 (15.8–21.0)
Screening	6.8 (5.2–8.4)	15.8 (13.0–18.5)	22.8 (19.5–25.5)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial. Within-stage benefit is modeled by applying a hazard ratio of 0.7 to survival curves for early-stage cases under screening.
† All comparisons are with the no-screening group of the 1975 trial.

Appendix Table 7. Breast Cancer Mortality Results of Virtual Screening Trials in Which Screening Reduces Advanced-Stage Incidence by 15% and Systemic Treatments Are Not Efficacious for Advanced-Stage Cases*

Variable	Virtual Trial		
	1975	1999	2015
Cumulative breast cancer mortality			
No screening	48 (43–52)	46 (42–50)	43 (39–48)
Screening	43 (39–47)	41 (37–45)	38 (34–43)
MRRs within trials	0.91 (0.89–0.93)	0.90 (0.87–0.92)	0.88 (0.86–0.91)
MRRs across trials†			
No screening	1.0	0.96 (0.94–0.98)	0.91 (0.89–0.93)
Screening	0.91 (0.89–0.93)	0.86 (0.83–0.89)	0.80 (0.77–0.83)
ARRs within trials	4.4 (3.2–5.6)	4.7 (3.5–6.0)	5.1 (4.0–6.5)
ARRs across trials†			
No screening	0.0	1.9 (1.0–2.6)	4.4 (3.1–5.5)
Screening	4.4 (3.2–5.6)	6.7 (5.1–8.0)	9.5 (7.9–11.0)

ARR = absolute risk reduction; MRR = mortality rate ratio.
* Results reflect 10 years of follow-up in a female cohort of size 100 000 aged 50 years in 2000, with 95% uncertainty intervals across 100 simulations. Cumulative mortalities and ARRs are reported per 10 000. MRRs reflect the ratio of cumulative mortalities. MRRs and ARRs across trials indicate the combined effect of screening and treatment compared with the no-screening group of the 1975 trial.
† All comparisons are with the no-screening group of the 1975 trial.

Appendix Figure. 10-year MRRs for trials in which treatment efficacies vary by stage and screening reduces advanced-stage incidence by 15%.

Advanced-Stage HR	Early-Stage HR 1.00	0.75	0.50	0.25
1.00	0.91	0.90	0.88	0.87
0.75	0.92	0.91	0.89	0.87
0.50	0.94	0.92	0.90	0.88
0.25	0.98	0.96	0.94	0.90

Each cell contains the within-trial MRR of screening for a trial in which a single treatment is given to all early-stage cases and another treatment is given to all advanced cases. The columns indicate the early-stage HRs, or benefit of the early-stage treatment in the trial, and the rows indicate the HRs for the advanced-stage treatment in the trial. The top left cell indicates that with no effective early- or advanced-stage treatments, the stage-shift model projects an MRR of 0.91 as the effect of screening on mortality. Trials in which advanced-stage treatment is better than early-stage treatment find a smaller effect of screening (dark green cells) than trials in which early-stage treatment is better than advanced-stage treatment (white cells). HR = hazard ratio; MRR = mortality rate ratio.