ORIGINAL ARTICLE

Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

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ABSTRACT

BACKGROUND

To reduce mortality, screening must detect life-threatening disease at an earlier, more curable stage. Effective cancer-screening programs therefore both increase the incidence of cancer detected at an early stage and decrease the incidence of cancer presenting at a late stage.

METHODS

We used Surveillance, Epidemiology, and End Results data to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older.

RESULTS

The introduction of screening mammography in the United States has been associated with a doubling in the number of cases of early-stage breast cancer that are detected each year, from 112 to 234 cases per 100,000 women — an absolute increase of 122 cases per 100,000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased by 8%, from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women. With the assumption of a constant underlying disease burden, only 8 of the 122 additional early-stage cancers diagnosed were expected to progress to advanced disease. After excluding the transient excess incidence associated with hormone-replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years of age, we estimated that breast cancer was overdiagnosed (i.e., tumors were detected on screening that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years. We estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for 31% of all breast cancers diagnosed.

CONCLUSIONS

Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer. Although it is not certain which women have been affected, the imbalance suggests that there is substantial overdiagnosis, accounting for nearly a third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death from breast cancer.

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There are two prerequisites for screening to reduce the rate of death from cancer.[1,2] First, screening must advance the time of diagnosis of cancers that are destined to cause death. Second, early treatment of these cancers must confer some advantage over treatment at clinical presentation. Screening programs that meet the first prerequisite will have a predictable effect on the stage-specific incidence of cancer. As the time of diagnosis is advanced, more cancers will be detected at an early stage and the incidence of early-stage cancer will increase. If the time of diagnosis of cancers that will progress to a late stage is advanced, then fewer cancers will be present at a late stage and the incidence of late-stage cancer will decrease.[3]

In the United States, clinicians now have more than three decades of experience with the widespread use of screening mammography in women who are 40 years of age or older. We examined the temporal effects of mammography on the stage-specific incidence of breast cancer. Specifically, we quantified the expected increase in the incidence of early-stage cancer and determined the extent to which this has led to a corresponding decrease in the incidence of late-stage cancer.

Methods

Overview

We obtained trend data on the use of screening mammography and the stage-specific incidence of breast cancer among women 40 years of age or older. To calculate the number of additional women with a diagnosis of early-stage cancer (as well as the reduction in the number of women with a diagnosis of late-stage cancer), we determined a baseline incidence before screening, calculated the surplus (or deficit) incidence relative to the baseline in each subsequent calendar year, and transformed data on the change in incidence to data on nationwide counts.

We used the direct method to adjust the incidence rates according to age in the U.S. standard population in the year 2000. All analyses were performed with the use of either (SEER*Stat or Microsoft Excel software. In an effort to make our method transparent, the data on Surveillance, Epidemiology, and End Results (SEER) stage–specific incidence and all calculations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Both authors vouch for the completeness and accuracy of the reported data and analysis and the fidelity of the study to the protocol.

Data Sources

We obtained trend data from the National Health Interview Survey on the proportion of women 40 years of age or older who underwent screening mammography.[4,5] Trend data on incidence and survival rates were obtained from the nine longstanding SEER areas[6]; these data accounted for approximately 10% of the U.S. population.[7] Annual estimates of the population of women 40 years of age or older were obtained from the U.S. Census.[8]

Stage at Diagnosis

We used SEER historic stage A as the foundation for our categorization of early- and late-stage cancer. The four stages in this system are the following: in situ disease; localized disease, defined as invasive cancer that is confined to the organ of disease origin; regional disease, defined as disease that extends outside of and adjacent to or contiguous with the organ of disease origin (in breast cancer, most regional disease indicates nodal involvement, not direct extension[9]); and distant disease, defined as metastasis to organs that are not adjacent to the organ of disease origin. We restricted in situ cancers to ductal carcinoma in situ (DCIS), specifically excluding lobular carcinoma in situ, as done in other studies.[10] We defined early-stage cancer as DCIS or localized disease, and late-stage cancer as regional or distant disease.

Baseline Incidence

The incidence data from the first year in which breast-cancer incidence was recorded (1973) were almost certainly spuriously low (which would bias our estimates of excess detection upward). The data from the subsequent 2 years (1974 and 1975) were above average for the decade, reflecting the sharp uptick in early detection after First Lady Betty Ford's breast-cancer diagnosis.[11] Consequently, we chose the 3-year period 1976 through 1978 to obtain our estimate of the baseline incidence of breast cancer that was detected without mammography. During this period, the incidence of breast cancer was stable and few cases of DCIS were

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detected; these findings are compatible with the very limited use of screening mammography.

CURRENT INCIDENCE AND REMOVAL OF THE EFFECT OF HORMONE-REPLACEMENT THERAPY

We based our estimate of the current incidence of breast cancer on the 3-year period from 2006 through 2008. To eliminate the effect of hormone-replacement therapy, we truncated the observed incidence each year from 1990 through 2005 if it was higher than the estimate of the current incidence (Table S2 and Fig. S1 in the Supplementary Appendix). In other words, we did not allow the annual incidence of DCIS to exceed 56.5 cases, localized disease to exceed 177.5 cases, regional disease to exceed 77.6 cases, and distant disease to exceed 16.6 cases (all expressed per 100,000 women) during the period from 1990 through 2005. Other researchers have dated the end of the effect of hormone-replacement therapy at 2006.[12] Thus, our approach was simply to remove all excess incidence in previous years.

ESTIMATES OF THE NUMBER OF WOMEN AFFECTED

Base-Case Estimate

For each year after 1978, we calculated the absolute change in the incidence of early- and late-stage cancer relative to the 1976–1978 baseline incidence (after removing the transient increase in incidence associated with hormone-replacement therapy during the period from 1990 through 2005, as described above). To calculate the excess in the number of women with a diagnosis of early-stage cancer detected on screening mammography, we multiplied the absolute increase in incidence observed in a given year by the number of women in the population who were 40 years of age or older in the same year. We used a similar approach to calculate the reduction in the number of women with a diagnosis of late-stage cancer. Finally, we summed the data across the three decades.

Subsequent Estimates

The base-case estimate implicitly assumes that, with the exception of the effect of hormone-replacement therapy, the underlying incidence of breast cancer is constant. To make an inference about any other changes in the underlying incidence, we examined incidence trends in the portion of the population that generally did not have exposure to screening: women younger than 40 years of age. In this age group, the SEER calculation for the annual percent change from 1979 through 2008 was 0.25% per year (95% confidence interval [CI], 0.04 to 0.47). To account for this growth, we repeated our analysis, allowing our baseline incidence among women 40 years of age or older to increase by 0.25% per year (applied to both early- and late-stage disease). We called this estimate the "best guess."

Finally, we wanted to provide estimates that were clearly biased in favor of screening mammography — ones that would minimize the surplus diagnoses of early-stage cancer and maximize the deficit of diagnoses of late-stage cancer. First, we assumed that the underlying incidence was increasing at a rate of 0.5% per year — twice as high as that observed among the population of women who were younger than 40 years of age. We called this estimate the "extreme" assumption. Second, in addition to the increase of 0.5% per year, we revised the baseline incidence of late-stage breast cancer by using the highest incidence observed in the data (113 cases per 100,000 women in 1985) — thereby maximizing the deficit of diagnoses of late-stage cancer. We called this estimate the "very extreme assumption."

RESULTS

CHANGES IN INCIDENCE ASSOCIATED WITH IMPLEMENTATION OF SCREENING

Figure 1A shows the substantial increase in the use of screening mammography during the 1980s and early 1990s among women 40 years of age or older in the United States. Figure 1A also shows that there was a substantial concomitant increase in the incidence of early-stage breast cancer among these women. In addition, a small decrease is evident in the incidence of late-stage breast cancer. As shown in Figure 1B, there was little change in breast-cancer incidence among women who generally did not have exposure to screening mammography — women younger than 40 years of age.

Table 1 shows the changes in the stage-specific annual incidence of breast cancer over the past three decades among women 40 years of age or older. The large increase in cases of early-stage cancer (from 112 to 234 cancers per 100,000 women — an absolute increase of 122 cancers per 100,000) reflects both detection of more cases of localized disease and the advent of the detection of DCIS (which was virtually not detected before mammography was available). The smaller

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decrease in cases of late-stage cancer (from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women) largely reflects detection of fewer cases of regional disease. If a constant underlying disease burden is assumed, only 8 of the 122 additional early diagnoses were destined to progress to advanced disease, implying a detection of 114 excess cases per 100,000 women. Table 1 also shows the estimated number of women affected by these changes (after removal of the transient excess cases associated with hormone-replacement therapy). These estimates are shown in terms of both the surplus in diagnoses of early-stage breast cancers and the reduction in diagnoses of late-stage breast cancers — again, under the assumption of a constant underlying disease burden.

OVERDIAGNOSED CANCER AND EFFECT OF SCREENING ON REGIONAL AND DISTANT DISEASE

Table 2 shows the effects of relaxing the assumption of a constant underlying disease burden on the estimate of the number of women with cancer that was overdiagnosed. The base-case estimate incorporates the data in Table 1. In the best-guess estimate, it was assumed that the trend in the underlying incidence was best approximated by the incidence observed among women younger than 40 years of age (Fig. 1B). This approach suggests that the excess detection attributable to mammography in the United States involved more than 1.3 million women in the past 30 years. In the extreme and very extreme estimates, it was assumed that the underlying incidence was increasing at double the rate observed among women younger than 40 years of age. Finally, in the very extreme estimate, it was assumed that the incidence of late-stage cancer was the highest incidence ever observed (thereby maximizing the deficit of diagnoses of late-stage cancer).

Regardless of the approach used, our estimate of overdiagnosed cancers attributable to mammography over the past 30 years involved more than 1 million women. In 2008, the number of women 40 years of age or older with overdiagnosed cancers was more than 70,000 per year according to the best-guess estimate, more than 60,000 per year according to the extreme estimate, and more than 50,000 per year according to the very extreme estimate. The corresponding estimates of the proportions of cancers that were overdiagnosed are 31%, 26%, and 22%.

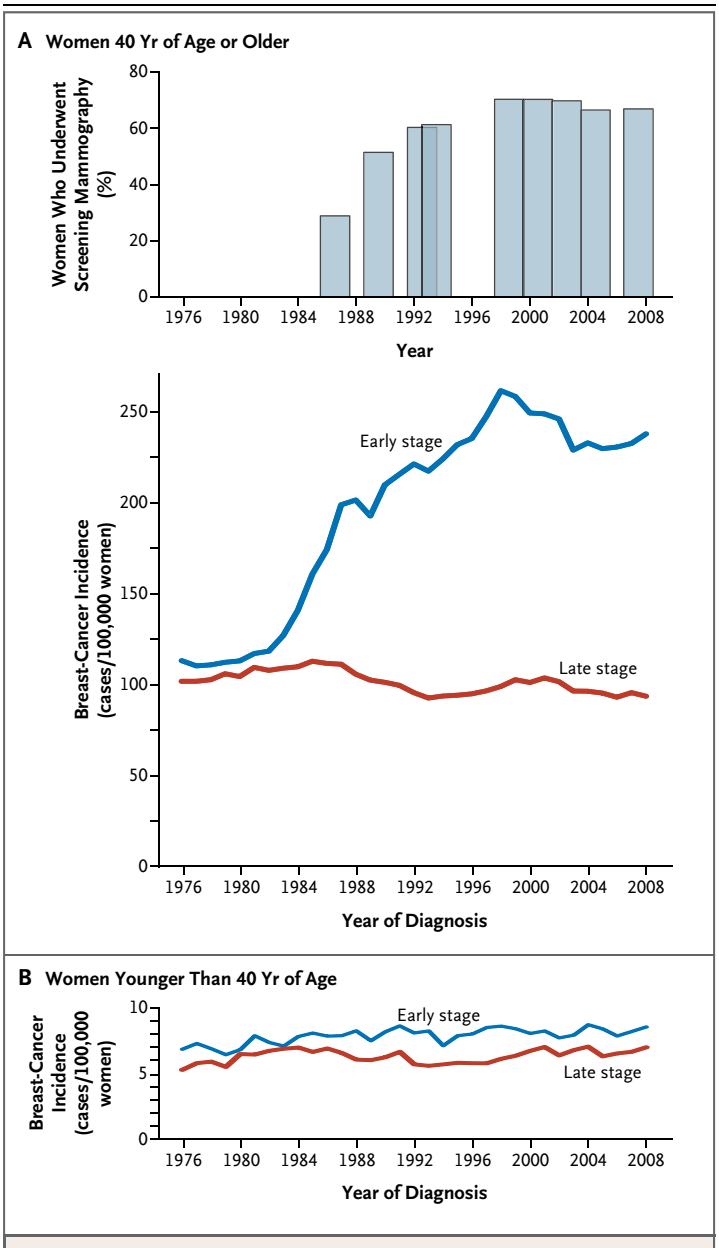

Figure 1. Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the United States, 1976–2008.

Panel A shows the self-reported use of screening mammography and the incidence of stage-specific breast cancer among women 40 years of age or older. Panel B shows the incidence of stage-specific breast cancer among women who generally did not have exposure to screening mammography — those younger than 40 years of age.

Figure 2 shows the trends in regional and distant late-stage breast cancer. The variable pattern in late-stage cancer (which includes the excess diagnoses associated with hormone-replacement therapy in the late 1990s and early 2000s) was

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Table 1. Absolute Change in the Incidence of Stage-Specific Breast Cancer among Women 40 Years of Age or Older after the Introduction of Screening Mammography.*

Variable	Annual Breast-Cancer Incidence			Women Affected over the Three Decades†
	Before Mammography (1976–1978)	Three Decades Later (2006–2008)	Absolute Change	
	number of cases per 100,000 women			*estimated number of women*
Increase in cases of early-stage breast cancer				
DCIS	7	56	50	573,000
Localized disease	105	178	72	1,012,000
Total	112	234	122	1,585,000
Decrease in cases of late-stage breast cancer				
Regional disease	85	78	–8‡	59,000
Distant disease	17	17	0§	8,000
Total	102	94	–8	67,000

* DCIS denotes ductal carcinoma in situ.
† These data exclude excess cases associated with hormone-replacement therapy.
‡ Because of rounding, the absolute change appears to be inconsistent with the subtracted values for annual breast-cancer incidence. See Table S1 in the Supplementary Appendix for precise values.
§ Without rounding, the absolute change is –0.3.

virtually entirely attributable to changes in the incidence of regional (largely node-positive) disease. The incidence of distant (metastatic) disease, however, has remained unchanged (95% CI for the annual percent change, –0.19 to 0.14).

DISCUSSION

Screening can result in both the benefit of a reduction in mortality and the harm of overdiagnosis. Our analysis suggests that whatever the mortality benefit, breast-cancer screening involved a substantial harm of excess detection of additional early-stage cancers that was not matched by a reduction in late-stage cancers. This imbalance indicates a considerable amount of overdiagnosis involving more than 1 million women in the past three decades — and, according to our best-guess estimate, more than 70,000 women in 2008 (accounting for 31% of all breast cancers diagnosed in women 40 years of age or older).

Over the same period, the rate of death from breast cancer decreased considerably. Among women 40 years of age or older, deaths from breast cancer decreased from 71 to 51 deaths per 100,000 women — a 28% decrease.[6] This reduction in mortality is probably due to some combination of the effects of screening mammography and better treatment. Seven separate modeling exercises by the Cancer Intervention and Surveillance Modeling Network investigators provided a wide range of estimates for the relative contribution of each effect: screening mammography might be responsible for as little as 28% or as much as 65% of the observed reduction in mortality (the remainder being the effect of better treatment).[13]

Our data show that the true contribution of mammography to decreasing mortality must be at the low end of this range. They suggest that mammography has largely not met the first prerequisite for screening to reduce cancer-specific mortality — a reduction in the number of women who present with late-stage cancer. Because the absolute reduction in deaths (20 deaths per 100,000 women) is larger than the absolute reduction in the number of cases of late-stage cancer (8 cases per 100,000 women), the contribution of early detection to decreasing numbers of deaths must be small. Furthermore, as noted by others,[14] the small reduction in cases of late-stage cancer that has occurred has been confined to regional (largely node-positive) disease — a stage that can now

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Table 2. Four Estimates of the Excess Detection (Overdiagnosis) of Breast Cancer Associated with Three Decades of Screening Mammography, 1979–2008.

Estimate	Assumption Regarding Underlying Incidence of Breast Cancer	Surplus in Diagnoses of Early-Stage Disease	Reduction in Diagnoses of Late-Stage Disease	Excess Detection
		number of women		
Base case	It was constant	1,585,000	67,000	1,518,000
Best guess	It increased at a rate of 0.25%/yr*	1,507,000	138,000	1,369,000
Extreme assumption	It increased at a rate of 0.5%/yr†	1,426,000	213,000	1,213,000
Very extreme assumption	It increased at a rate of 0.5%/yr and baseline incidence of late-stage disease was the highest ever observed‡	1,426,000	410,000	1,016,000

* This increase in incidence was observed among women younger than 40 years of age.
† This increase in incidence was twice that observed among women younger than 40 years of age.
‡ The peak in the incidence of late-stage breast cancer was 113 cases per 100,000 women in 1985.

often be treated successfully, with an expected 5-year survival rate of 85% among women 40 years of age or older.[15,16] Unfortunately, however, the number of women in the United States who present with distant disease, only 25% of whom survive for 5 years,[15] appears not to have been affected by screening.

Whereas the decrease in the rate of death from breast cancer was 28% among women 40 years of age or older, the concurrent rate decrease was 42% among women younger than 40 years of age.[6] In other words, there was a larger relative reduction in mortality among women who were not exposed to screening mammography than among those who were exposed. We are left to conclude, as others have,[17,18] that the good news in breast cancer — decreasing mortality — must largely be the result of improved treatment, not screening. Ironically, improvements in treatment tend to deteriorate the benefit of screening. As treatment of clinically detected disease (detected by means other than screening) improves, the benefit of screening diminishes. For example, since pneumonia can be treated successfully, no one would suggest that we screen for pneumonia.

Our finding of substantial overdiagnosis of breast cancer with the use of screening mammography in the United States replicates the findings of investigators in other countries (Table S5 in the Supplementary Appendix). Nevertheless, our analysis has several limitations. Overdiagnosis can never be directly observed and thus can only be inferred from that which is observed — reported incidence. Figures 1 and 2 are based on unaltered, long-standing, carefully collected federal data that are generally considered to be incontrovertible. Tables 1 and 2, however, are based on assumptions that warrant a more critical evaluation.

First, our results might be sensitive to the period (1976 through 1978) that we chose to obtain data for the baseline incidence of breast cancer (before mammography). If the period were expanded to begin with the first years of SEER data (i.e., 1973 through 1978), the baseline incidence of early-stage cancer would be slightly lower (0.9%) and the incidence of late-stage cancer would be slightly higher (1.4%). These changes offset each other and have a negligible effect on our estimates.

Second, our ability to remove the effect of hormone-replacement therapy (Fig. S1 in the Supplementary Appendix) is admittedly imprecise. Although there is general agreement that this effect had largely ceased by 2006, its onset is not as discrete. We chose to cap the incidence of each disease stage as far back as 1990. However, the pattern of regional disease (Fig. 2) suggests that the bulk of the effect of hormone-replacement therapy probably began later, in the mid-1990s, such that our assumption probably overcorrects for the effect of hormone-replacement therapy.

Third, we were forced to make some assumptions about the pattern of the underlying incidence — the incidence that would have been observed in the absence of screening. The simplest approach was to assume that the underlying incidence was constant (the base case). In our best-guess estimate, however, we posited that the

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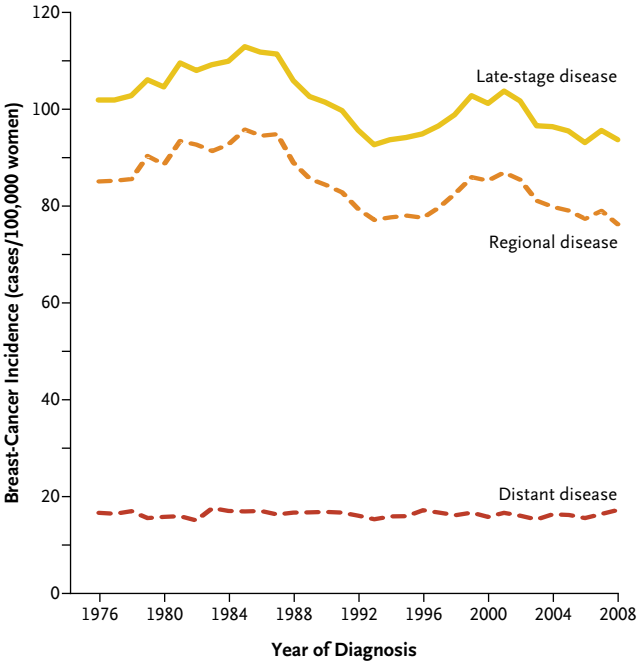

Figure 2. Trends in the Annual Incidence of Late-Stage Breast Cancer and Its Two Components (Regional and Distant Disease) among U.S. Women 40 Years of Age or Older, 1976–2008.

underlying incidence was that observed in the population of women without exposure to mammography; this underlying incidence was increasing at a rate of 0.25% per year. Our assumption of an increase of 0.5% per year (in the extreme and very extreme estimates) was admittedly arbitrary. It was twice the rate of increase observed among women younger than 40 years of age and was outside the 95% confidence interval. Perspective on the uncertainty about the underlying incidence, however, is provided in Figure 2. The finding of a stable rate of distant disease argues against dramatic changes in the underlying incidence of breast cancer.

Fourth, our best-guess estimate of the frequency of overdiagnosis — 31% of all breast cancers — did not distinguish between DCIS and invasive breast cancer. Our method did not allow us to disentangle the two. We did, however, estimate the frequency of overdiagnosis of invasive breast cancer under the assumption that all cases of DCIS were overdiagnosed. This analysis suggested that invasive disease accounted for about half the overdiagnoses shown in Table 2 and that about 20% of all invasive breast cancers were overdiagnosed; these findings replicate those of other studies.[19]

Finally, some investigators might point out that our best-guess estimate of the frequency of overdiagnosis — 31% — was based on the wrong denominator. Our denominator was the number of all diagnosed breast cancers. Many investigators would argue that because overdiagnosis is the result of screening, the correct denominator is screening-detected breast cancers. Unfortunately, because the SEER program does not collect data on the method of detection, we were unable to distinguish screening-detected from clinically detected cancers. Self-reported data from the National Health Interview Survey, however, suggest that approximately 60% of all breast cancers were detected by means of screening in the period from 2001 through 2003.[20]

Breast-cancer overdiagnosis is a complex and sometimes contentious issue. Ideally, reliable estimates about the magnitude of overdiagnosis would come from long-term follow-up after a randomized trial.[21] Among the nine randomized trials of mammography, the lone example of this is the 15-year follow-up after the end of the Malmö Trial,[22] which showed that about a quarter of mammographically detected cancers were overdiagnosed.[23] Unfortunately, trials also provide a relatively narrow view involving one subgroup of patients, one research protocol, and one point in time. We are concerned that the trials — now generally three decades old — no longer provide relevant data on either the benefit with respect to reduced mortality (because treatment has improved) or the harm of overdiagnosis (because of enhancements in mammographic imaging and lower radiologic and pathological diagnostic thresholds).

Our investigation takes a different view, which might be considered the view from space. It does not involve a selected group of patients, a specific protocol, or a single point in time. Instead, it considers national data over a period of three decades and details what has actually happened since the introduction of screening mammography. There has been plenty of time for the surplus of diagnoses of early-stage cancer to translate into a reduction in diagnoses of late-stage cancer — thus eliminating concern about lead time.[24] This broad view is the major strength of our study.

Our study raises serious questions about the value of screening mammography. It clarifies that the benefit of mortality reduction is probably

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smaller, and the harm of overdiagnosis probably larger, than has been previously recognized. And although no one can say with certainty which women have cancers that are overdiagnosed, there is certainty about what happens to them: they undergo surgery, radiation therapy, hormonal therapy for 5 years or more, chemotherapy, or (usually) a combination of these treatments for abnormalities that otherwise would not have caused illness. Proponents of screening should provide women with data from a randomized screening trial that reflects improvements in current therapy and includes strategies to mitigate overdiagnosis in the intervention group. Women should recognize that our study does not answer the question "Should I be screened for breast cancer?" However, they can rest assured that the question has more than one right answer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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