Is Mammographic Screening Justifiable Considering Its Substantial Overdiagnosis Rate and Minor Effect on Mortality?

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Abbreviation:
DCIS = ductal carcinoma in situ

Potential conflicts of interest are listed at the end of this article.

See also the articles by Kopans et al and Tabár et al in this issue.

Proponents of mammographic screening generally say that the benefit is large and established beyond doubt, that there is little overdiagnosis, and that screening leads to less invasive treatment (1–3). The truth is that the benefit is doubtful, that overdiagnosis is substantial and certain, and that screening increases the number of mastectomies performed.

Breast Cancer Mortality

All health care interventions can cause harm. Most also have benefits, and their justification relies on the balance between these harms and benefits. This value judgment has no "correct" answer in scientific terms, but the relationship between overdiagnosis and lives prolonged is crucial in the mammographic screening debate.

Screening advocates often claim that mammographic screening reduces the relative risk of breast cancer mortality by at least 30% (1). The Swedish Two-County Trial (4) was the most optimistic and pivotal for the introduction of screening, but subsequent trials of higher quality found smaller effects. Comprehensive systematic reviews of all trials by two independent groups—the U.S. Preventive Services Task Force and the Nordic Cochrane Centre—have suggested an effect of 15%–16% (5,6).

The Cochrane Collaboration, which was established in 1993, is an independent, not-for-profit, international network of scientists who prepare and update systematic Cochrane reviews, which are published online in the Cochrane Library. The risk of bias in the included randomized trials is evaluated in a standardized fashion on the basis of empirical evidence. The U.S. Cochrane Center is located at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, with a branch at the University of California in San Francisco.

There have been substantial advances in treatment since most of the trials were performed, and these advances must have reduced the effect of screening. Antihormone therapy and polychemotherapy are also effective when the cancer has metastasized (7), and the declines in breast cancer mortality we have seen have occurred rather uniformly across prognostic groups (8).

Daniel Kopans has stated that "one might expect to see a reduction in the number of late-stage cases if a screening intervention was effective" (9). We agree, but this has not happened. There has been a large increase in ductal carcinoma in situ (DCIS) and localized invasive breast cancers in the United States but a very small decrease in cancers with metastases (Figs 1, 2) (10,11). Similarly, a systematic review of several countries found that, on average, the rate of cancers larger than 20 mm was not affected by screening (12). If screening does not reduce the incidence of advanced cancers, it does not work, and one can conclude that the increase in localized cancers over the increase in background incidence, which coincides with the introduction of screening, is due to overdiagnosis and not early diagnosis.

In contrast to screening, an increase in breast cancer awareness has likely been important in the observed reduction in mortality. In Denmark, the average tumor size was 33 mm in 1978–1979 but only 24 mm in 1988–1989 (13). This change occurred before screening started, and, contrary to screening, breast cancer awareness is unlikely to cause overdiagnosis (14). The observed difference of 9 mm is much greater than the average difference in mean tumor diameter between the screened and control groups in the trials, which was only 5 mm (15–18) despite the fact that the small overdiagnosed tumors would tend to spuriously exaggerate the difference.

There are many poorly designed observational studies that claim to show that mammographic screening has a large effect on mortality. These studies often use statistical models with unsupported assumptions or misleading comparisons (19). The better studies rely on unmodified data. Denmark has a unique control group because only 20% of the population was screened during a 17-year period. The annual decrease in breast cancer mortality in the age group that could benefit from screening (55–74 years) and in the time period when an effect was expected was 1% in the screened areas and 2% in the nonscreened areas. In women who were too young to benefit from screening, the decreases were larger—5% and 6%, respectively (20). In addition, screening had no visible effect on mortality when comparing age groups in the United Kingdom (Fig 3), Sweden, and Norway (20–22). The Norwegian study was criticized because the average follow-up of 2.2 years was too short; however, this is a misunderstanding. This was the follow-up after diagnosis. The follow-up from the start of screening was 6.6 years, which is when an effect was seen in the trials (5).

The decline in breast cancer mortality in the United States coincided with the widespread propagation of screening in the mid-1980s; however, correlation does not equal causality—even though Kopans seems to think so (1). A study in the United States reported an effect on the mortality rate from breast cancer through screening of approximately 15% from 1975 to 2000 (23), meaning that about half of the total decline of about 30% was due to screening; however, this result can be questioned. The statistical models were adjusted for an increase in breast cancer incidence even though this was caused by screening and should not have been adjusted for (23).

Unlike women in the United States, women in Europe are rarely offered screening before the age of 50 years. The mean decrease in breast cancer mortality between 1989 and 2005 in European women younger than 50 years was 37%, whereas it was 21% in women aged 50–69 years (24). The declines began before organized screening in many countries and fitted better with the introduction of tamoxifen, which helps explain the larger decline in young women who often have estrogen-sensitive tumors (Fig 3).

Screening advocates have claimed that screening is the reason why breast cancer mortality rates are lower in Sweden than in Denmark (25), but this is wrong. The difference existed decades before screening, and the reductions in breast cancer mortality in the screening period (1989–2006) were larger in Denmark. Breast cancer mortality in women younger than 50 years decreased 49% in Denmark versus 36% in Sweden; however, half of these women are invited to screening in Sweden versus none in Denmark (24). In those aged 50–69 years, the reduction was 26% in Denmark versus 16% in Sweden, although only 20% of Danish women were invited to screening versus all in Sweden (where more than 80% participated) (24,26).

Despite the fact that Sweden has the longest running program, the widest age range, and the shortest screening interval in Europe (26), the reductions in breast cancer mortality are lower than the European median (24). A recent Swedish study (27) claimed that screening reduced breast cancer mortality by 26% in women aged 40–49 years; however, the study methods are unclear and the result compares poorly with other data (20,24).

Overdiagnosis

Overdiagnosis is the detection of cancers that would not have been identified clinically in a woman's lifetime. Overdiagnosis is inevitable, as some women will die of causes other than breast cancer before their screening-detected cancers would have appeared clinically (28).

Overdiagnosis of breast cancer can be estimated accurately from large randomized trials where all women are followed up until death from any cause and where no screening occurs in the control group during or after the randomized phase. The overdiagnosis would then be the difference in the lifetime risk of getting a breast cancer diagnosis between the two groups. Because no such data exist, we must consider the various biases in the best trials. In the Malmö Mammographic Screening Trial (15), the randomized phase was maintained for a long time—9 years. However, women were followed up for an additional 15 years and then had an overdiagnosis rate of approximately 10% (29). This estimate was therefore considerably diluted. Furthermore, 24% of women in the control group were screened during the randomized phase. After adjustment for these biases, which is a straightforward process, the rate of overdiagnosis was 25% (30). Only 7%–9% of cases were DCIS (28), indicating that there is likely more overdiagnosis in other countries.

Overdiagnosis was mentioned in the 1986 report that paved the way for screening in the United Kingdom (31). There were only two trials at that time. One was the New York Health Insurance Plan Trial, which found a similar number of breast cancers in the screened and control groups after 7 years (31). The authors of the report, therefore, believed that overdiagnosis was not a problem; however, the reason that the Health Insurance Plan Trial did not find more cancers with screening was that many cancers in the control group had been diagnosed before randomization and should have been excluded—as they were in the screened group (5). The other trial, the Swedish Two-County Trial (4), found 20% more breast cancers after 6 years in the group invited to screening than in the control group. The investigators recommended performing further follow-up to determine whether this excess persisted for the lifespan of the women (31). The results of further follow-up would have been inconclusive, however, because the trialists introduced overdiagnosis in the control group by inviting the women to undergo screening after the randomized phase (5).

The Cochrane review reported 30% more cancers in the screened group, which corresponds to 10 cases of overdiagnosis for every life prolonged (5). Because the excess incidence persisted, screening advocates needed a new model

Figure 1

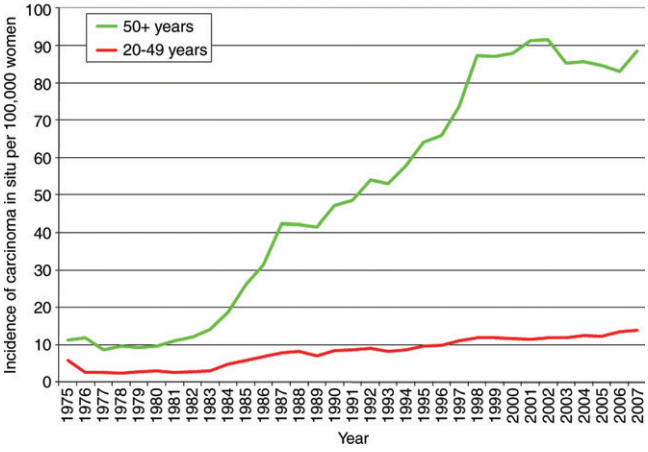

Figure 1: Graph shows age-adjusted incidence rates of DCIS in the United States from 1975 to 2007. Detection rates increased fourfold in women younger than 50 years and eightfold in women 50 years or older after screening became widespread in the mid-1980s (11).

Figure 2

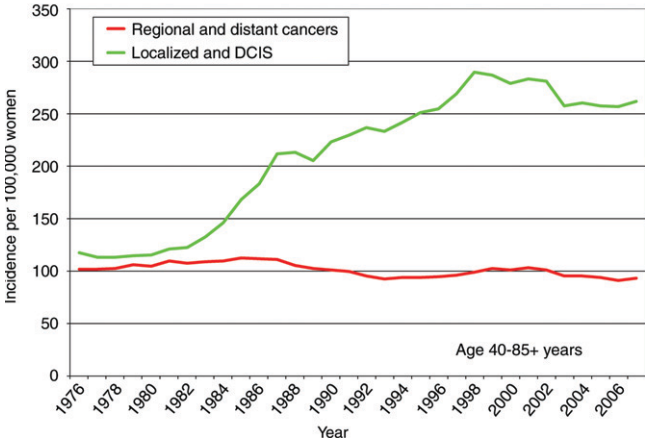

Figure 2: Graph shows age-adjusted incidence rates of metastatic (regional and distant) and nonmetastatic (DCIS and localized) breast cancers in the United States from 1976 to 2007. The small decline in metastatic cancers derives from regional cases, with no change for distant cases (not shown). It does not compensate for the large, persistent increases in nonmetastatic cancers. Localized and in situ cases each contribute to about half of the doubling in the incidence of nonmetastatic cases seen after screening started in the mid-1980s (11).

to explain that this was not a problem. In a much-cited letter from 1994, Boer et al (32) claimed that the extra incidence was due to early diagnosis and would be compensated for by a massive decline in incidence when women passed the upper age limit for screening because their cancers had already been detected (Fig 4). As noted by the U.S. National Cancer Institute, however, this decline has never been observed (33). In fact, screening has led to large, persistent increases everywhere—with very little or no compensatory declines in women who are no longer screened. This is best studied in countries with long-running, publicly organized screening programs that cover specific age groups—with little opportunistic screening. In a systematic review of such countries, we found an overdiagnosis rate of 52%, including DCIS (34). Our findings of substantial overdiagnosis of invasive breast cancer have been confirmed by others using different methods (35). Persistent increases in incidence due to overdiagnosis are also common when screening for other cancers (eg, prostate and lung cancer) (28).

Kopans has argued that combining incidence and prevalence screenings provided misleading estimates of overdiagnosis in our systematic review because women undergoing their first screening examination at 50 years would inflate the incidence with prevalent cases (36). Women invited to screening at age 50 years, however, do not represent much more than one in 20 of the invited age group (aged 50–70 years) in a given year, and screening proponents have shown that this mixing effect from women turning 50 causes "a very minor change" in the estimate of overdiagnosis (37). What is important is that the increase in incidence is not compensated for by a decrease once screening ends, even after more than 20 years with organized screening (34). In fact, this decrease in incidence should have included compensation for those extra cases detected on the prevalence screen of women who turn 50 years. Critics of our analysis have ignored this fact.

Data from the United Kingdom are particularly worrisome (Fig 5). When screening was extended to women aged 65–70 years in 2001, a sharp increase in incidence occurred in these women even though they had been offered screening many times when they were younger and had already contributed to a massive increase in the incidence of DCIS and invasive cancers. This is difficult to explain unless we assume that many screening-detected cancers would have regressed spontaneously if left alone, a possibility supported by an elegant study from Norway (38).

Screening has also led to a large and persistent increase in incidence in the United States (Figs 1, 2) (10). The possible existence of a compensatory decline would be hard to investigate but also unlikely, as there is no upper age limit for screening. However, it is clear that screening has greatly increased the lifetime risk of becoming a breast cancer patient.

In the United States, DCIS accounts for approximately one in four breast cancers, and there are no data showing that the detection of DCIS with screening saves lives (39). Although the incidence of DCIS has increased manyfold with screening (Fig 1), screening advocates have ignored the lack of a corresponding decrease in invasive cancers (10). Results of autopsy studies suggest that less than half of DCIS lesions progress (40); however, if we assume that half of them do, the minimum overdiagnosis rate (ignoring invasive cancers) would be approximately 13%. Lower estimates of overdiagnosis cited by screening advocates (41,42) are flawed because they rely on statistical modeling with unsupported assumptions (ie, how much

Figure 3

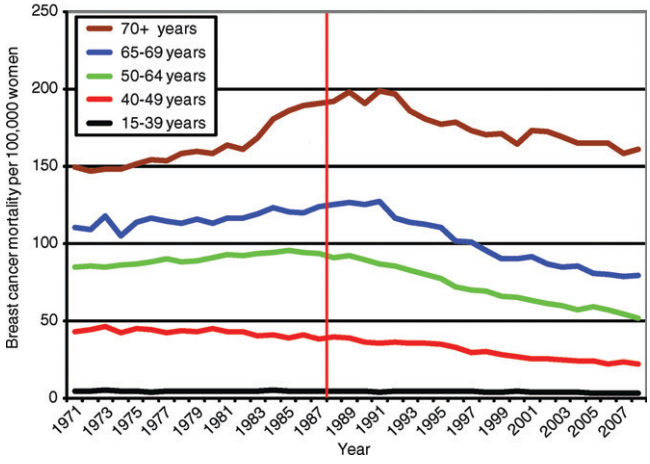

Figure 3: Graph shows breast cancer mortality rates in the United Kingdom from 1971 to 2008. The largest decrease is seen in women aged 40–49 years, who were not eligible for screening (decrease of 50% from the early 1980s). In women aged 50–64 years, screened from 1988, the decline began before screening was introduced in 1988 (vertical line)—long before an effect would be expected (decrease of 45% from mid-1980s) (21)

Figure 4

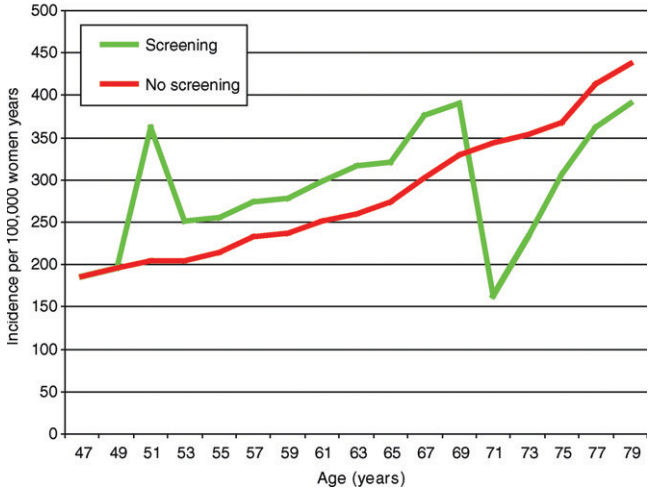

Figure 4: Speculative model of expected development in breast cancer incidence in a population with organized breast screening in women aged 50–69 years. A large decline in incidence when women pass the upper age limit for screening was modeled to compensate for the large increases in incidence when these women were screened. The large compensatory decline is purely hypothetical and has not been observed anywhere (32).

screening brings forward the time of diagnosis [lead time]).

Screening Increases Mastectomies

The trials have shown that the mastectomy rate is 20% higher in women who undergo screening mammography (5), and observational data also show an increase. In Denmark, the large increase when screening was introduced has not been compensated for (Figs 6–8). If the initial increase in the number of mastectomies was due to cases detected on the prevalence screen, we would expect to see correspondingly fewer mastectomies in the screened areas later on, either in the screened age group or in previously screened age groups. This has not occurred; in fact, the mastectomy rate some years after the introduction of screening is practically identical in screened and nonscreened areas (Figs 6–8). The mastectomy rates have declined in recent years, but equally in screened and nonscreened areas—with the largest decrease in women too young to be screened, reflecting a general change in treatment policy.

Screening advocates (2) and the Danish National Board of Health (44) have referred to the fact that the percentage of lumpectomies increases with screening; however, this is misleading. Although a particular woman might be spared a mastectomy, overdiagnosis means that the number of lumpectomies and mastectomies both increase.

The increase in mastectomies as a result of screening seems impossible to avoid. DCIS, for example, contributes substantially to overdiagnosis, as many of these lesions would never have progressed to invasive cancer. In the United Kingdom, 29% of DCIS lesions are treated with mastectomy, compared with 26% of invasive cancers (45). DCIS is often multifocal, which adds to debunking the myth that early detection prevents mastectomies (46).

Implications for Radiologists

Breast imagers, like other physicians, prefer to think that their daily activities improve health and save lives. However, the average breast imager could be doing more harm than good. During a 10-year period, starting in women aged 40, 50, and 60 years, an estimated 41%–46% of screening-detected breast cancers in the United States will represent overdiagnosis (47).

In 2003, 7% of U.S. radiologists read more than 5000 mammograms a year, 20% read 2000–4999 mammograms, 18% read 1000–1999 mammograms, and 11% read 480–999 mammograms (48). Assuming an overdiagnosis rate of 30% and a 15% reduction in breast cancer mortality (5,6), a breast imaging specialist in the United States who reads 9000 mammograms annually from women in their 50s would prevent two future breast cancer deaths the entire year. Predicted follow-up events include 820 recalls, approximately 68 negative and 42 positive biopsies, and 18 cases of overdiagnosis. A radiologist who reads 1000 mammograms a year from women in their 40s would take 10 years to prolong one life yet burden one woman every year with overdiagnosis and overtreatment (47).

The goal of screening mammography is earlier detection of only those invasive tumors that would otherwise be lethal. New technology or more intensive screening will not solve the overdiagnosis problem; in fact, it might aggravate it. For example, an increase in sensitivity owing to supplemental imaging with additional modalities such as

Figure 5

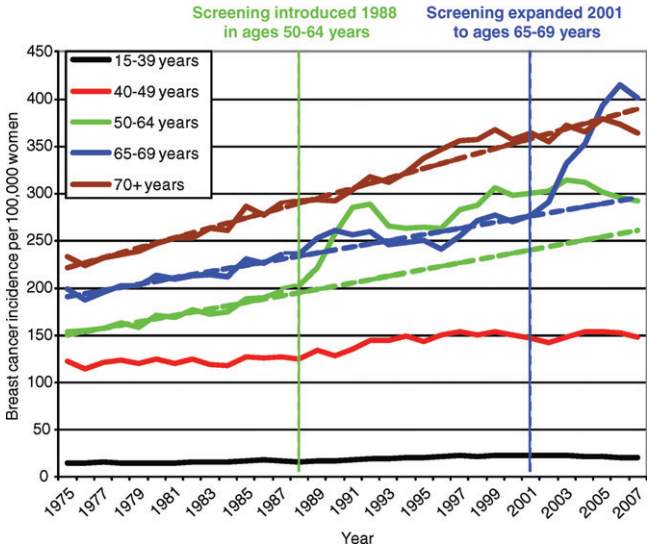

Figure 5: Graph shows incidence rates of invasive breast cancer (DCIS not included) in the United Kingdom from 1975 to 2007. Compared with the increasing background incidence projected from the prescreening trends (dotted lines), screening caused a massive increase in incidence in screened age groups; there was no decrease in incidence in age groups that have passed the upper age limit for screening. The sharp increase in incidence in previously screened women aged 65–69 years when the program was expanded in 2001 is unexpected and worrisome (21).

Figure 6

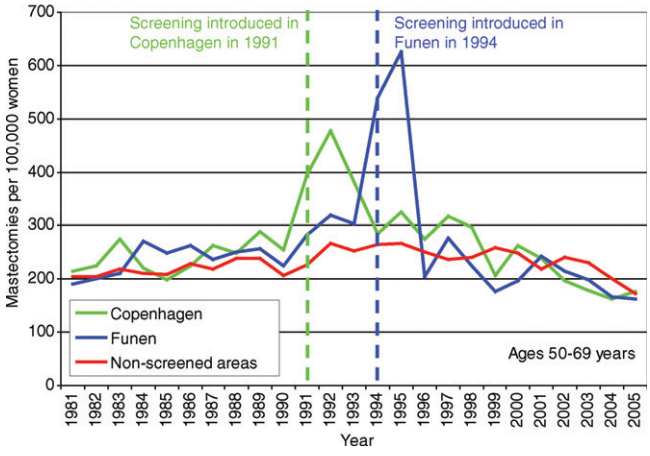

Figure 6: Graph shows mastectomy rates in women aged 50–69 years in Denmark. Screening in this age group began in 1991 in Copenhagen and in 1994 in Funen. Nonscreened areas represent 80% of the Danish population (43).

Figure 7

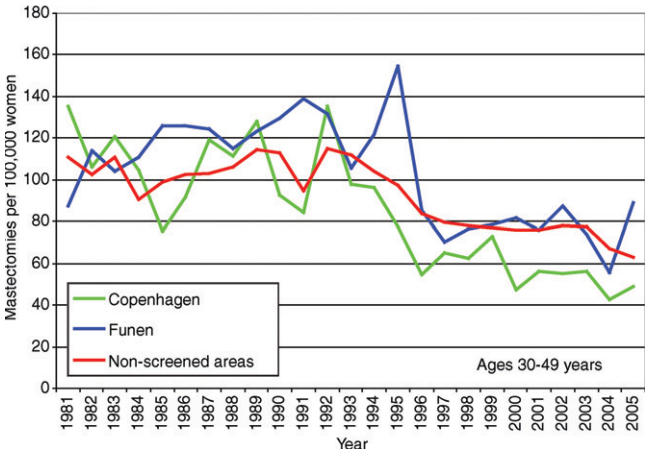

Figure 7: Graph shows mastectomy rates in women aged 30–49 years in Denmark. Women in this age group are not offered screening, and opportunistic screening is rare. A marked decline in the use of mastectomies is seen in all areas, representing a policy change (43).

Figure 8

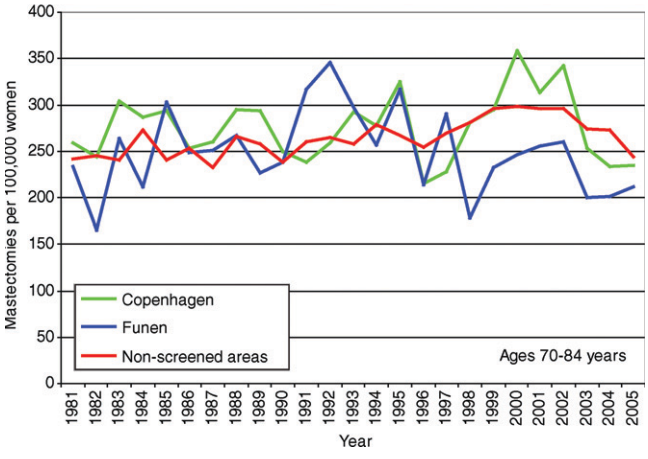

Figure 8: Mastectomy rates in women aged 70–84 years in Denmark. Women in this age group are not offered screening, and opportunistic screening is rare. No clear change in mastectomy rates is seen in areas with or without screening, although early detection in younger women would have been expected to decrease the number of mastectomies—particularly toward the end of the observation period (43).

ultrasonography or computer-aided detection inevitably creates harmful "true-positive" overdiagnoses in addition to the extra usual false-positive findings. Unfortunately, the existence of overdiagnosis makes the problem of excessive recalls in the United States worse (49). Hall (50) recommends that U.S. radiologists perform fewer biopsies of low-suspicion microcalcifications.

Are Breast Screening Programs Justified?

Substantial overdiagnosis and overtreatment increases mortality (eg, from heart disease and lung cancer caused by radiation therapy) (51). The net effect of screening on all-cause mortality, if any, must be minimal, even if screening still had some

effect on breast cancer mortality today (which is doubtful).

Screening carries other important harms (eg, false-positive findings leading to psychologic distress). This was previously downplayed as mild and temporary but is now recognized as severe and potentially long-lasting (52). In the United States, the estimated cumulative risk of a false-positive result after 10 mammograms is 49%; 19% of women who do not have breast cancer would have undergone biopsy after 10 mammograms (53).

We should remind ourselves that it is generally more important to prevent cancer from occurring than to detect it early (54). The U.S. Center for Medical Consumers noted that, if we wish to reduce incidence, there is nothing as effective as avoiding screening mammograms (55). In the screened age group, this reduces the risk of becoming a breast cancer patient by one-third (34).

The time has come to reassess whether universal mammographic screening should be recommended for any age group because the declines in breast cancer mortality can be ascribed mainly to improved treatments and breast cancer awareness; we have seen that screening has only a minor effect on mortality (if any). Equally important, overdiagnosis has profound human costs because it increases rates of mastectomy and death. For these reasons, we question the justification for mammographic screening.

Disclosures of Potential Conflicts of Interest:
K.J.J. No potential conflicts of interest to disclose.
J.D.K. No potential conflicts of interest to disclose.
P.C.G. No potential conflicts of interest to disclose.

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