The 2009 US Preventive Services Task Force (USPSTF) Guidelines are not Supported by Science: The Scientific Support for Mammography Screening

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• Scientific support • Breast cancer screening

Mammography screening is one of the major medical accomplishments of the past 40 years. In the United States, before 1990, the death rate from breast cancer had been unchanged for the preceding 40 years. In the middle of the 1980s there was a sudden increase in the incidence of breast cancer that was initially believed to represent an epidemic until it was realized that this was caused by the start of mammography screening[1] in sufficient numbers to affect national statistics. There was no new epidemic of breast cancer. Mammography screening was simply detecting cancers that had been building up in the population (prevalence cancers) that had not yet been clinically detected, and it was also detecting cancers from the future (early detection) that had not reached clinical detection thresholds. This sudden increase in incidence was a marker for the onset of screening on a national scale. Periodic screening is unlikely to detect rapidly growing cancers that are soon to be lethal because of the well-known phenomenon of length bias sampling. It is more likely to interrupt moderate and slower growing cancers. These are no less lethal (see later discussion), but have sufficiently slow growth characteristics that they can be interrupted before metastatic spread, and future death can be prevented. Thus, it is not surprising that 5 to 7 years after the onset of mammography screening, the death rate from breast cancer in the United States suddenly began to decrease.[2] According to data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute, the death rate as of 2005 (national statistics lag behind) from breast cancer is now down by almost 30% since 1990 (**Fig. 1**).

This decline in deaths is predominantly a result of mammography screening. In 2005, Berry and colleagues[3] published a summary of 7 computer models that had been queried to determine whether the decrease in breast cancer deaths was a result of mammography screening or

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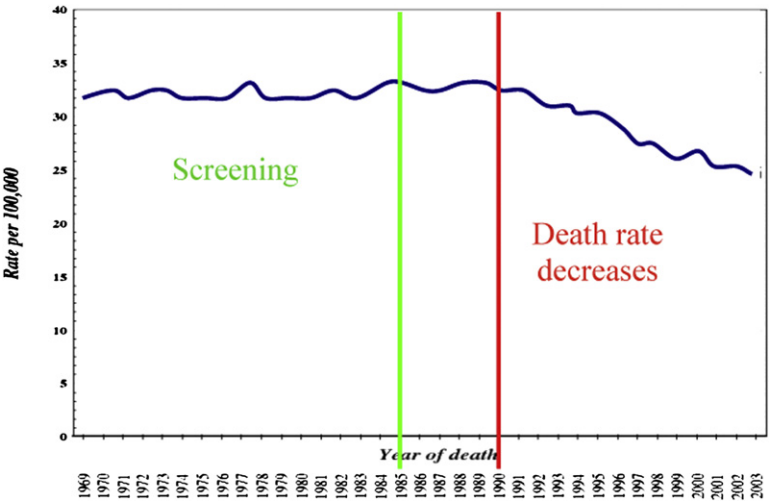

Fig. 1. The breast cancer death rate has decreased in relationship to mammography screening. The death rate was unchanged for decades until mammography screening began in the mid-1980s. Soon after the death rate began to decrease and it has continued to decrease as more and more women participate in screening. By 2005 it was down by 30%. (*Adapted from* Surveillance, Epidemiology, and End Results [SEER] Program [www.seer.cancer.gov] SEER∗Stat Database: Mortality - All COD, Public-Use With State, Total U.S. [1969–2003], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006. Underlying mortality data provided by NCHS [www.cdc.gov/nchs].)

improvements in breast cancer therapy. The computers provided an estimate of the portion of the benefit that was caused by mammography that ranged from 28% to 65% (median 46%). These, however, were computer models and not direct measures. They did, however, show that the contribution of mammography screening in these models was as high as 65%. It is unclear why anyone would rely on computer models when direct measurements are available to determine what happens when screening is introduced for the general public. There have been 4 studies that have directly measured the effect of mammography screening in real populations. In 2001 Tabar and colleagues[4] published their study of the 2 counties in Sweden that had been involved in the Two County Mammography Screening Trial in the 1980s. The investigators looked at the death rate from breast cancer in the prescreening era from 1968 to 1977 during which there was no mammography screening. They compared this with the death rate from 1977 to 1987 during which the Two County Trial was screening part of the population aged 40 to 74 years, and both periods were compared with the period 1988 to 1996 when all women aged 40 to 69 years were invited to participate in mammography screening. The death rate from breast cancer in these 3 periods is similar to a dose-response curve. As more women participated in screening, the death rate from breast cancer declined. When the women who actually participated in screening during the final period (general population) were evaluated, the death rate (a measure that is independent of cancer detection rates and overdiagnosis/pseudodisease bias) decreased relative to the initial prescreening period by 63%. This is not computer modeling, but an actual measure in a real population. When all women who were offered screening (some women refused) were evaluated, the death rate was still decreased by 50%.

The investigators found a slight decrease in the number of deaths in the same period among women aged 20 to 39 years, who were never invited for screening and therefore had no mammograms, and they also found only a slight decrease in deaths among women in the screening ages who had refused to be screened. These latter 2 groups had access to all of the new therapeutic approaches in the same period of time, with no major decline in deaths. This suggests that mammography screening was the primary reason that the number of deaths had decreased in the 29 years encompassed by the review.

In 2002, Duffy and colleagues[5] published a similar study that included women in 7 counties, which amounted to 30% of the women in Sweden. Their results were similar to the Two County review. There was a major decline in breast cancer deaths among the women who participated in screening with only a small decline among women who refused screening in the same period, but had access to new therapies.

In 2003, Otto and colleagues[6] published an analysis of the effects of mammography screening and the use of adjuvant therapy on the death rate from breast cancer in the Netherlands. In the Netherlands, care is based on municipal health systems. Breast cancer mortality had been increasing at approximately 0.3% each year despite the introduction of modern adjuvant therapies. It was not until mammography screening was introduced into each municipality that the death rate began to decline by 1.7% each year. This was direct evidence that the decline in breast cancer mortality is the result of screening with little effect from improvements in therapy.

These direct measures of death rate in these general populations before and after the introduction of mammography screening are not conclusive proof that mammography screening is the main reason that the death rates have declined. As noted later, comparisons of populations at differing points in time (historical controls) are subject to many biases that could confound the interpretation. However, mammography has been shown to decrease deaths in randomized controlled trials (RCT; the most rigorous of scientific studies), and these service screening studies show that mammography screening has fulfilled the expectation that the death rate should decline when it is introduced into the general population. Were all women aged 40 year and older to participate in screening, the studies and estimates of potential benefit suggest that the death rate from breast cancer could be decreased by 50%.[7] No one has ever suggested that mammography screening is the ultimate solution to breast cancer, but there is clear evidence that mammography screening can and is saving tens of thousands of lives each year.

OPPOSITION TO SCREENING

Despite these clear benefits, the past decades have witnessed numerous issues that have been raised concerning the efficacy of mammographic screening that have clouded physician's and the public's understanding of the test. The most recent effort to reduce access to screening came in November 2009 when the United States Preventive Services Task Force (USPSTF) dropped support for screening women aged 40–49 years and supported biennial instead of annual screening for women aged 50–74 years. This latest effort to prevent access for women to mammography screening is scientifically unsupportable (see later discussion). However, some of the issues raised are important.

Screening is very different from caring for individuals who are ill. Screening involves healthy individuals, most of whom do not have breast cancer. There are negative consequences that accompany screening. Some of these are economic and psychological. Women must take time away from home, family, and work to have the study. There is anxiety associated with having a test to look for cancer. As with any test, there are false-positive mammography screening examinations. False-positive studies can cause harms among women that they would not have faced had they not undergone the test in the first place. Although most of these can be resolved with a few additional mammographic projections or ultrasound, some lesions detected at screening require a biopsy to determine whether they are benign or malignant, adding physical trauma to the list of incurred harms. As discussed later, there are clearly some indolent cancers that may not be lethal that are nonetheless treated as if they could be lethal because it is not yet possible to determine which lesions, diagnosed as cancer, do not need to be treated. None of these unnecessary interventions would have occurred were it not for screening. These harms need to be considered because they involve women who may never develop breast cancer. The benefit is that some women will not die from breast cancer because it is found at screening and interrupted before successful metastatic spread. The bottom line is that mammography screening saves lives, but it is not without negative consequences. Women should understand that screening is not a guarantee that they will not die from breast cancer, but that screening can prevent many breast cancer deaths. In a recent study from Harvard, almost 75% of the women who died of breast cancer were among the 25% who were not being screened with mammography.[8]

In light of the downstream consequences of any screening test, it was critical that mammography screening be challenged. There have been many legitimate challenges, as well as many challenges that are not scientifically based but have gained credibility because of repetition. The latter have led to a great deal of confusion among women and their physicians. The aim of this review is to dispel many of the misunderstandings that have developed in the past 5 decades and, hopefully, reduce the confusion that has occurred. Mammography screening does not find all breast cancers and does not

find all cancers early enough to result in a cure, but it is a major advance, and women should not be denied access to its benefits.

THE ISSUES

Mammography screening has undergone greater scrutiny than any other screening test. It has been shown to be able to detect cancers at a smaller size and earlier stage than waiting for a lump to develop.[9] It has been shown in RCTs to be able to reduce deaths from breast cancer,[10] and when mammography screening is provided in the general population, the death rate declines dramatically.[2,4–6] None of the issues raised in opposition to screening have negated the scientific evidence supporting its benefit.

How to Prove a Benefit from Screening

In the 1960s the fundamental question was raised: How do we know that screening will save lives? Comparing survival data between women screened and women who have not been screened is subject to too many possible biases to be scientifically acceptable. The only way to prove that screening saves lives is through the use of RCTs. A large population of women is divided randomly into 2 groups. If the allocation is truly random, the same number of women will be destined to die each year from breast cancer over time in both groups. If one group is screened, and if there are statistically significantly fewer deaths in the screened group, over time, and because this is the only difference between the 2 groups, then this mortality reduction is proof that screening reduces deaths. RCTs are the only way to eliminate such biases as leadtime, length bias sampling, selection bias, and so forth.[11]

RCT Underestimate Benefit

The first RCT of breast cancer screening, the Health Insurance Plan of New York (HIP), showed a 23% decrease in breast cancer deaths for 32,000 women aged 40 to 64 years invited to be screened.[12] What many do not realize is that the RCTs of mammography screening are actually trials of the invitation to be screened. Because no one can be coerced to participate in screening, some women who are invited decline to be screened. To avoid introducing selection bias into the trial, these women are still counted as having been screened. Even if they die of breast cancer they are still counted as deaths among the screened group even though they were never actually screened (noncompliance). Similarly, no one can stop women who are allocated to the unscreened control group from going out and getting a mammogram on their own outside of the trial (contamination). These women are still counted as having not been screened even if the mammogram outside the trial saved their lives. As a result of noncompliance and contamination, the RCT actually underestimates death reduction.

Population (Service) Screening

In the 1970s the question was raised: How can we possibly screen millions of women? This resulted in the Breast Cancer Detection Demonstration Project (BCDDP).[9] Approximately 275,000 women were screened every year for 4 years in several centers across the United States. The BCDDP showed that mammography can indeed find breast cancer at a smaller size and earlier stage than clinical examination. It also showed that large numbers of women could be screened efficiently, and at low cost. This has been confirmed by the experience of the past 20 years during which hundreds of millions of screening mammograms have been performed efficiently and effectively.

Radiation Risk

In 1976 concern was raised that the radiation from mammography would cause more cancers than would be cured.[13] This proved to be a marked overestimate of risk. Nevertheless, in the late 1970s and 1980s, there were major efforts to dramatically lower the doses used for mammography. The use of 1 rad or more per exposure in the HIP trial was reduced to less than 300 mrad per exposure as today's standard. Subsequent studies showed that radiation risk for the breast is highly age related. It is not surprising that the immature undifferentiated breast is more radiosensitive than the mature differentiated organ. This is clearly seen among women who were treated with mantle radiation for Hodgkin disease while in their teens. They have a 35% risk of developing breast cancer in the next 20 years.[14] However, women more than 30 years, who received the same treatment had no excess risk. By the time a woman is 40 years there is no direct evidence of any radiation risk to the breast from mammography and, even the theoretic risk is much less than the smallest benefit derived from detecting breast cancer earlier.[15] Although not conclusive proof, if mammograms were causing cancers, that there have been hundreds of millions of mammograms performed since the 1980s should lead to an increasing incidence of breast cancer. In fact, the incidence of breast cancer is decreasing.

Screening Using Clinical Breast Examination

It has been suggested that much of the benefit from screening may come from performing clinical breast examination (CBE), because the screening used in the HIP study included CBE, and it has been suggested that perhaps all that was needed was CBE to find cancers. There are no other RCT data for CBE since the HIP to support this concept. Earlier detection is a relative phenomenon. It is likely that finding breast cancers earlier than the usual situation will save some lives. Before the 1960s many women with breast problems kept them secret. Mastectomy was the only treatment option and a woman with a lump feared that she would go into hospital for surgery under general anesthesia, and would be put to sleep not knowing if, when she awoke, she would still have her breast. Women feared the diagnosis so much that they would often delay seeking care until the cancer was large and advanced. Any form of earlier detection, such as the CBE performed in the HIP trial, would likely result in reduced deaths. However, as breast cancer became highly visible as a major health concern, cancers began to be found by the individual women at a smaller size. It is unlikely that, at the present time, CBE adds much in terms of downstaging. There have been no RCTs since the HIP study that have included CBE that have shown any independent benefit for CBE. The RCTs of mammography screening in Sweden (5 trials) confirmed that deaths can be reduced by at least 20% by mammography screening alone.[16]

Confusing Guidelines in the Past

In the 1980s several organizations were issuing various guidelines for screening that were confusing to women and their physicians. In 1989 The American Cancer Society, the National Cancer Institute, the American College of Surgeons, the American College of Radiology, and other groups got together and developed the Consensus Guidelines that recommended screening women aged 40 to 49 years every 1 to 2 years and women aged 50 years and older every year. This consensus did not end the debates. There were still some who did not believe that screening benefited women aged 40 to 49 years, and there were no direct data that could accurately determine the appropriate interval between screens.

The Age of 50 Years Becomes a Scientifically Unsubstantiated Breast Cancer Threshold

Because breast cancer is fairly clearly related, at least in part, to hormones, investigators had wondered how menopause might affect the value of screening. None of the RCTs were designed to evaluate women with regard to their hormone (menopausal) status. Consequently, the age of 50 years was chosen as a surrogate for menopause. Although the trial was not designed to permit age stratification, the data in the HIP study were broken into 2 groups[17,18] and women aged 40 to 49 years were evaluated as a separate subgroup. In the early years of follow-up of these younger women, there was no evidence of any difference in deaths between the screened women and the control women. It was not until 5 to 7 years after the first screen that the curves began to diverge with fewer deaths among the screened women than the controls. Although there were questions raised as to which cancers and cancer deaths to include in the follow-up studies[19] and with regard to the timing of analysis after the screening began, it was argued that because the data did not show a statistically significant benefit for women aged 40 to 49 years, there was no benefit. This unplanned, retrospective subgroup analysis of data that lacked statistical power to permit such analysis is the basis for the fallacy that continues today that screening is less effective before the age of 50 years than for women aged 50 years and older. As discussed later, analysts who wanted it to appear as if something suddenly changed at the age of 50 years divided screening data into 2 groups: those younger than 50 years and those aged 50 years and older, making it seem as if the findings jumped suddenly at the age of 50 years when, in fact, there are no ungrouped data (analyzed by individual ages) that show that any of the parameters of screening change abruptly at the age of 50 years, or any other age.

The RCTs of Mammography Screening Demonstrate a Statistically Significant Decrease in Breast Cancer Deaths

In the 1980s a trial was undertaken in 2 counties in Sweden in which part of the population, randomly chosen, was offered mammography screening and the other part of the population was not invited for screening and acted as unscreened controls. In 1985, preliminary results were published showing a statistically significant 30% decrease in breast cancer deaths among women aged 40 to 74 years as a result of mammography screening.[20] There were also trials being conducted in Stockholm, Malmo, and Gothenburg in Sweden, and another screening trial in Edinburgh, Scotland. In 1994, Shapiro published an analysis of these trials which, when combined, showed a 25% mortality

reduction for screening women aged 40 to 74 years.[21] The RCTs, when analyzed as they were designed, were showing a statistically significant benefit (mortality reduction) for screening women beginning at the age of 40 years and continuing up to the age of 74 years.

Major Flaws in the Canadian National Breast Screening Study

Based on the results of age stratification in the HIP trial that had raised questions about the benefit of mammography screening for women aged 40 to 49 years, an RCT was undertaken in Canada to try to answer the specific question as to whether or not mammography screening could reduce deaths from breast cancer among women aged 40 to 49 years. The preliminary results of this trial were published at the end of 1992.[22] Not only did the trial fail to show any early benefit, but, incongruously, there were more breast cancer deaths among women in the mammography arm of the trial.

The Canadian National Breast Screening Study (CNBSS) was given great credibility and was the primary reason that, at the end of 1993, the National Cancer Institute (NCI) decided to drop support for screening women aged 40 to 49 years. Despite hopes that it would resolve the question concerning women aged 40 to 49 years, a careful review of the design and execution of the CNBSS showed that it had major flaws. It was seriously underpowered. This meant that there were not enough women expected to participate in the trial to have enough women who would develop breast cancer, and enough women who would be expected to die from breast cancer to be able to show a statistically significant decrease in deaths among the screened women that was anything less than 40%. Without any contamination or noncompliance, the CNBSS1 did not even plan to recruit sufficient numbers of women to be able to show anything less than a 40% or higher decrease in deaths.[23] The HIP trial had suggested a 25% benefit was likely so that the CNBSS1, before it even began, lacked the power that was needed to prove a benefit. Furthermore, this was a trial of mammography screening yet, by the trial's own review, the quality of the mammography was poor.[24,25] Their own reference physicist stated that the quality of the mammography in the CNBSS, a trial of mammography screening, was far from state-of-the-art, but was even poorer than the quality of mammography being practiced in Canada at the same time.[26]

Although the poor quality of the mammography in the CNBSS was a major problem, it is overshadowed by the design and execution of the CNBSS. To produce 2 identical groups, RCTs require random allocation of the participants. It is well established that randomization must be blinded. Those performing the random assignment can have no information about the participants. This is critical to avoid any compromise of the randomization process and potentially biasing the trial. Almost in complete disregard for this fundamental requirement, the participants in the CNBSS were given a CBE before allocation, and the allocation into the screened group or the control group was then done on open lists. This meant that the nurses and clerks who were assigning women to be in the mammography screening group or the unscreened control group knew, before allocation, which women had clinically evident breast lumps as well as which women had palpable axillary lymph nodes signifying advanced incurable cancer. It is likely that the findings on the clinical examination biased the allocation and indeed there was an excess of advanced cancers allocated at the start of the trial to the mammography group.[27] A study by an analyst at the National Cancer Institute showed that there were statistically significantly more women with 4 or more positive axillary lymph nodes who were allocated to the mammography group.[28] Thus, it is not surprising that there were more deaths among women in the screened group. Given the importance of strict blinded allocation in RCTs, the major failures in the CNBSS raise significant doubt about its conclusions. It is unclear why the CNBSS, a truly compromised trial, continues to be described as a well-performed trial (see later discussion).

In 1993, the NCI, for the First Time in Its History, Ignored the Advice of the National Cancer Advisory Board and Dropped Support for Screening Women Aged 40 to 49 Years

Based on the preliminary data from the CNBSS1, the NCI, at the start of 1993, convened an International Workshop on Breast Cancer Screening. The stated aim was to review all the data with regard to breast cancer screening. One of the major issues was support for screening women aged 40 to 49 years. For unexplained reasons, I was the only expert invited to argue in support of screening these women. The NCI required that a mortality reduction from screening had to appear within 5 years of the start of a trial. This was an overly optimistic goal because it is well known that, because of length bias sampling, periodic screening tests are more likely to find moderate and slower growing cancers rather than fast-growing cancers. This meant that it would be unlikely for a benefit to

appear so soon after the start of the screening trials. The HIP trial seemed to show an immediate benefit for women aged 50 to 64 years, so it was assumed that screening should be able to show an immediate benefit. Given length biased sampling, it was the immediate benefit seen for the older women that should have been questioned, rather than the delayed benefit that was found among the younger women. Furthermore, none of the RCTs were designed to permit legitimate subgroup analysis of women aged 40 to 49 years to guide medical recommendations because they had not been powered to support age stratification. Even the CNBSS1 was underpowered. In fact, in an analysis that I presented to the 1993 Workshop, we showed that the RCT cannot be legitimately used to analyze women aged 40 to 49 years as a subgroup and expect a statistically significant benefit within 5 years of the start of screening[29] as the NCI had required. The NCI had set a requirement that was mathematically impossible to achieve given the numbers of women at these ages in the RCT. The trials, when analyzed as they had been designed, showed a statistically significant benefit for screening women aged 40 to 74 years. There was in fact a decrease in breast cancer deaths that was evident among women aged 40 to 49 years even though the trials were not designed to analyze them separately, but because this benefit was not statistically significant it was discounted. The summary of the workshop did not support screening women in their 40s and gave only passing mention of the power problem[30] even though it showed that what the NCI required was scientifically unsupportable.

At the end of 1993, the National Cancer Advisory Board (NCAB), having been informed of the problems with the CNBSS1, and the inappropriate use of subgroup analyses to make medical recommendations, voted 13 to 1 and advised the NCI to not change their guidelines. For unexplained reasons, the NCI Director, for the first time in the history of the NCI, ignored the advice of the NCAB, and dropped support for screening women aged 40 to 49 years. When asked by a Congressional Panel as to why he had ignored the NCAB he stated that the vote (13 to 1) was "not unanimous."[31] I would speculate that because the NCI Director had been advising the Clinton administration[32] that their health care package, being formulated at the end of 1993, would not have to pay for women aged 40 to 49 years and could screen women aged 50 years and older every 2 years, had he not changed the guidelines, the Clinton Health package, unveiled the next month, would have been financially out of balance.

The Age of 50 Years was Established as a Threshold for Screening Even Though None of the Parameters of Screening Change Abruptly at the Age of 50 Years or Any Other Age

Following the NCI decision, numerous articles were published that supported the concept that the age of 50 years was a valid threshold for initiating screening.[33–39] However, there are actually no data to support this. The age of 50 years is nothing more than an arbitrary threshold, but it continues to be used as if there was scientific support for its use when there is none.[40] The age of 50 years was supported as a real threshold by grouping all women aged 49 years and younger as if they were a uniform group and comparing them with all women aged 50 years and older as if they were a uniform group. Such dichotomous analyses make variables that change gradually with increasing age, such as breast cancer detection rates, appear to change suddenly at the age of 50. The clear example of how this can be misleading is seen in an often-quoted paper from the University of California.[41] The actual data in the paper show that the breast cancer detection rate increases steadily with increasing age with no abrupt change at any age as would be expected. However, the investigators decided to group the data and analyze it dichotomously. Furthermore, they added the results for screening women in their 30s to the results for women in their 40s. This made it appear as if the cancer detection rate jumped suddenly from 2 cancers per 1000 for women aged 30 to 49 years to 10 cancers per 1000 women for women aged 50 to 74 years. No explanation is given for including women in their 30s because no one was suggesting that women in their 30s should be screened. However, their inclusion clearly pulls down the detection rate among women less than the age of 50 years just as grouping women aged 60 years and older with women aged 50 to 59 years makes it appear that there is a large jump in cancer detection at the age of 50 years when there was actually no evidence of this in the ungrouped data. Clearly, this analysis was misleading for many readers. Even a well-known commentator on public health issues was misled when he wrote in a review of this paper

> *The yield [of cancers] of the first mammogram was five times higher in women 50 years of age and older (10 cancers per 1000 studies compared with 2 cancers per 1000 studies)… Clearly mammography is much more efficient in detecting breast cancers in older women.*[42]

There are other concepts that have been used to buttress the importance of age 50 years as having biologic significance such as the importance of breast density. This is actually a measure of the x-ray attenuation of the breast tissues on mammograms and has nothing to do with the firmness of the tissues on clinical examination. It is still suggested that, because young women (<50 years) are believed to have firm breasts, they must be dense breasts and dense tissue can hide a cancer. In fact, there is no relationship between breast density on mammography and firmness on clinical examination. There is no question that large numbers of young women have dense breast tissues, but the percentage of women with dense breasts decreases gradually with increasing age with no sudden change at the age of 50 years or any other age.[43] There are many women in their 50s, 60s, 70s, and 80s who still have dense breasts and there also many women less than the age of 50 years who have fatty (not dense) breasts. Once again, by grouping the data dichotomously, and analyzing all women as 2 groups, breast density (which actually changes gradually with increasing age) is made to appear to change abruptly at the age of 50 years. Furthermore, although breast tissue density does reduce the sensitivity of mammography, it does not eliminate it, and many early cancers are found among women with dense breasts, regardless of age.

Years of Life Lost to Breast Cancer and Relative Versus Absolute Numbers of Cancers

Other arguments have been made against screening women aged 40 to 49 years. It is argued that breast cancer is not an important problem for women in their 40s. In fact, at least 41% of the years of life lost as a result of breast cancer are from cancers diagnosed in women less than 50 years of age.[44] It is argued that because the incidence of breast cancer doubles at age 50 years, breast cancer is not an important problem before the age of 50 years. Approximately 1 woman in 1000 will be diagnosed with breast cancer each year during their 40s, 2/1000 among women in their 50s, 3/1000 among women in their 60s and 4/1000 among women in their 70s. I suspect that most women will not see a big difference between 1/1000 and 2/1000 even though the incidence doubles. What is never pointed out is that the incidence of breast cancer among women aged 70 to 80 years is twice the incidence among women in their 50s yet we do not disparage the importance of screening for women in their 50s.

Although the incidence of breast cancer increases with increasing age (with no abrupt change at the age of 50 years), the absolute number of women diagnosed with breast cancer at a given age is based on the number of women at that age (total number of women at a specific age with breast cancer = incidence at that age × number of women at that age). In 1995 there were actually more women aged 40 to 49 years who were diagnosed with breast cancer than there were women aged 50 to 59 years, but this was overlooked by comparing women in their 40s with all women aged 50 to 74 years. No decade of life accounts for more than 25% of all breast cancers each year but women in their 40s were (and continue to be) singled out as being unimportant.

Age Creep: A Lie that Persists

In 1995 de Koning and colleagues[45] wrote a paper suggesting that decreased deaths among women in their 40s in the RCTs was because the participants reached the age of 50 years during the trials, and screening began to work. This was subsequently termed age creep.[46,47] This concept was restated by de Koning at the 1997 Consensus Development Conference (see later discussion). However, when the Swedish trialists provided him with more complete data he announced to the Consensus Development Conference that he now realized that the benefit was actually primarily due to screening before age 50 years. Although he reaffirmed this to me in an e-mail,[48] he has yet to publish a retraction. Even though age creep actually did not exist in the RCTs, it is still used as an argument against screening women aged 40 to 49 years.

1997 CONSENSUS DEVELOPMENT CONFERENCE TO REVIEW THE NCI GUIDELINES THAT NO LONGER SUPPORTED SCREENING WOMEN AGED 40 TO 49 YEARS

In 1997 the NCI convened a Consensus Development Conference to review their policy concerning women aged 40 to 49 years. Although convened to review the latest follow-up data from the RCTs, the Panel summary, presented to the media on the final day of the conference, somehow failed to include any of the new Swedish data. Even though the RCTs were not designed to permit separate subgroup analysis of women aged 40 to 49 years, with longer follow-up the Malmo trial showed a 35% statistically significant benefit for screening women in their 40s, and Gothenburg showed a 44% statistically significant benefit. The 5 Swedish trials together showed a 29% statistically significant benefit for screening women in their 40s.[49] Ignoring these facts (they were not even mentioned to the media), the Panel suggested

that any benefit from screening women aged 40 to 49 years was because of CBE. This was problematic in that none of the Swedish trials included CBE, yet they showed a statistically significant mortality reduction of 29%. The public was told that the Panel could find no reason to encourage women in their 40s to be screened. Having heard much of the testimony at the Consensus Development Conference himself, Dr Richard Klausner, the Director of the National Cancer Institute, was surprised at the Panel conclusion (I was seated next to him), and he asked a reporter to ask him his opinion. He then stated that he disagreed with the Panel conclusion and would have the NCAB review the new data. The NCAB undertook a review and several months later the NCI once again threw its support behind screening for women aged 40 to 49 years. Once again, the truth was corrupted. To this day, Dr Klausner's statement at the Consensus Development Conference has been forgotten, and writers and reporters continue to insist that the 1997 guideline change was not based on science but on congressional pressure.[50]

A Cochrane Review Raises Questions About Screening for Women at Any Age

In 2000 Gotzsche and Olsen[51] published an article suggesting that the RCT did not show a benefit from screening for women at any age. Because of the amount of criticism engendered by their review, the *Lancet*, allowed them to publish the same material again in 2001[52] asserting that they had re-reviewed the data and were correct in their first analysis. These analysts reached their conclusions by dropping the results from 4 of the Swedish Trials and claiming that the Malmo trial showed no benefit when it actually did show a screening benefit. Even though the Canadian NBSS1 was completely compromised by major trial violations (see earlier discussion) the investigators called it fairly well done and, because it showed no benefit, they concluded that there was no benefit from screening for women at any age. This stimulated multiple re-analyses of the data in multiple countries. These repeat analyses concluded that these Danish analysts were incorrect and that there was an approximately 30% reduction in breast cancer deaths as a result of screening.[53,54]

The American College of Physicians Advises Women in Their 40s to be Screened Based on Their Risk of Developing Breast Cancer

In 2007, The American College of Physicians (ACP) advised women in their 40s to consider their risk for developing breast cancer when deciding whether or not to be screened.[55] The committee that promulgated the guidelines never explained why women aged 40 to 49 years were being advised separately given that the age of 50 years has no biologic or screening significance (see earlier discussion). Furthermore, the RCT of mammography screening did not stratify by risk so there are no data that show that screening only high-risk women will actually saves lives. The third major fallacy in these guidelines is that, depending on what is considered increased risk, only 10% to at most 25% of women who develop breast cancer would fall into the ACP high-risk group.[56] If the ACP guidelines were followed, 75% to 90% of women who develop breast cancer would not be screened.[57]

Breast Cancers do not Melt Away

There has always been concern that mammography screening might lead to overdiagnosis; namely the detection of insignificant nonlethal cancers that, in the absence of screening, would have gone undetected and not bothered the individual during her lifetime. Most of the studies have suggested that this is a minor possibility[58] until 2008 and 2009 when it was suggested that mammography finds numerous cancers that, if left undiscovered, would melt away. Both papers made major methodological errors. In the first paper[59] the investigators compared the incidence of breast cancer in a cohort of women in the prescreening era (1992–1997) with the incidence of breast cancer among screened women in a totally different cohort at a later period of time (1996–2001). This use of historical controls can be dangerously misleading. The investigators compared the incidence of breast cancer as if it were a constant over time and that the higher incidence among the second cohort was to the result of mammography finding cancers that would have never bothered the women had they remained undiscovered and been left alone. Not only did they forget about the effect of prevalence cancers adding to the data (see later discussion) but they discounted that the incidence of breast cancer had been increasing in the past 50 years even before there was any screening so that a more recent cohort would be expected to have a higher incidence than one from earlier years.

The second paper[60] recognized that when screening begins, there are a large number of cancers diagnosed in the first year. This includes future cancers detected by the screening 1 or more years before they would have been detected in the absence of screening. It also includes

a prevalence bump. These are cancers that have been building up in the population. Some of these are even palpable, but have gone undetected, or ignored by the patient and/or her doctor. Because cancers arise in the population at a fairly steady (although increasing) rate, once everyone is being screened, the annual rate of detection should return to the level before the start of screening and before the prevalence bump, but the incident cancers should be at a smaller size and earlier stage because the screening is detecting them at a new threshold. The investigators noted that once screening began, the incidence did not return to the prescreening baseline, but remained somewhat increased. They incorrectly attributed this to excess melt away cancers that were only found because of screening. In fact, the investigators made a fundamental mistake. In the countries whose data they evaluated, screening is offered to women aged 50 years and older. Every year a new cohort of women reaches the age of 50 years and begins screening. This means that every year there is a new prevalence bump that would add breast cancers to the annual incidence more than the number that would be seen if only the same women (cohort) were being screened without the new women. The suggestion that the failure to return to baseline is because of unimportant breast cancers detected by mammography is not supported by these analyses.

The only way to accurately evaluate overdiagnosis is in RCTs where the cohort of women is the same and they are studied over the same time period. In the RCTs the highest estimate of overdiagnosis was less than 10%[58] and this might decrease further with longer follow-up.[61]

Has Mammography Failed Because it Does Not Detect Fast-growing Aggressive Cancers?

A recent article raised still another argument against mammography screening by disparaging it because it is not perfect and does not detect the fast-growing aggressive cancers.[62] It is certainly not a new observation that mammography does not find all cancers and does not find all cancers early enough to effect a cure. This has been stated since screening began. The death rate from breast cancer has decreased by 30% since the institution of mammography screening. This is a remarkable achievement. However, it is fundamental to all periodic screening tests that they are unlikely to detect fast-growing aggressive cancers in time to prevent metastatic spread. This is the well-known effect of length bias sampling. Nevertheless, there are many cancers that are moderate and even slow growing which, if not detected early, will be lethal years later. Finding a moderate growth cancer in a 45-year-old woman, and, as a result, preventing her from dying 7 years later at age 52 years, is no less a benefit than finding a fast-growing cancer in a 50-year-old woman and preventing her from dying at age 52 years.

Therapy Needs to be Tailored to the Individual and Her Tumor

There are no cures on the horizon. It was suggested by Esserman and colleagues[62] that care needs to be tailored to the virulence of the tumor and the host's response to it. There is no question that breast cancer is not a single malignancy. There are some breast cancers that have very low virulence and may not kill the individual, even if not treated. This is clear because, even before there was any screening or treatment of breast cancer, not all women died of their tumors. The suggestion that therapy needs to be tailored is far from new. For more than 40 years, efforts have been made to try to individualize therapy (the TNM grading system). No one has ever disputed that many women are overtreated for their breast cancers, both those presenting clinically and those detected with screening. The problem is that we are still unable to safely determine who can be treated minimally. Efforts continue to try to refine our ability to do this, but, because lives are a stake, only certain therapies can be safely tailored at this time. Furthermore, it is not the fault of mammography screening that therapy has not caught up to early detection. Mammography should not be faulted for finding cancers at a smaller size and earlier stage.

What Should be Done about Ductal Carcinoma in Situ?

Before mammography screening, only large palpable lesions of ductal carcinoma in situ (DCIS) were diagnosed and these made up only 2% to 5% of all breast cancers. DCIS now makes up 20% to 30% of cancers detected by screening mammography.[63] The treatment of these lesions continues to raise important unanswered questions. The debate about its proper treatment has not been resolved, and the relationship of these lesions to invasive cancer is also unclear. According to Page and colleagues,[64] even the most innocuous appearing of these lesions, if followed for 15 to 20 years can lead to death. Unfortunately, because surgeons and medical oncologists have not determined how best to treat these lesions, this has probably led to some overtreatment. Those who believe that DCIS is being overtreated

should launch trials to investigate how best to treat these lesions, but it is dangerous to condemn mammography screening because, in addition to detecting invasive cancers earlier, it also finds DCIS.

Esserman and colleagues[41] suggested that finding DCIS by mammography has not led to a decline in the incidence of invasive cancers as would be expected if it is a precursor to invasive cancer. However, their argument is not supported by the facts. They correctly expect that if DCIS is a precursor lesion, then the incidence of invasive cancers should have dropped to less than the baseline incidence that was present before screening began. I believe that this is a correct expectation. However, they made 2 mistakes. There has indeed been a decrease in the incidence of invasive breast cancer. They accepted the unsubstantiated suggestion that the recent decline in incidence was to the result of the marked reduction in hormone use that accompanied the publication of data from the Women's Health Initiative linking the use of estrogen plus progesterone to a small increase in breast cancer risk.[65] That paper[66] argued that the decline in incidence began in 2003 when it clearly began in 1999, well before publication of the Women's Health Initiative paper. Zahl and Maehlen[67] clearly showed that decreasing hormone use has no effect on breast cancer incidence. Esserman and colleagues[41] also misjudged the baseline incidence. There has been a steady increase in incidence in the United States since 1940, and this increase was going on long before there was any screening. If the baseline incidence is projected appropriately, it appears that the present incidence may have dipped below baseline and this may well be because DCIS has been removed preventing invasive lesions from developing.

The USPSTF Drops a Health Care Bomb

In November 2009, the USPSTF caused major confusion by promulgating new guidelines for breast cancer screening.[68] These were actually the same guidelines promulgated (and then rescinded) by the National Cancer Institute in 1993. They recommended against mammography screening for women aged 40 to 49 years, and recommended that women aged 50 to 74 years be screened every 2 years instead of annually. There were no mammography screening experts on the Panel. There were no medical oncologists or surgical oncologists on the Panel. Although billed as an expert panel, they clearly had no expertise in mammography screening.

It is clear that the USPSTF did not understand mammography screening, and had not thought through the consequences of their guidelines. Arguing against CBE as well as teaching women to examine themselves, the Task Force was essentially telling women in their 40s to return to breast cancer detection at the level found in the 1950s and 1960s. These women would now have to wait until they could no longer ignore the lump in their breast and then seek treatment when it was likely too late. The Task Force admitted that their approach would result in unnecessary deaths that could be prevented by screening, but the guidelines would reduce the false-positive studies, which they decided was more important than saving lives.

The USPSTF made it clear, and this was dispassionately repeated in Dr Kerlikowske's accompanying editorial,[69] that screening every 2 years would mean that as many as 30% of the lives that could be saved with annual screening would be lost by switching to biennial screening.

What has been overlooked in the media coverage of these new guidelines is that the USPSTF guidelines denying screening mammography for women aged 40 to 49 years are unsupported by the science. As noted earlier, there are absolutely no data to support the use of the age of 50 years as anything but an arbitrary threshold when it comes to mammography screening. Instead of using the old dichotomous analysis around the age of 50 years, the task force used age grouping by decade that made cancer detection rates and benefit increase in steps jumping at age 50 years and again at age 60 years (**Fig. 2**). These jumps do not exist. They are artifacts of age grouping to make it appear that there are jumps when there are none.

The USPSTF also do not understand the RCT data. As noted earlier, the RCTs underestimate the benefit from screening because of noncompliance and contamination. The USPSTF chose to use a 15% decrease in breast cancer deaths, which is the lowest possible estimate (by including the CNBSS1), and they did not even acknowledge that this was an underestimate of benefit. The USPSTF, which had supposedly reviewed all the data, was clearly unaware of the decrease in deaths seen in Sweden and the Netherlands as a result, almost completely, of mammography screening and, instead of using direct data, the task force chose to use computer modeling focusing on a measure of the number of women needed to be screened to save one life (NNTS). Among women aged 40 to 49 years they calculated approximately 1900 women as the NNTS, whereas for women aged 50 to 59 years the NNTS was approximately

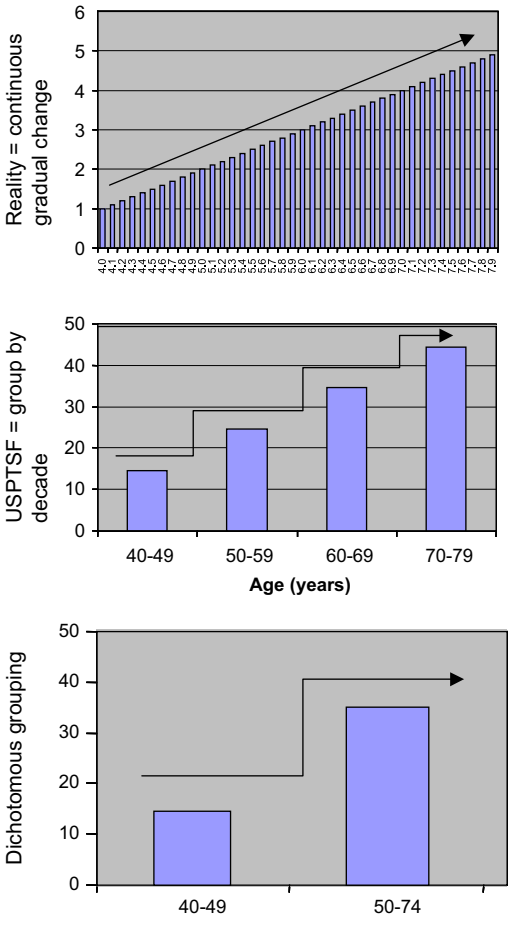

Fig. 2. Data grouping creates false impressions. Age grouping has been used to make data that actually change gradually with increasing age appear to change suddenly at the age of 50 years. In the upper graph the incidence increases by 0.1 each year. In the middle graph the same data are grouped by decade making it appear that there is a sudden jump at the age of 50 years and another at the age of 60 years. In the bottom graph the same data are grouped 40 to 49 years and compared with 50 years and older making it appear that there is a larger jump at the age of 50 years.

1300, and for women aged 60 to 74 years it was 300. The USPSTF has claimed that cost was not a factor in their calculations, but NNTS is clearly a surrogate for cost. Every woman gets screened only once each year, so that the NNTS is not important to her except as an estimate of risk. Furthermore, true cost-effectiveness analysis addresses additional issues such as the years of life saved, which the USPSTF clearly did not want to take into account because it has already been shown that screening annually beginning at the age of 40 years is cost-effective.[70]

The USPSTF ignored the studies listed earlier that showed at least a 30% reduction in deaths that occurs when screening is provided for the general public. Had they used the actual data instead of computer models, the NNTS of 1900 when a 15% benefit was used becomes 950 when a 30% reduction is used, and this would be well below the 1300 threshold that they set.

The USPSTF suggested, as had the ACP, that high-risk women in their 40s might be the only group that should be screened. As noted earlier, there are no data to support this approach. There is no evidence that screening only high-risk women will save lives and screening only high-risk women will miss the 75% to 90% of women who develop breast cancer each year because they are not at high risk.

SUMMARY

Enough is enough. The misinformation that opponents of screening have thrown up as impediments for women to participate in screening needs to stop. The age of 50 years is biologically meaningless. Its use as a threshold should be demonstrated with ungrouped data or it should cease to be a threshold. There is no reason to use computer modeling when direct data clearly show a benefit from mammography screening in the general population that has reduced deaths by 30% to 40%. There are no data that show that screening based on high risk will save lives, and it is clear that most women with breast cancer would be excluded from screening using this approach. The harms of screening have been overstated. In our practice the numbers vary, depending on the age of the woman, because the risk of breast cancer goes up steadily with increasing age. However, if 1000 women are screened, we recall approximately 80 women for additional evaluation. Among these false-positives, as defined by the USPSTF, in approximately 45 women (56%), a few extra images or an ultrasound examination will show that there is nothing to require any further work-up. In 25% (20/80) of these women the radiologist may want to have them return in 6 months just to be careful (<2% chance of malignancy). In approximately 15 (19%) women they will recommend a needle biopsy using local anesthesia. Approximately, 5 of these 15 women will be found to have breast cancer. False-positive mammograms are usually discussed without a frame of reference. There is a higher percentage of false-positives with cervical cancer screening yet there are only 11,000 new cases of invasive cervical cancer each year and fewer than 5000 deaths.

Mammography screening has been faulted for leading to overdiagnosis and overtreatment, but this is inappropriate. Any overdiagnosis is not the fault of mammography, but the inability, as yet, for the pathologists to determine the specific lethality of an individual's lesion. Similarly, overtreatment needs to be addressed by the therapists and is not the fault of mammography.

I would repeat again that it has never been suggested that mammography is a perfect test, nor the ultimate solution for breast cancer. It does not find all cancers and does not find all cancers early enough to effect a cure. However, it has now saved tens of thousands of lives. A decrease in the death rate of 30% translates to 15,000 to 20,000 lives saved by mammography screening each year. We all support intensive efforts to find a cure or to develop a safe way to prevent breast cancer, but these are not on the horizon. Rather than disparaging this lifesaving test, efforts should be directed toward adding to the success of mammography and improving our ability to detect early breast cancer. Those involved in therapy will continue their efforts to develop tailored treatments for the range of cancers detected by screening, but screening should not be withdrawn because of this range. The death rate from breast cancer, unchanged for 50 years, has been dramatically reduced with the use of screening mammograms. This is a remarkable achievement that should be applauded and not vilified. The unjustified attacks on mammography should cease and efforts should be made to build on its success while we continue intensive efforts to find the cure.

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