

KOPANS: WHY THE CRITICS of screening mammography are **WRONG**

BY DANIEL B. KOPANS, M.D.

Mammography screening is one of the major medical successes of the past several decades, yet this fact seems unable to break free of the doubts promulgated by such articles as Dr. Leonard Berlin's, published in an issue of *Diagnostic Imaging* earlier this year ("Disagreement continues to dog screening mammography," April, page 31). I suspect that few people are aware of the fact that the death rate from breast cancer, the second leading cause of cancer deaths among women, has decreased by almost 30% since 1990. This is a remarkable achievement, especially in light of the fact that the death rate had remained unchanged for the preceding 50 years.

The statistically significant mortality reduction in the randomized, controlled Two County trial of mammography

screening in Sweden¹ led to the onset of widespread screening in the U.S. This initiation of nationwide screening led to a sudden increase in annual breast cancer incidence in 1984-85. The sudden decrease in cancer deaths that began in 1990 is clearly related to the preceding, equally sudden, increase in earlier cancer detection.² Although oncologists, citing computer modeling, would like to claim that improvements in therapy are responsible for the decline in deaths,³ studies in Sweden^{4,5} and the Netherlands,⁶ using direct population data, have shown that at least two thirds of the decrease in deaths is due to mammography screening (this result is also shown in Berry's computer model, but it has been ignored by opponents of screening).

I am unaware of any test that has been as completely studied or challenged and has so successfully met the challenges as mammography screening. Three steps are required to prove that a screening test for breast cancer is efficacious. The first is that it must be able to detect breast cancers at a

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smaller size and earlier stage than is possible without the test. The Breast Cancer Detection Demonstration Project (BCDDP) in the 1970s proved this.⁷ The second is that randomized, controlled trials must show the test brings about a statistically significant reduction in mortality. Such a decrease in deaths has been clearly demonstrated by the seven randomized, controlled trials of mammography screening.⁸ The third is that when the screening test is introduced into the general population, the death rate declines. Mammography has fulfilled all three requirements.

It has been argued that women have been misled into believing that screening will save all of them from breast cancer, and even that women are being coerced into being screened. This is a gross exaggeration and a distraction. There is no question that some organizations have engaged in some hyperbole, but radiologists involved in these debates have always made it clear that mammography screening is far from perfect and does not save all lives. There are no perfect tests and mammography is no exception. However, this does not mean that it does not provide very important, life-saving benefit for many women. Tens of thousands of lives have been saved since 1990.

Despite overwhelming proof of a benefit, there continue to be those who question the efficacy of mammography screening and suggest that there is real ambiguity in the benefit. In fact, any ambiguity is due to unscientific data analyses that have taken place over the past 40 years. The use of retrospective subgroup analysis of data from the randomized controlled trials that lacked the statistical power to permit stratification by age, and making medical recommendations against screening women in their 40s based on these analyses, is a major misuse of science.⁹ The use of data grouping to make it appear that results change suddenly at an arbitrary age when there is no evidence to support this, and the decision by some analysts to exclude data that they do not like, are violations of appropriate scientific analysis. That all have happened is not a secret. Those who continue to rely on these fallacious arguments are either ignorant of scientific analysis or are maliciously misleading women and their physicians.

MISUSE OF DATA

As is discussed below, many of the arguments against screening are based on scientifically unsupportable analyses and misuse of data. Unfortunately, these efforts have been propped up by journals that publish articles whose peer reviewers clearly do not understand scientifically supportable data analysis. Rather than explaining how opponents of screening have misused and manipulated data, it is argued that the two sides in the debate have equally valid assessments but view the facts differently. We often hear that "individuals of good faith can look at the same data and come to opposite conclusions." I have no doubt that

there are times when this approach is supported by facts, as when a glass can be viewed as half full or half empty. However, this approach is an interpretation of the facts. It does not speak to the facts themselves. And there are actual facts in this debate.

What has been repeatedly overlooked is that truths exist. The Earth is not flat. It is our responsibility as physicians and scientists to seek the truth and not merely throw our hands up and "agree to disagree," especially when lives are at stake. The problem lies in the fact that very few physicians, and certainly few radiologists, have taken the



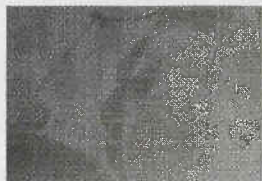
'There are no perfect tests and mammography is no exception. But it does provide life-saving benefit for many women.'

time to understand the data that support mammography screening. Because few understand the studies and the data they have generated, most are unable to recognize when data are being scientifically analyzed and when they are being manipulated. The controversies over mammography screening are due not to the inherent ambiguity of the data, but to the scientifically unsupportable ways that those data have been manipulated to generate doubt.

Numerous controversies over mammography screening have arisen over more than 40 years. As a result of these controversies, mammography has been disparaged rather than acknowledged as a major medical achievement. As someone who has been directly involved in the debates since the 1970s, I see the problem not as a disagreement over the meaning of the facts, but as a manipulation of the facts designed to produce the disagreement.

Few of us have sufficient interest or time to review all of the data under discussion and to determine what are the actual facts. We rely on others to distill the findings, and our own critical review is often lacking. Unfortunately, this includes peer reviewers for medical journals who support the publication of "studies" that provide misleading information due to major scientific flaws that escape the reviewers. A recent article by Jørgensen and Gøtzsche¹⁰ suggested that mammography finds cancers that would have "melted away" if the women had not been screened because the "incidence" of breast cancer did not return to baseline once screening had been established in several countries. But the authors had not taken into account the new prevalence of cancers that would contribute to new annual incidence figures as each year new women reached the age at which screening begins. The annual diagnosis of breast cancer would not be expected to return to baseline because what they termed "incidence" was actually a combination of incidence and prevalence. This is a fundamental error that completely escaped peer review.

An important example of a similar oversight by peer reviewers occurred when an oft-quoted paper by Kerlikowske et al was published in the *Journal of the American Medical Association*¹¹ during the debate over whether to screen women aged 40 to 49. The authors stated that since the breast cancer detection rate was two in 1000 for women aged 30 to 49 and 10 in 1000 for women aged 50 to 74, we should concentrate on screening women aged 50 and over. What the authors failed to point out is that the ungrouped data pro-



'Opponents of screening have been allowed to persist in using arguments that ignore science.'

vided in the paper show a steady increase in breast cancers detected with increasing age (as would be expected) with no abrupt change at the age of 50. It was only by grouping the data and analyzing those above 49 as if they were a uniform group and comparing them with those 49 and younger as if they were uniform group that the authors made it appear that there was a sudden change at the age of 50.

In addition, women in their 30s were not even being considered for screening, so why did the authors include them in the analysis? Could it be that by grouping women in their 30s with women aged 40 to 49, the lower incidence of breast cancer among the younger women was used to bring down the detection rate for women under the age of 50? Not only did this pass peer review, but though I alerted the lead author to the fact that her analysis was misleading prior to the publication of the paper, nothing was changed, and readers of the study were led to believe that something really changed suddenly at age 50.¹² This clear artifact of

data grouping passed peer review and is now a major support for the myth—which persists today—that age 50 has biological significance for the incidence of breast cancer.

I do not mean to suggest that I possess the “truth,” but there are facts, and these facts have been ignored by many opponents of screening, or distorted to support their position. I apologize for my tone, but this has gone on far too long. The controversies persist because few are willing to take the time to understand the issues and seek the truth, or to challenge much of the nonscience that gets published. With true humility I say that no one yet has refuted any of the arguments summarized in this article.

A prime example of how opponents of screening have provided misinformation and avoided addressing the facts could be seen when the American College of Physicians put forward guidelines in 2007, which recommended that women aged 40 to 49 should consider screening based on their risk of developing breast cancer.¹³ What these supposed experts failed to understand, and what I pointed out in a letter to the editor¹⁴ (limited to a few hundred words), was that:

- The guidelines implied that the age of 50 was a legitimate threshold. But there are no data to support using the age of 50 as anything but an arbitrary threshold.
- No data from the randomized, controlled trials support screening based on risk since none of the trials stratified the participants by risk. No data show that this will save any lives.
- Since 75% to 80% of breast cancers occur in women who are not at elevated risk, screening based on risk would miss most of them.

Rather than explaining why my concerns were incorrect, the authors' reply was, essentially, “We disagree with Dr.

A reply from Dr. Leonard Berlin

Dr. Kopans criticizes me and others for being “unable to break free of doubts” about the efficacy of mammography and says those who suggest there is ambiguity in its benefit are using “unscientific data analyses” and “scientifically unsupportable” data that have “been manipulated to generate doubt.”

Despite these assertions, there are credible questions about mammography. Just this year there have been a plethora of articles in various medical journals that highlight such potential downsides of screening mammography as overdiagnosis. As Dartmouth professor H. Gilbert Welch wrote in a *British Medical Journal* editorial this past July, overdiagnosis is a “vexing problem,” and causes some women to undergo unnecessary treatment. Welch, however, does not disparage mammography; instead, he writes, “Mammography is one of medicine’s ‘close calls’—a deli-

cate balance between benefits and harms—where different people in the same situation might reasonably make different choices. Mammography undoubtedly helps some women but hurts others. No right answer exists; instead it is a personal choice.”

As I wrote in my April 2009 *Diagnostic Imaging* article, I believe there is sufficient, albeit not incontrovertible, evidence that mammography does reduce mortality from breast cancer, and that radiologists and other physicians should, after discussing both the pros and the cons of screening, encourage but not coerce women to undergo annual screening mammography. At the same time, however, acknowledging rather than denying the existence of controversies regarding mammography will assist the public at large to develop a realistic appraisal of mammography's role with regard to breast cancer.

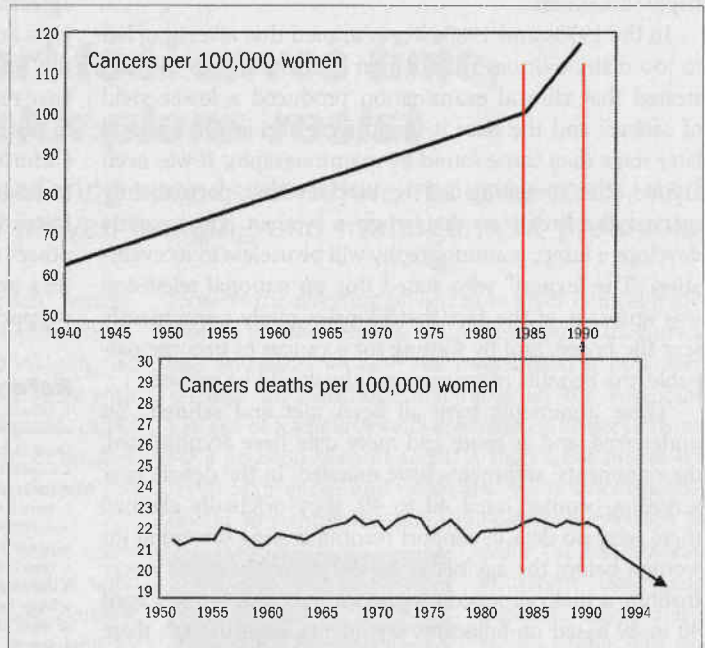
Kopans.” This is indicative of why the controversies continue. Supporters of screening have argued the scientific evidence and responded to all attacks on the benefits of screening with science and logic. Opponents of screening have developed pseudo-arguments that are not supported by facts and they have been allowed to persist in using arguments that ignore science. When those of us who have defended screening based on the data have challenged interpretations of the data disseminated by opponents, rather than defend their position with facts, they merely “disagree.” What many fail to understand is that it is impossible to resolve a disagreement when one side refuses to acknowledge facts and ignores the scientific evidence, saying “we disagree.” Those who advise the public should not be allowed to simply “disagree.” In science and medicine one must be able to provide scientifically derived data and facts.

Gøtzsche and Olsen were provided with two chances, once in 2000 and again in 2001 (most of us get only one chance at publication), to publish an attack on screening mammography for all women^{15,16} by deciding that they did not like the way five of the randomized, controlled trials were performed and dropping them from their analysis (this is scientifically inappropriate). These included four of the Swedish trials that showed a clear benefit. They claimed the Canadian National Breast Screening Study (CNBSS) was well done, despite the indisputable fact that the CNBSS is an example of how not to perform a randomized, controlled trial.¹⁷

Discounting that the CNBSS was underpowered, and that the quality of the mammography was indefensibly poor for a trial of mammography screening,¹⁸ these analysts also ignored the fact that the CNBSS violated fundamental rules for randomized, controlled trials. The randomization was unblinded and all women had a clinical breast examination before they were allocated to the screened or unscreened control groups. Women with lumps and palpable axillary lymph nodes were allowed to participate in this trial of mammography screening. The allocation was on open lists so lines could be skipped to place women with advanced cancers in the screening group. Indeed, they placed significantly more women with advanced cancers in the screening group,¹⁹ thereby rendering completely suspect the trial results. There can be no argument that these are major violations of the rules for randomized, controlled trials, yet Gøtzsche and Olsen were permitted to argue that the CNBSS was a well-executed trial, and since it showed no benefit from screening, there was no benefit.

They also accepted the Malmo^{15,16} results but failed to acknowledge that Malmo actually showed a benefit. Their

DROP IN DEATHS FOLLOWS INCIDENT SURGE



A sudden increase in incidence of invasive cancer and DCIS indicates the start of widespread screening, followed five to seven years later by a sudden decrease in deaths, as would be predicted.

nonscientific approach would have been ignored by the scientific community, but it was published on the front page of *The New York Times*,²⁰ leading to doubts being raised, inappropriately, around the world and suspicion about screening that persists even though all of the authors' concerns were shown to be unsupported.^{21,22} The CNBSS clearly violated the fundamental rules of randomized, controlled trials. How did *The Lancet* allow them to use its results to tell women there was no benefit, while ignoring the well-done studies that show a benefit? How can it be suggested that there are two equivalent sides to these debates?

UNJUSTIFIED CLAIMS

Since the 1970s, opponents of mammography screening have repeatedly thrown impediments in front of mammography screening with, unjustified claims. In 1976, Bailar²³ raised concerns over radiation risk that actually resulted in stopping the screening of women aged 40 to 49 in the Breast Cancer Detection Demonstration Project (BCDDP). Yet his fears were subsequently shown to be based on gross overestimates of risk. In fact, radiation risk to the breast is predominantly to women in their teens and early 20s²⁴ and even the smallest benefit far outweighs any theoretical risk among women aged 40 and over.²⁵ If mammography was causing cancers, why, after imaging hundreds of millions of women over the past 20 years, is the incidence of breast cancer decreasing rather

than increasing? Yet radiation risk continues to be used to frighten women.

In the 1970s and 1980s it was argued that screening led to too many biopsies with benign results until we demonstrated that clinical examination produced a lower yield of cancers and the ones it found were at a larger size and later stage than those found by mammography. It was even argued that screening led to biopsies that permanently scarred the breast so that when a woman subsequently develops a lump, mammography will be useless in its evaluation. The "expert" who stated this on national television was ignorant of the fact that biopsies rarely permanently scar the breast, and by waiting for a cancer to become palpable, the benefits of mammography would be missed.

These arguments have all been met and refuted. Yet undeterred, and as more and more data have accumulated, the opponents' arguments have mutated. In the debate over screening women aged 40 to 49, they originally claimed there were no data to support recommending screening for women before the age of 50. In 1993, the National Cancer Institute actually dropped support for screening women aged 40 to 49 based on fallacious arguments, even though there were always data that supported screening these women when the trials were analyzed the way they were designed to be analyzed. As the data became increasingly robust, those who opposed screening grudgingly admitted that there was a benefit, but instead of acknowledging that they had been wrong, they argued that it was too small to justify screening. Because the fallacious analyses of the past were allowed to be circulated unopposed, a mythology has developed that younger women do not benefit from screening. We should insist that anyone who disparages the benefit of screening be required to address the issues described in this article and refute the conclusions. This could greatly reduce the nonsense that continues to be foisted on the public.

As I documented in 2005, several medical journals have an unacknowledged bias in what papers they select for publication.²⁶ Clearly, recent arguments against screening have had an effect by suggesting that both sides of the debates have equal weight when this is not true. Several medical journals have knowingly refused to provide women with accurate information.²⁷ It is due to either the willful misrepresentation of data or the sheer ignorance of opponents of screening that there is still controversy about screening women aged 40 to 49. Many European countries as well as Canada do not support, or at any rate do not encourage, screening before the age of 50 and have lied to their populations by suggesting that the data did not show a benefit. I use harsh language because there are no data to support age 50 as any kind of threshold, yet women continue to be told there are.

There are legitimate issues that pertain to screening: cost, false alarms, and possibly overtreatment, but these are clouded by the numerous fallacious arguments that have

become legitimized by their repetition. The continuing disagreements over screening come from the fact that radiologists and scientifically driven epidemiologists have argued the science and the facts, while opponents of screening have repeatedly violated the basic rules of scientific analysis to plant doubts that have persisted for more than 40 years. Unfortunately, most physicians have insufficient knowledge to know when they are being misled. Enough is enough. Instead of reinforcing the misuse of science, Dr. Berlin and others should be urging us all to learn and understand the data and to argue in support of science and scientifically supportable data analysis. ■

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