Kopans offers point by point rebuttal to Caruncho

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I very much appreciate Dr. Caruncho’s thoughtful and detailed response to my article in *Diagnostic Imaging*. It is ironic I wrote the article before the U.S. Preventive Services Task Force published its new guidelines. Their scientifically unsupportable analysis merely reinforced the concerns I expressed in *Diagnostic Imaging*. The fact those of us who have an understanding of the data, and how the data have been manipulated, have been prevented from presenting the opposing information in such journals as the *New England Journal of Medicine*, the *Annals of Internal Medicine*, and the *Journal of the American Medical Association* over the past two months is testimony to the concerns that I have raised.

There has been major management of the interpretation of the scientific evidence occurring even today (1). The writer’s review of what I have written in *Diagnostic Imaging* is the first effort anyone has made to address the concerns I have raised over the years and I appreciate the effort. I am indeed angry because this “debate” has gone on for more than 30 years. I have seen data, repeatedly, misused and lives have been, unnecessarily, jeopardized as a result. It is easy to say, “Let’s agree to disagree,” but this is not a debate over the glass being half full or half empty. It is about the fundamental facts. The critique is thoughtful, but not scientifically accurate. Unfortunately, I am being limited in my response so that I cannot address all of the issues raised, but I will try to address the most important.

Countries that told their populations they were not screening before the age of 50 because the data did not show a benefit were, in fact, “lying.” The randomized, controlled trials (RCT) of screening, when analyzed as they were designed have always shown a statistically significant benefit for screening beginning at the age of 40 (2). The reason the age of 40 is a threshold today is that those of us who argue from the science recognize that the RCT only included women beginning at the age of 40 (Gothenberg did recruit women age 39). Consequently, since RCTs are the only scientifically acceptable way to prove a benefit, the age of 40 is, scientifically, supportable as a threshold. The age of 50 was first chosen, as the writer correctly understands, as a surrogate for menopause. The statistician in the first RCT, the Health Insurance Plan of New York trial (HIP), decided to retrospectively evaluate his data, convinced that hormones must have some effect on the benefits of screening. They had not collected menopausal status so he chose 50 as a surrogate and divided the data and looked at women ages 40-49 and women ages 50-64.

The trial lacked the statistical power to permit this, but this has been repeatedly ignored, and the trials that followed also had their data broken, and analyzed retrospectively. It was only through unplanned, retrospective subgroup analyses of trials that were not designed to permit age stratification, due to lack of statistical power, that the age of 50 was imbued with unsupportable importance (3).

In 1993, the National Cancer Institute (NCI) misled the public (4) by dropping support for screening women ages 40-49 because they had set a requirement the RCT had to show a statistically significant mortality reduction within five years of the start of the trials (5). The data clearly showed a decrease in deaths for women in their 40s, but since the trials were not powered to permit this retrospective stratification, it was mathematically impossible for this to be “significant.”

Dr. Caruncho clearly does not understand if unplanned, retrospective, subgroup analysis of data from trials that lacked the statistical power to permit such stratification is legitimate for making
medical recommendations, then we should be able to examine smaller and smaller subgroups, and would ultimately only need two women in a trial. Clearly this is scientific nonsense, but our NCI and other governments have lied to their populations by using these scientifically unsupportable subgroup analyses to make medical recommendations. There are two alternatives. Either they were lying to their populations, or they simply did not understand appropriate trial data analysis and should not be advising anyone.

Opponents of screening also set a requirement that in the trials women ages 40-49 had to show a significant decrease in breast cancer deaths within five years of the start of the trial (5). Not only was this a mathematical impossibility (3), but, given length bias sampling (periodic screening detects moderate and slow growing cancers), why was an immediate benefit expected? When the death rate from screening women ages 40-49 in the trials became statistically significant, with longer follow-up (6), it was completely ignored (7) or discounted, as suggested by Dr. Caruncho, because it was “delayed.” A “delayed benefit” is actually what would be expected in an RCT, yet it has been discounted. De Koning even suggested that the benefit for younger women was due to women in the trials reaching age 50 and screening suddenly beginning to save lives (8). When he was presented with more complete data he recanted in public (and in an e-mail to me) (9) and agreed most of the benefit was from screening before the age of 50, but he has neglected to publish a written retraction, I would surmise, because his original paper was so often quoted (it was the basis for the Age Trial) that a written retraction would be too embarrassing.

Dr. Caruncho states that age 50 is appropriate because breast cancers “behave differently before and after menopause.” The writer may understand the therapy data, but clearly does not understand the screening data.

Opponents of screening women in their 40s have repeatedly taken data that change gradually with increasing age, and grouped them dichotomously (40-49 compared to 50 and over) as if they were two uniform groups. This makes the changes that take place gradually falsely appear to change abruptly at the age of 50. Data grouping can be used to make any age appear as a “jumping” point.

There are no ungrouped data that show any of the parameters of screening (callback rates, biopsy recommended rates, cancer detection rates, etc.) change abruptly at the age of 50 or menopause (10). It is only by grouping data that the age of 50 has been imbued with unsupportable importance (10).

One often quoted paper grouped women ages 30-49 and compared them to all women ages 50 and older (11). No one was arguing in support of screening women in their 30s, but adding them to women in their 40s brought down the cancer detection rate for the younger group to make it appear there was a sudden jump at the age of 50 when their ungrouped data show, as would be expected, a steady change with age with no jump at any age. What would Dr. Caruncho call this—legitimate scientific analysis, or manipulation of data?

It is fine for Dr. Caruncho to say that the age of 50 is “arbitrary,” but I would challenge the writer to identify, in the arguments against screening women ages 40-49, anywhere it is clearly stated this is an “arbitrary” threshold. If women had been told they were being denied access to screening, arbitrarily, until age 50, despite the fact that screening could decrease deaths while they were in their 40s, I suspect there would have been a “discussion.” Instead they were told the trials showed no benefit so the discussion was eliminated. The dichotomy between premenopausal screening and postmenopausal screening is in the mind of the reviewer, and not in the screening data. The writer points to Berry’s article, which summarizes seven computer models that were asked to determine what percentage of the 30% decrease in breast cancer deaths in the United States that has occurred since 1990 was due to screening, and what was due to therapy. One has to ask, why would Berry choose computer models when there are direct data from the Netherlands (12) and Sweden (13, 14, 15) that show the vast majority of the benefit is due to screening, with only a small component due to improved therapies, and screening the general public decreases breast cancer deaths by more than 30% (including women in their 40s)?

Models are only as good as the assumptions programmed into the computer. Sophisticated financial computers said the economy was sound in 2008. Why would the writer have confidence in the
models without knowing what assumptions were used? Clearly you can make one intervention appear superior to another by using assumptions that favor your bias. Direct population data reduce the chance that the results can be biased. Furthermore, I suspect that most medical oncologists would agree that therapy is only successful at saving lives, with rare exceptions, when breast cancers are found early. I didn’t think I had to point this out, but the only way to detect cancer early, with proven mortality reduction, is with mammography screening.

With regard to the two trials that “specifically address mammography screening in women under their 50s,” the writer states the CNBSS1 has “withstood the criticisms.” One has to ask those that have continued to support this trial–why? The CNBSS1 was a completely corrupted trial. In addition to being underpowered from the start (16), and using mammography that their own reference physicist admits was below the quality of even that being used in the communities, (17), the indisputable fact is the CNBSS1 violated the most fundamental requirements of a randomized trial–blinded randomization.

They examined everyone before allocation so they knew who had palpable masses and palpable axillary lymph nodes (advanced cancers) BEFORE allocation. Then they assigned women ON OPEN LISTS so that a line could be skipped to insure a woman with advanced cancer would be placed in the mammography group. That this occurred and biased the trial was clearly shown by Tarone (18). Enough is enough. The CNBSS1 violated the fundamental rules of an RCT yet, incredibly, it continues to be defended and used to pull down the benefit from screening for women ages 40-49. What is the point of having any requirements for scientific analysis if those rules can be violated with impunity? I am surprised that Dr. Caruncho is clearly unaware of what took place in the Age Trial (19). The principal investigator of the Age Trial freely admits her trial was compromised. The “Age Trial” used single view mammography, which the investigators knew misses 20-25% of cancers (20). Furthermore, the investigators admitted they did not biopsy clustered calcifications, which are well known to be indicators of early breast cancer (21).

I have not seen any publication that speaks to what percentage of women in the supposedly unscreened control group had mammograms outside the trial (contamination). I am surprised this did not occur to Dr. Caruncho as an explanation for their “20% decrease in mortality.” If your trial misses a large number of early cancers in the screened group because you failed to biopsy them, and control women had their lives saved by screening outside the trial, why would you be surprised that the trial showed little benefit?

Radiation risk to the breast is inversely proportional to age at exposure. There is no direct evidence of any risk from mammography for women age 40 and older. Even the extrapolated risk for women age 40 and older is easily outweighed by even a 5% benefit (22). Certainly not proof, but hundreds of millions of mammograms have been performed in the U.S. since the 1980s. If mammography were causing cancer the incidence would be increasing. In fact, the incidence is decreasing.

Years ago Rosenquist and Lindfors showed that annual screening beginning at the age of 40 was cost effective (23). With regard to “absolute benefit,” I believe that breast cancer accounts for, approximately, 3% of all deaths each year. Reducing this by 30% will have little impact on the total number of deaths in the U.S. However, a 30% reduction amounts to 15,000-20,000 lives that are being saved, each year, primarily due to mammography screening. The writer feels this is trivial. I do not.

I appreciate the writer’s other critiques, but DI will not permit me additional space. The writer only reinforces my premise. There is no lack of individuals who are willing to speak out on the screening issues, but there is a real lack of individuals who actually know and understand the data.

The scientific evidence clearly shows that mammography screening, significantly, reduces deaths among women beginning at the age of 40.


17. Yaffe MJ. Correction: Canada Study. Letter to the Editor JNCI 1993;85:94


Disclosures:

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