

## **Response to: “U.S. Preventive Services Task Force Recommends Mammography Starting at age 50” (November 16, 2009)**

**By Alan B. Hollingsworth, M.D.  
Medical Director, Mercy Women’s Center  
Mercy Health Center – Oklahoma City**

Here we go again. For 30 years, the government and its agencies have been waffling on the benefits of screening mammography. Prior to 1993, the National Cancer Institute endorsed mammography every 1-2 years in women ages 40-49. Then, a consensus conference in 1993 prompted the NCI to change policy and begin an aggressive advertising campaign for starting mammograms at age 50. In 1996, the NCI decided on “no policy,” then in 1997, they re-instated their original policy of mammography every 1-2 years for women in their 40s according to pre-1993 standards. Notably, this embarrassing scenario was not based on new clinical trials, rather, a re-hashing of old trials ad nauseum, while buckling to external pressures in both directions.

Today’s news is no different – while claiming “new data” has prompted new guidelines from the U.S. Preventive Services Task Force, the mortality benefit (saved lives) for women aged 40-49 who undergo routine mammographic screening is *identical* to what this same group calculated in 2002, only this time, they have reversed their position for mammographic screening prior to age 50.

Stoically, the American Cancer Society (ACS) has maintained age 40 as the starting point for screening mammography from the start. Granted, the benefit is smaller for women aged 40-49, but the ACS has taken the position that, given the controversy, we should err on the side of benefit for mammography. Furthermore, take a close look at the latest evidence-based recommendations from the ACS for high-risk women – not only should we add annual breast MRI to annual mammograms, but also we should start using these *2 modalities at age 30* – two decades before what we’re being told now by the U.S. Preventive Services Task Force.

This is not a new controversy. In the years prior to the 1993 NCI reversal in policy, there were 14 medical organizations that weighed in on the 40-49 group, 9 in favor of mammographic screening, 5 opposed. Interestingly, the U.S. Preventive Services Task Force was among the 5 in opposition back then, so they have a long track record of waffling, endorsing 40-49 screening in 2002, and now reversing themselves once again.

At the heart of the controversy is a distinction few appreciate – that is, the difference between what is best for a “population” versus what is best for the individual. Epidemiologists are interested in recommendations for populations based on data and statistics, in order to establish public health policy. And, of course, policy is linked to funding and the economics of medicine. On the other hand, practicing physicians are focused on individuals, i.e., “What is best for the patient I’m talking to right now.” Remarkably, these 2 distinct goals can have different recommendations. For instance, if you were to ask – “Limited to one imaging method, what’s the best way to find breast cancer in an individual?” – the answer would *not* be mammography. There are several imaging tools, most notably breast MRI, that will find twice the number of cancers as mammography. However, these methods are impractical when it comes to screening the general population. The blurring of these goals is most evident when a breast cancer expert makes this statement, as is often done: “The best tool to detect breast cancer is still mammography.” That expert, perhaps unwittingly, has just removed his or her “clinical physician” hat and replaced it with an “epidemiologist” hat.

In this controversy, breast radiologists are prone to cry “foul” in that there were no breast radiologists on the Task Force, nor were there any radiologists on the 6-member team of cancer experts that presented evidence to the larger 16-person panel. This doesn’t look good at all, and it represents such a diplomatic faux pas that one very prominent breast radiologist was quoted in the media as calling the Task Force “idiots.” While *ad hominem* attacks benefit no one, I would agree that at least one breast radiologist should have been included on the 6-member team. But at the same time, I would point out that this is a much bigger question than X-rays or their interpretations. It’s a controversy about the epidemiology of screening for cancer, a science unto itself. You can plug in colonoscopy, PSA, etc., and the exact same issues are a problem for all cancer screening. And while quoting the American College of Radiology and its endorsement of early-age screening is nice, frankly, the policy needs to come from neutral sources. While some would claim the American Cancer Society is not neutral either, I’ve followed their analysis of this issue for many years, and they have monitored the very same clinical trials as the ones being reviewed by these “think tanks.” In addition, rising above the “statistical snobbery” inherent in public health think tanks (after all, the heavily worshipped “p-value” in statistics is an arbitrary dividing line), the ACS has also have reviewed the non-randomized trials and the countless studies on tumor biology that add a broader understanding of screening, even if this additional information is not as statistically powerful as randomized studies.

Another issue that distorts the controversy is when patients (and physicians...including radiologists) equate a cancer discovered by mammography as being another life saved. This is not the case. Some breast cancers are fatal even though discovered on mammography, while others would *not* have been fatal even if a diagnosis had been made without mammography one or two years later. In fact, one of the most pro-mammography radiologists on the planet, Dr. Laszlo Tabar from Sweden, once calculated that only 1 in 7 cancers discovered on mammography actually translates to a saved life. Others have, more recently, placed this number at 1 in 5. Nevertheless, it is actually the *minority* of cancers discovered on mammography where a life is saved. Perhaps, this fact alone allows you to understand how epidemiologists can seem so callous in their recommendations, especially when women come out of the woodwork to declare, “I wouldn’t be alive today had it not been for mammography finding my tumor at 41.” Epidemiologists in this controversy are focused on “mortality rates” that are only indirectly related to discovery rates.

That said, the evidence for saving lives through screening mammography is still stronger than any other type of cancer, with the exception of Pap smears for cervical cancer. Admittedly, the evidence for supporting the starting age of 40 is not as strong as age 50, and it never has been. There are multiple biases that occur in cancer screening, and these can only be eradicated (well, almost eradicated) by prospective, randomized trials. Even then, a prospective randomized trial can have a poor study design, a major concern since many of the mammography trials were begun in the 1960s and 1970s, prior to today’s level of sophistication in study design. Given all this background, **what are the facts generated from the historic mammography screening trials when only those women between 40 and 49 are studied?**

There were 8 historical trials where patients were prospectively randomized, some showing benefit for younger women, some not, *but none of the 8 trials showing a clear-cut statistically significant mortality reduction for women aged 40-49* (remember those arbitrary p-values, though – when a trial does not meet a predetermined p-value, that does not rule out a benefit). Without a single trial showing a “significant” mortality reduction for women in their 40s, the pro-mammography argument does not sound as strong, does it?

However, most of these trials were not designed to study the 40-49 group independently, and there were not enough participants to draw firm statistical conclusions. Therefore, researchers have attempted to combine these 8 trials into a “meta-analysis,” such that statistical significance will be more meaningful. Amazingly, there have been as many meta-analyses (8) as original trials, and unfortunately, these 8 meta-analyses don’t fully agree. But if we’re going to stick to facts rather than emotion, here’s what the 8 meta-analyses show: 7 of 8 reveal a reduction in mortality, i.e., lives are saved. And the one that did not show benefit is a jaundiced look at the evidence where researchers were so offended by the quality of the historical trials that they refused to include 6 of the 8 original trials. Thus, their unique negative outcome is based on only 2 of the 8 studies, hardly a “meta-analysis.”

But now for the bad news. Even though 7 of 8 meta-analyses indicated that lives were saved, in a range from 7% to 23% for relative mortality reduction, only 3 of the 7 meta-analyses were statistically significant. I would note that the 4 *excluded trials all showed a benefit*, and they came very close to statistical significance. It’s not like the outcomes were half-and-half. Nevertheless, the purists toss such findings out the window quicker than you can say, “I love p-values.” So, we’re down to only 3 meta-analyses that support screening younger women, yet the benefit of mortality reductions are: 15%, 16%, and 18%, remarkably consistent across all three studies. This is in contrast to the 30% risk reduction we see in women between the ages of 50 and 75.

And here’s the punch line: One of the 3 groups that performed a *favorable* meta-analysis, showing statistical significance that *mammography saves lives* was this same U.S. Preventive Services Task Force, reporting these findings in 2002 and prompting their recommendation to screen women in their 40s. So, when today’s news was released, it was easy to assume that “new data” had resulted in the numbers no longer being “statistically significant,” i.e., that we could no longer prove that mammography saves lives in the 40-49 age group. The reality, though, turned out to be worse than imagined.

Yes, there was new data, but it only *reinforced the fact that mammography saves lives*. In fact, the reduction in mortality calculated in 2009 (15% reduction) is identical to the mortality reduction this same group calculated in 2002 (15%). Furthermore, it’s the same mortality reduction seen in women aged 50-59! So, the reversal in policy by the Task Force seems as ludicrous as the waffling that occurred with the National Cancer Institute from 1993 to 1997.

If the mortality reduction for women in their 40s is the same as for women in their 50s, then why is there a different recommendation for these 2 groups? Here’s how the argument goes: Because breast cancer is less common in the 40s, then this *relative* risk reduction of 15% does not translate into the same *absolute* benefit as it does for women in their 50s. Put in algebraic terms, 15% of X is not as large as 15% of 2X. Or, as the American Cancer Society’s chief medical officer, Dr. Otis Brawley, cleverly phrased it: “The task force advice is based on its conclusion that screening 1,300 women in their 50s to save one life is worth it, but that screening 1,900 women in their 40s to save one life is not.” (Incidentally, according to the Task Force, you only have to screen 377 women in their 60s to save one life.)

So what was the “new data” that didn’t really change the facts, but changed the recommendation? The “government” Task Force (government-funded, rather than government employees) states their “new” information comes from updates on an old trial plus a single new trial, the Age Trial in the U.K. where the mortality reduction was 17% (consistent with results we’ve seen before). As with every trial in the past, the numbers from the Age Trial were not enough to reach statistical significance as a solo study, prompting incorporation into the general “meta-analysis” as had been done previously. As an aside, *when researchers looked at the patients actually in compliance in the Age Trial, there was a 24% mortality reduction that missed statistical significance only by a hair.*

What do I mean by “*compliance?*” You may be shocked to learn that when someone is randomized to undergo mammography in a prospective trial, but then they *don't* proceed with actually having it performed, they are still counted as having had mammography; and, the reverse is true – if a woman is randomized to “no mammography,” but then gets one or more screenings on her own, she remains in the “no mammography” group. You would be further surprised to learn how poor the compliance rate is, and how it declines over time throughout these multi-year studies. This practice may be “statistically correct,” but it is a major barrier to proving a benefit to screening mammography. Realizing how ridiculous it seems to ignore compliance, researchers and their statisticians will also compute the data according to the actual numbers of women who underwent serial mammograms, but this is of secondary interest only, realized only by those of us who read the fine print. Bottom line: there is enormous “wobble room” in this controversy and you can do most anything with the data that you want.

Along with the Age Trial from the U.K., there was also update information from a Swedish trial that was also favorable. And when merged into the “meta-analysis,” the outcome was the same as 2002 – a statistically significant 15% relative reduction in mortality. So why stop doing mammograms in the 40s? The Task Force believes that the bad outweighs the good. And what is the bad? False-positives are bad. Costly false-positives. Anxiety-provoking false-positives (as if the anxiety of a false-positive is equal to the anxiety of premature death by breast cancer). A little-known fact about false-positives is this: epidemiologists count any call-back as a false-positive. That's right. Just receiving a phone call from the breast center asking you to come back for additional mammography views and possible ultrasound is a false-positive, even if no biopsy is required. So, in this balance of risks versus benefits, one has to ask: “How many callbacks, or even how many benign biopsies, does it take to equal a young woman dying of breast cancer?” Only the epidemiologists know for sure.

But the epidemiologists weren't focused on just one controversy. Another change that the Task Force recommended was switching from annual mammography to every 2 years for women over 50. This change was based on a “thought experiment.” Now, as bizarre as it may seem, these “mathematical models,” if the correct data is considered, can actually be pretty accurate. In fact, most studies of cost-effectiveness use this mathematical modeling. So, let's accept the data generated by the Task Force's thought experiment and see if we draw the same conclusion. The Task Force concludes that if we switch from “every year” to “every 2 years” for mammography, then most (81%) of the mortality reduction for women aged 50-74 could be preserved, while cutting the false-positives in half. With all these percentages – some absolute, some relative – what does this mean?

Example: Let's take the 60-69 age group where the benefit of mammography is at its peak, a 32% mortality reduction. Then using the Task Force's model, “81% of the 32% will be maintained” by screening every 2 years instead of every 1 year. They call this a “good thing,” especially since so many women will be spared the horrors of a false-positive. And that's why they state this as “81% of the benefit will be maintained,” rather than expressing the result of this policy in its truest form: *more women will die of breast cancer*. More math: 81% of 32% is 26%, still good, still statistically significant. But still, some women will die due to a policy change.

Let's look at this in different terms, absolute terms, using the same sort of “thought experiment” as the Task Force. If you were performing a large screening trial, randomizing patients aged 60-69 to 3 groups – 1) no mammography, 2) annual mammography, and 3) mammography every 2 years – then if **100** women die of breast cancer in the *no mammography* group, **68** will die in the *annual mammography* group (100 minus 32), and **74** will die in the *mammography every 2 year* group (100 minus 26). If you're one of the 6 who

are going to die because of a policy change, your final words are not going to be, “Well, thank goodness I was able to spare all those women from being called back to the breast center.” (note in the math above: we are *not* talking about how many cancers are detected...I am using the epidemiologist’s focus – deaths due to breast cancer).

Remarkably, another “think tank,” the Cochrane Collaboration, rushed to support the U.S. Task Force recommendations, noting: “no loss of benefit from biennial screening.” This is grossly misrepresenting the Task Force conclusions. The Task Force admitted there would be more lives lost, even though their rhetoric expressed this as “most of the benefit maintained.” However, the “*don’t talk to us unless you speak in p-values*” Cochrane Collaboration altered this statement in their media response, by claiming nothing at all would be lost through biennial (every 2 year) screening.

I don’t want to dismiss the enormous anxiety and cost imparted by mammographic screening, but I have yet to meet the woman who’d rather die of breast cancer than undergo a biopsy. Benign biopsies are not “unnecessary” as routinely labeled by anti-mammography forces. They are a *necessary* part of our current state-of-the-art technology and interpretations. Many researchers are working on methods to reduce the call-back rates and the biopsy rates, but these inconveniences pale in comparison to dying of breast cancer. Granted, women have not been fully informed about the downside “risks” of screening mammography, and it is true, too, that the benefits have been exaggerated, but what we need is *improved informed consent*, not a policy that knowingly allows more women to die.

There’s more. The Task Force recommends *against* teaching breast self-exams (and, incidentally, the Task Force notes there is insufficient evidence to make recommendations about clinical breast exams, digital mammography, or MRI). You may say, “What harm could there be in self-exams?” Well, for the anti-screening forces, there is plenty of harm. A detected lump leads to...mammography. It leads to ultrasound. It leads to “unnecessary biopsies.” And it does this when there is no evidence that lives are saved through self-exam. Thus, in their interpretation of the data, self-exams are nothing but harmful. Granted, there is precious little data to support self-exams with regard to mortality reduction, but it’s a question that does not readily lend itself to scientific scrutiny. (How do you randomize patients to a control group where you don’t touch your breasts?) In my view, it’s one of those practices where common sense has to play a role. To epidemiologists, “common sense” is dangerous, leading to such erroneous conclusions as “The Sun revolves around the Earth once each day.” Personally, I would like to see the day when all cancers are detected so early through some form of breast imaging that they are never felt. In the meantime, let’s use common sense.

While “evidenced-based medicine” is being treated with god-like reverence, the truth is that it is extremely difficult to arrive at conclusive evidence when it comes to human health. Two well-designed studies will sometimes show conflicting results; alternatively, one study can easily lend itself to two conflicting opinions about the same results. Also, let’s hope there are other endpoints to consider besides mortality because, best I can tell, overall morality is always 100%. When it comes to breast cancer, why didn’t the Task Force address the higher number of women who can undergo lumpectomy rather than mastectomy when their cancer is discovered by mammography? Why didn’t they analyze the fewer number of women requiring chemotherapy through mammographic early detection? Why didn’t they analyze the cost of end-of-life care in those women whose lives would have been saved by early detection? After all, they looked at a broad range of potential harms, including the possible adverse effects of radiation with mammography, a non-issue for women over 40, settled long ago. (Even this radiation risk didn’t escape notice, with one ex-CEO of a major health insurer praising the Task Force findings, noting that if science proves mammograms are a waste of time in younger women, why do them?... *especially given the “radiation risk.”*)

The very nature of science requires reviewing new data and pruning old beliefs accordingly. This works well in the laboratory. But in the clinical setting where information is made readily available to the public, it is fraught with problems, especially in screening controversies where the evidence is so difficult to interpret. Government efforts have made a mockery of science and confused women everywhere with their vacillating recommendations that are generated primarily through re-hashing of old data. In 1993, it was the National Cancer Institute...in 2009, it's the U.S. Preventive Services Task Force. Kudos to the American Cancer Society and the other medical organizations for erring on the side of "lives saved" by sticking to their original recommendations.

In breast cancer screening, we have built only "half a bridge" through mammography. It's not a perfect tool. Worse than the false-positive issue being magnified by the Task Force is the *false-negative problem* – stated alternatively, the low sensitivity of mammography allowing cancers to go undetected. The Task Force claims the "Sensitivity" of mammograms (the percentage of cancers detected) to be between 77% and 95%, but these high numbers are accompanied by a powerful caveat – they apply only to the first mammogram – that is, when there are more cancers and larger cancers present for the first-time screening event. Published sensitivities for mammography are always 20-30% higher *when limited to this first screening event*. What women want to know is, "What are the chances of my cancer being discovered through mammographic screening *long-term*?" Unfortunately, this number ranges from 40% to 70%, depending on how one defines a "missed cancer." The Task Force then goes on to minimize the power of breast MRI by quoting a similar range of sensitivity (71% to 100%), failing to note the overwhelming evidence that breast MRI, as performed in the United States, is in the range of 90% sensitivity. In head-to-head comparisons of mammography and MRI, breast MRI will identify *twice the number of cancers as mammography*! In fact, it was this overwhelming MRI data that prompted the American Cancer Society to endorse breast MRI for high-risk screening beginning at age 30.

Why would the Task Force overstate the sensitivity of mammography, making it appear better at detection than it really is, while on the other hand, recommending it be used *less*? Because the implication is unthinkable to them: If mammograms are missing half of detectable cancers, even more so in younger women, then building the other half of the bridge, by adding breast MRI, is the best solution...but it's a solution that carries much higher costs that would overwhelm available resources (and, of course, add to the "false-positive" problem).

In response to a bridge half-built, the Task Force has said we need to return to 1993, to go back to where this controversy began. Many breast radiologists, experts no less, have proclaimed that we need to entrench ourselves at the halfway point and insist on maintaining the status quo. But there is a third alternative, an approach to which I ascribe – we need to build the other half of the bridge. We need to do *more*, not less.

The historical screening trials showed us that breast cancer *biology* is vulnerable to early detection, unlike many other forms of cancer. But a major conclusion from those trials has been glossed over, or not appreciated at all. That is, mammography was able to accomplish this mortality reduction with relatively poor sensitivity – not the oft-quoted "80-90% detection rate," but more in the range of 50%. Since we have already demonstrated that lives are saved by finding *half* of the detectable cancers, imagine what we could do if we could find the other half!

To this end, many are working on incorporating breast MRI into screening regimens, given that MRI has the ability to find most of the remaining cancers missed by mammography. A complementary approach is to offer improved risk assessment for women, especially younger women, more properly selecting patients for early-age mammography and breast MRI. An example where I'm involved with improving risk assessment strategies is the utilization of

nipple aspirate fluid (NAF) cytology to identify women at risk for more aggressive screening. Finally, I have proposed for many years that we need a low cost screening blood test to complement mammography, again for the proper selection of patients to undergo breast MRI. To that end, considerable progress is now being made by my colleagues and others. Yet, the first government grant to begin work on a screening blood test for breast cancer was issued only in 2002, wherein it should have been a top priority for decades.

Compare the sparse funding available for the research agendas above to the amount of money spent to re-hash mammography outcomes for 30 years and to waffle over recommendations that assure more women will die from breast cancer, all of this resulting in a disillusioned, dismayed, confused public.

The first half of the bridge, built through screening mammography, was a great start, but it doesn't get us to our goal. While we work hard at building the other half, it is improbable, if not frightening, that a government-funded outreach is working to blow up portions of the bridge half-built. We have already disenfranchised the 6% of all breast cancer victims who are under 40 at the time of diagnosis. We offered them nothing until the American Cancer Society opened the door with their 2007 recommendation to begin high-risk screening at age 30. And now, the Task Force is recommending that we disenfranchise another 15-20% of eventual breast cancer victims in their 40s, offering them nothing...indeed, even stripping them of the potential benefit of self-exams! It's time to direct all efforts toward building the other half of the bridge, a place where death from breast cancer is a rarity.

\* \* \*

Copyright© 2009  
Alan B. Hollingsworth, M.D.