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The Controversy Over Screening Mammography

A Roundtable Discussion of its Current Indications and Uses

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Dr. Oyer: The Winter 2012 issue of the *Journal of Lancaster General Hospital* contained a Roundtable discussion of the increasingly controversial Prostate Specific Antigen (PSA) screening test for prostate cancer.[1] In an accompanying editorial entitled On Controversial Screening for Cancer,[2] Editor-in Chief Dr. Lawrence Bonchek noted that early detection of cancer has great promise and intuitive appeal but cautioned that the benefits of cancer screening may not be as great as we had hoped, and he asked that we conduct a similar discussion on the current indications and uses of mammography screening for breast cancer. Both our discussants have written about controversies in the use of screening mammography in this *Journal*.[1,4] The following discussion will focus on:

1. Principles of screening.
2. Benefits and harms associated with using mammography for breast cancer detection in standard risks patients. We will not be addressing breast imaging in individuals with genetic mutations or medium or high risk indications.
3. Current mammography screening guidelines.
4. Concept of risk-based mammographic screening.

Breast cancer is the most common cancer diagnosed in women in the United States; it affects one in eight women, or approximately 12% of the population at some point in their lifetime. The annual incidence of breast cancer in this country is approximately 290,000, and it causes approximately 40,000 deaths per year.

In the late 1960s the World Health Organization elucidated fundamental principles to guide the introduction of any screening test. Three of these principles are:

1. There should be a suitable test or examination to identify a condition.
2. Treatment of the condition identified should be better at an earlier stage.
3. The natural history of the condition including development from latent to declared disease should be adequately understood.

I'd like to ask Dr. Peterson first, does mammography fulfill these principles, and second, how has the discipline of evidence-based medicine taught us to more critically question the overall risk-benefit ratio of any health screening test such as mammography?

Dr. Peterson: In answer to your first question, let's look at the WHO principles.

First, "There should be a suitable test or examination to identify the condition." This is precisely the discussion that the US Preventive Services Task Force (USPSTF) has raised. If a tumor is large enough to be felt, it can be evaluated. The USPSTF has stated that in women over 40 there is insufficient current evidence to assess any added benefits and harms of clinical breast exam over screening mammography. This leaves us to consider mammography as the "suitable test to identify the condition."

The second, "Treatment of the condition identified should be better at an earlier stage" is generally true for breast cancer, but all breast cancers are not

the same, as we will discuss later. Third, "The natural history of the condition, including development from latent to declared disease, should be adequately understood," but we don't truly understand all breast cancer natural history, especially, for example, that of ductal carcinoma in situ, or DCIS.

There are two other principles that should be examined. First, there should be an agreed upon policy on whom to treat. Second, the cost of case finding should be economically balanced across the healthcare system in terms of expenditure of health care resources as well as possible harms and benefits.

Concerning your second question, the concept of evidence-based medicine, originally proposed by Dr. David Sackett of Ontario, encourages the use of scientific reasoning and modern research to guide clinical practices. Medical interventions are evaluated based on the risks and benefits revealed, preferably from randomized, placebo-controlled clinical trials. Evidence-based medicine moves us away from our personal opinions and intuition to one requiring formal quantitative and explicit methodology for determining the overall risk, harm, and benefit profile of a given test or procedure in a population. We need to understand the net balance of both harms and benefits. It helps to make us aware of the major biases that have misled us in screening: healthy volunteer bias, lead time bias, length-biased sampling, and over-diagnosis, which is an extreme type of length-biased sampling. Slow growing tumors which may never cause harm are over-represented in tests designed to detect clinically occult disease.

The Canadian task force on periodic health examination and the USPSTF contributed to a conceptual shift in medicine, laying out and challenging explicit core assumptions and intuitions in clinical practice, especially in early detection. Unfortunately, evidence-based medicine is inconsistently applied to early detection programs, policies, and interventions in the United States.

Dr. Oyer: Dr. Tanna, is mammography the best screening test available for breast cancer? What other breast imaging technologies are available?

Dr. Tanna: Among the other fundamental properties of a screening test are wide-spread availability, affordability, and accepted sensitivity and specificity and mammography meets those criteria. Furthermore, it is a time-tested modality, and innumerable well planned randomized controlled studies have shown the benefits of mammography in reducing mortality.[3] Of course it is important to have a good discussion of potential harms of mammography, but it is proven to pick up cancers at the earliest stages possible. A good screening test should detect disease at an earlier stage, diminishing both the morbidity and mortality associated with diagnosing the same disease at a later stage. As I have written previously, the efficacy of mammography should not just be assessed from mortality alone.[3] Detecting clinically occult disease before it manifests in advanced disease is best achieved by mammography in all populations, but especially in younger women.[5] In the previous issue of JLGH, I have also shown and illustrated several typical examples of clinically occult, mammographically and pathologically proven extensive disease representing a typical sampling of what we see when mammography screening is not routinely performed.[3]

Other specific breast imaging modalities include hand held breast ultrasound, though a multi-center trial performed several years ago does not support its use as a routine screening modality. Automated whole breast ultrasound was recently approved by the Food and Drug Administration and awaits further trials.

In specific high-risk populations, breast MRI is an invaluable validated adjunct to screening mammography. In these populations, the cost benefits ratios have been tested and meet acceptable criteria supporting routine use[6,7] However, for the purposes of our roundtable discussion, we are focused on the standard and not intermediate or high risk populations. Additionally, we expect that the evolving technology known as 3D mammography, also known as breast tomosynthesis, will add accuracy and lower recall rates compared to 2D full field digital mammography.

I would also add that the American College of Radiology states there is insufficient evidence to utilize thermography, breast specific gamma imaging, positron emission mammography and optical imaging in breast cancer screening.[8,9]

Dr. Oyer: At this point, we agree that the goals of early detection of breast cancer are: 1) establishing an early diagnosis of breast cancer, which favorably affects treatment recommendations, and 2) improving survival and cure rates.

Dr. Peterson, what options are there to establish an early diagnosis of breast cancer?

Dr. Peterson: There are four main options to establish early diagnosis. The first is mammography, which identifies most early breast cancers; no one

argues this point. Sensitivity of mammography screening ranges from 77 to 95% and specificity ranges from 94 to 97%.[10] I would like to briefly summarize the other three:

1) *Professional clinical breast exams:* These are provided either when a woman feels an abnormality, which prompts a medical visit, or when a clinician is doing a routine physical examination and identifies a breast mass. Sensitivity varies from 40 to 69% and specificity from 88 to 99%. There is no current standard approach, and there was no mortality benefit in intervention groups in two large studies done outside the United States. As noted above, the USPSTF states that in females 40 years of age or older the current evidence is rated insufficient to assess the additional benefits and harms of clinical breast examination.
2) *Breast self- examination:* The USPSTF recommends against teaching breast self-examination, and gives it a D-rating, meaning there is moderate or high certainty that it has no net benefit or that the harms outweigh the benefits. The breast self exam sensitivity is only 12 to 41%.5
3) *Self-awareness:* Several organizations, such as the American Cancer Society and the Komen Foundation, suggest methods that help women to be more aware of their bodies in general, and specifically their breasts, in the context of promoting screening recommendations and educating about cancer risk. I note again that clinical examinations are insufficient and self-examination of the breast may actually be harmful.

Dr. Tanna: I would offer as a counter point that mammography combined with the clinical exam and the breast self-examination yields the highest rate of cancer protection.

Dr. Peterson: And also may yield the most harm.

Dr. Tanna: But when you couple a breast self or physician's exam with an imaging examination, you can then sort out what is truly a real finding versus a false physical examination finding. This reassurance can actually allay a patients' anxiety. Most women know someone with breast cancer and having this added reassurance actually benefits rather than harms. Additionally, while I understand the USPSTF position, there is also evidence that women and physicians do indeed pick up interval cancers developing between screening examinations and even those that are mammographically occult.

Dr. Oyer: Dr. Tanna, you and your colleagues are active members of our Multidisciplinary Breast Cancer Treatment Planning program. How do mammographic findings determine what treatment options are available to the patient newly diagnosed with breast cancer?

Dr. Tanna: The breast cancer diagnosis most often starts with the screening mammogram done in an asymptomatic patient, and may be followed by an ultrasound or additional detailed mammograms. I would again emphasize that 90% of women undergoing routine screening mammography have normal results and are reassured with those results. The early detection of breast cancer provided by routine and regular mammography has three benefits in terms of treatment recommendations: less radical surgery, less likelihood to have chemotherapy, and fewer recommendations for invasive axillary staging or more aggressive surgery.

Dr. Peterson: To take an example from the USPSTF,[11] statistics have shown that screening 1,000 women every 2 years from age 50 to 69 results in: 5 breast cancer deaths averted; 780 false-positive results; 55 unneeded biopsies; and an unknown number of complications from breast cancer treatment, aside from the potential harms that are known.

If one starts screening at 40, statistically we can prevent one added death in this group, but to do so we will cause an *additional* 470 false positives (which gives a total of 1,250 false positives when added to the screening exams done between ages 50-69) and an *additional* 33 unneeded biopsies (totaling 88).

Dr. Oyer: In terms of survival, localized breast cancer is associated with a 98% five-year survival rate compared to 84% when there is regional spread to lymph nodes and 24% five-year survival when there is distant spread. This is clear documentation that early stage cancer is associated with a significant survival advantage, which drives our approach to screening.

Dr. Tanna, the SEER (Surveillance, Epidemiology, and End Results) data from the NCI show a greater than 40% reduction in mortality from breast cancer over the past 30 years.[11] Can we forge a causative link between our mammographic screening programs and the observed reduction in breast cancer mortality? And, if so, can we

isolate the effect of mammography from other factors that have also changed over the past 30 years?

Dr. Tanna: The ground work that supports the use of screening mammograms are some of the earlier data where factors such as advances in treatment were not as readily apparent. Data from the past four decades, such as the Swedish data, showed a 25% to 60% reduction in mortality after institution of screening mammograms.[5] Some of the data are not entirely free of the effect of treatment advances, though randomized controlled studies do show a statistically significant benefit. As we move into the 21st century, treatment advances and screening mammography remain closely connected and the differential survival impact of one vs. the other may be difficult to separate quantitatively. Furthermore, mortality cannot be the only metric we gauge from a good screening program, as you have stated Randy.

Dr. Oyer: Would it be fair to summarize that the reduction in breast cancer mortality over the past 30 years is related to three things primarily: mammographic screening, better patient and better breast awareness, and improvements in systemic therapies? And although the individual contributions cannot be precisely separated, mammography is still felt to have a fundamental role among those three?

Dr. Tanna: Yes.

Dr. Oyer: Dr. Peterson, what are the potential harms of mammographic screening? Is the concept of over-diagnosis a valid one, and if so, is this is a danger related to mammography?

Dr. Peterson: Mammographic screening can be harmful when cancer is reported and none is present or the presence of cancer is questioned and additional testing is recommended. Over a 10-year period, between 30 and 50% of women screened every one to two years have a false positive result, and between 7% and 20% receive a false positive biopsy recommendation.[12] Potential harms from biopsies include discomfort, radiation exposure, cost, worry, and others.

Then there is the separate issue of over-diagnosis which is the detection of tumors on screening that have "no risk," meaning their biology is such that they will not cause clinical symptoms in the patient's lifetime. Over-diagnosis thus does not imply an incorrect diagnosis by the clinician or the pathologist. Estimates of total over-diagnosis in breast cancer range from 1% to 54%.[7] Bleyer, in 2012, claimed that 31% of breast cancers are over-diagnosed; i.e. that these cancers that were identified would not ultimately lead to harm. This argument is based on the fact that though screening has markedly increased the detection rate of early stage cancers, there has not been a concomitant decrease in late stage cancers.[13]

Ductal carcinoma in situ (DCIS) is a very common breast tumor that progresses to invasion in 14% to 53% of cases in various studies. Conversely, this means that in 47% to 86% of DCIS cases, invasive disease is over-diagnosed. Currently, there are no biological markers or clinical indicators to predict which cases of DCIS may ultimately become harmful. This biological uncertainly is a key factor in the performance of a screening test designed to identify the earliest signs of disease. Cancer detected by mammography may be less aggressive than cancer detected by the patient or clinician, which suggests to some that patients might safely be diagnosed with less intensive screening and still be treated successfully.[14] Unlike prostate cancer, there are no studies of watchful waiting or active surveillance for breast cancer.

Dr. Tanna: I agree that while we do not fully understand the natural history of DCIS, mammography is extremely effective at detecting clinically occult invasive disease, which we know advances over time and the benefits of detecting the invasive disease at an early stage have already been stated elsewhere. Let us also be clear that there is a difference between over-diagnosis and over-treatment. Screening mammography should not be held accountable for over-treatment.

Dr. Peterson: I disagree. Over-diagnosis frequently leads to over-treatment, since once the DCIS is found, over treatment often ensues because at present we can't determine which of the DCIS lesions will become invasive.

Dr. Oyer: The point about biological uncertainties includes both DCIS and invasive breast cancers. At autopsy, women without clinically apparent breast cancer have a 1.3% and 8.9% incidence of invasive breast cancer and DCIS respectively.

Dr. Tanna: In a good mammographic screening program such as ours, if you were to take 1000 women, 90% are told everything is fine, and they can go on to their next mammogram after an appropriate interval. 10% are recalled for additional workup. Of

the 10%, or 100 patients, who are then worked up, 85 of those are ultimately reassured that everything is fine with additional workup. Yes, there is anxiety associated with the additional workup; yes, there are costs associated with that, but of those 100, 15 typically go on to biopsy, and about 5-6 cancers are detected. This cancer detection rate is an accepted standard in a good screening program. Furthermore, the harms of biopsies are often exaggerated. The standard of care in diagnosis is a needle core biopsy not excisional biopsy. Most women tolerate a needle core biopsy without any complications. Most even go back to work after such a biopsy.

Dr. Oyer: In regard to false positives then, both of you have emphasized problems associated with false positive screening mammograms, including cost, anxiety, and additional workup. Would you now each take a moment to help us further understand the Bleyer and Welch paper published in the November 22, 2012, *New England Journal of Medicine*.[13] As Dr. Peterson mentioned earlier, those authors found that the number of early stage breast cancers identified has more than doubled in the mammography era, but the number of late cases has dropped by only 8%. In other words, if we are not seeing a reduction in the number of late cases of breast cancer, what does this reveal about the effectiveness of mammography?

Dr. Tanna: I have a couple of points on that article. One of the linchpins of that article is the mortality statistic. First of all, the whole study is a modeling study, and not a true observational or better yet randomized controlled study. They have taken data and modeled it, ending it with conclusions that one of the authors has previously published, raising the question of inherent bias.

Second, the authors group DCIS and early invasive ductal cancer in one category, and they also group invasive regional and advanced disease in another single category. Combining DCIS and early invasive disease obscures the true benefit of mammography—detection of early invasive disease. Further, their erroneous model characterizes an advanced cancer without nodal involvement as early stage disease based on size criteria alone. This analogy falsely increases early stage disease and underestimates advanced disease. These groupings are just not clinically applicable and the authors acknowledge that they are limited in terms of demographic data to be able to sort out these differences, and I think that too is a fundamental flaw in this article weakening the validity of any conclusions drawn.

Third, their fundamental assumption is a baseline increase in incidence of breast cancer of 0.5% per year, and that, I think is the linchpin of the error, because the SEER data over four decades show 1% per year increase in incidence of invasive disease.[15]

It is also unclear from this modeling study which women actually had mammography, the frequency of these examinations, or the type or extent of disease diagnosed; these are inherent further limitations of such a study. Not having mammography data and then drawing conclusions on mammography are flawed analyses.

Lastly, as you and Alan said, we really do not know the biology of DCIS as to which one of the DCIS cases will actually progress to invasive disease. But then why mix the DCIS with invasive disease?

Dr. Oyer: To summarize then, you disagree with their conception of the problem of over-diagnosis and these are the points you have made: this is a modeling study; there is inherent bias; the assumptions used are incorrect when compared to the incidence of invasive disease documented by four decades of SEER data; their categorization of disease extent is flawed; they don't have true mammography data in their analysis; and the change in expected baseline incidence does not account for the increase in invasive cancers seen over the same time.

Dr. Peterson, your comments about the Bleyer and Welch paper.

Dr. Peterson: First, I would remind everyone that Dr. Bonchek's editorial in the last issue also discussed that paper.[2] The paper reviewed United States statistics from 1976 to 2008, and it completely changed my recommendations of mammography to my patients. The fact that more than one million women, nearly one in three, were over-diagnosed during 30 years, is quite significant. The slight improvement in outcome with advanced, late-stage cancers was mainly due to better treatment. Some estimate that one-half to two-thirds of the better mortality statistics were due to better treatment and not to screening. Also important to me, this study does not stand alone, but confirms other studies that showed over-diagnosis rates of 20 to 40%, for example, studies in Connecticut, Europe, and Australia.

Right now, the suggested routine of annual mammograms beginning at age 40 and ending at 75 would mean 35 mammograms in a lifetime. If the USPSTF

recommendations are adhered to, that number would decrease to about 13. We now spend about $4 billion a year on breast cancer screening in the U.S.,[16] and an estimated $210 billion on over-diagnosis and over treatment. These numbers do not even consider other harms.

Of the twenty organizations involved with mammography guidelines, nine (mostly specialty and community groups) recommend mammography starting annually at age 40. Eleven (mainly primary care entities) don't recommend annual mammograms beginning at age 40.

In sum, the problem with mammography screening is not with detection, but rather that we detect a tumor and we do not know the prognosis, so we carry out additional studies that have harms as well as benefits. Particularly with DCIS, we need to find a more accurate way or ways to determine which cancers will become dangerous. Will it be the pathologist, radiologist, molecular biologist or others who will come up with the answer?

Dr. Oyer: Given our current level of knowledge, what are the recommendations regarding the use of screening? Dr. Peterson, the USPSTF has concluded that in the average risk woman, mammography is associated with a statistically significant relative reduction in breast cancer-specific mortality in women between 36 and 69 years of age. So they did not say there isn't any benefit for mammography; they recognize that there is benefit across this broad range of ages, but when you weigh the benefit and the harm, the harms outweigh the benefit at certain ages. Please outline the USPSTF recommendations for mammographic screening and explain how they have come to their conclusions that the harms of annual mammography outweigh the benefit in women ages 40-49 and that screening could be reduced to every other year in women ages 50-59.

Dr. Peterson: The recommendations you're referring to are the 2009 recommendations, which update the 2002 recommendation by providing specific recommendations for mammography screening by age. The 2002 statement recommended screening mammography every 1 to 2 years for all women older than 40 years. USPSTF now advises individual recommendations for each patient aged 40 to 49 years (C recommendation) that takes the patient's context into account including patient values regarding specific benefits and harms. They recommend biennial, i.e. every other year, screening mammography for all women aged 50 to 74 years (B recommendation) and they provide an "I," that's "Insufficient evidence," regarding screening for women older than 75 years.

The USPSTF now recommends against teaching breast self screening examination with a "D" recommendation, replacing the previous statement of insufficient evidence. For clinical breast examination the evidence continues to be assessed as insufficient. Digital mammography and MRI as screening tools were not addressed in the 2002 recommendations. Currently, the USPSTF concludes that the evidence is insufficient to assess the harms or benefits of these methods for screening.

Now for rationale: increasing age is the most important risk factor for breast carcinoma for most women. Film mammography is the historical standard for detecting breast carcinoma, and it decreases mortality of breast cancer. The greatest reduction (strongest evidence) is from 60 to 69 years, and there is a greater absolute reduction in the 50-74 year olds than in the 40-49 year olds. Over the age of 75 there is lack of evidence of benefit.

Evidence for benefits of digital mammography and MRI over film mammography in *reducing mortality* is lacking. USPSTF says it is not clear that digital mammography in patients under 50 or with dense breasts reduces mortality more than film mammography *even with increased detection.*

False positive tests are more common in the 40-49 year old group, and though detection by screening seems equivalent from 40-49 and 50-59, the incidence of breast cancer and the consequences or harms also differ between these two age groups. In women 40-49, the USPSTF emphasizes the adverse consequences for most women who will not develop breast cancer and, they conclude there is moderate evidence that the net benefit is small.[17]

The current USPSTF is further informed by a systematic review that incorporates a recent randomized control trial that estimates the number of women that must be invited for screening to extend one woman's life. This is calculated as 1,904 for women aged 40-49 years and 1,339 for women aged 50-59 years. Since the risk for breast carcinoma increases steeply with age starting at age 40 years, and the *relative* risk reduction is nearly identical for these two age groups (15% and 14%), screening of women ages 50-59 years, when breast cancer is more likely to be present yields greater *absolute* risk reduction than for women age 40-49 years,

in whom breast cancer is less likely to be present. This is why so many fewer need to be screened in the 50-59 year age group.

The USPSTF statement is also informed by the Cancer Intervention and Surveillance Modeling Network (CISNET) studies,[18] with consideration of both "mortality" and "life-years gained" outcomes. The task force emphasized the mortality outcomes from modeling studies of 8 screening strategies that were found to be most efficient. Six strategies start at age 50 years and two start at age 40 years. When screening is started at age 40 years, the mortality outcomes show only small gains, and larger numbers of mammograms are required. Since the harms remain at any age, and the additional benefit gained by starting screening at age 40 years rather than at age 50 years is small, the USPSTF gave annual screening at ages 40-49 a grade "C" recommendation. The task force encourages individualized, informed decision making about when to start mammography screening.

For biennial screening mammography in the 50-74 year old group, there is moderate certainty the net benefit of screening is moderate. Changing from annual to biennial screening reduces the harms of screening mammography by almost half.

Dr. Oyer: Dr. Tanna, would you outline the American Cancer Society recommendations for screening mammography and any supporting data for those recommendations?

Dr. Tanna: The American Cancer Society and other professional societies that Dr. Peterson alluded to recommend an annual mammogram starting at age 40.

Number one is that, although the incidence of breast cancer increases with advancing age, at LGH and other institutions about 20% to 22% of our patients present with breast cancer in their 40s. That is not an insignificant number to ignore if you skip mammograms at that age. Without a good mammography screening program, the likelihood of diagnosing more advanced disease in this group has other implications in terms of costs, as well as the morbidity and mortality of advanced treatment, more extensive operations, and other adjuncts such as chemotherapy.

Second, there is really no specific transition that happens at age 50; a 47-year-old is more like a 52-year-old than like a 40-year-old, and that transition is a gradual one, even though we arbitrarily pick the date of the 50th birthday. So our recommendations at Lancaster General are consistent with the important recommendations of the American Cancer Society and of the nine other professional societies; we recommend an annual mammogram starting age forty. We do not have a finite end of life cutoff, but individualized to a woman's health status. We do not continue screening when a woman would not be able to undergo additional testing or treatment if cancer is diagnosed.

In summarizing the USPSTF guidelines Dr. Peterson mentioned breast MRI, so I would only like to make it clear that for a patient who has a standard risk and is clinically free of breast cancer (i.e. is asymptomatic), no organization supports the use of Breast MRI. Such an average-risk patient has a 15% or less lifetime risk of breast cancer.

Dr. Peterson: Just a minor point here, but the "other professional societies" that Dr. Tanna refers to are not ALL the professional societies. There is a real split between the groups recommending starting mammography at 40 and those that feel they should not start then—because of more false positives in the younger group and adverse consequences for women who will not develop breast cancer.

Dr. Oyer: Given our current state of knowledge, is it possible to risk-stratify patients so that mammographic screening can be used more effectively? There are recognized risk factors such as breast density and family history of breast cancer which influence both breast cancer risk and screening performance. Can we use what we know today to modify the harms/benefit ratio for different populations?

Dr. Peterson: If stratification modalities are to be successful, they must be based on excellent registration data and model results that are validated by surveillance data such as these.

The first article that started biasing the balance of benefits and harms to favor starting screening mammography at age 40 was a comparative modeling study of risk.[19] The objective was to determine the threshold relative risk (RR) at which the harm/benefit ratio of screening women 40-49 years of age equals that of biennial screening for 50-74 year olds. Their data came from surveillance epidemiology and end-result, the SEER program, and the BCSC. They concluded that females 40-49 with a two-fold increase in risk have similar harm/benefit ratios for

biennial screening mammography as average risk women age 50-74 years. (Notably, the harm/benefit ratio for film mammography is more favorable than for digital mammography because film has a lower false positive rate.) Since relative harm/benefit ratios vary by screening method, interval, and outcome measure, this report was seriously limited because in calculating the harm/benefit ratio they included *only* false positive results of screening mammography as the harm; they did not consider the many other possible harms that we mentioned earlier. Over-diagnosis alone can range up to 54%.[20]

No randomized controlled studies have directly compared annual and biennial screening, and this one was no exception; the model outcomes largely depended on the inputs, as well as numerous assumptions. Other countries, however, have screening guidelines that are risk-based. The Netherlands uses a relative risk of 2 to 3 to offer annual screening at age 40. Australians offer annual screening before 50 if a relative risk is found at 1.5 to 3.

Another article reported a systematic review and meta-analysis of risk factors for breast cancer for women aged 40-49 years using the BSCS as well as MEDLINE, Cochran Central Register of Controlled Trials, Cochran Database of Systemic Reviews, and Scopus.[21] Sixty-six studies provided data for estimates. Extremely dense breasts on mammography or first degree relatives with breast cancer were associated with at least a two-fold increase in cancer risk. Prior breast biopsies, second degree relatives with breast cancer or heterogeneously dense breasts were associated with a 1.5 to a 2.0-fold increased risk. Clinical trials using breast density for risk assignment have not been done, and there are no proven and reproducible methods of density measurement.

Current use of oral contraceptives, nulliparity, and age 30 years or older at first birth were associated with a 1.0 to 1.5-fold increased risk. Although most women who develop breast cancer have no known risk factors, information about risk may help informed consent about screening.

In sum, I personally believe we need a randomized, controlled, evidence-based study on risk stratification for women ages 40-49.

Dr. Oyer: Thank you. Dr. Tanna, we know that certain recognized risk factors such as breast density and family history can double a person's risk of developing breast cancer. At this point, can these risk factors influence screening recommendations?

Dr. Tanna: I think we are a long way away. First of all, many women in their 40s tend to have dense breasts or heterogeneously dense breasts, the two upper echelons of breast density. Second, breast density measurement is a radiographic term. It is based on a subjective assessment of distribution of total fatty versus fibroglandular tissue as seen on mammography, and it is fraught with error. As a subjective assessment and what one person may call extremely dense another may call heterogeneously dense. There is a wide range in how it is labeled, and there are ongoing methodologies that are being developed to make assessment more quantitative.

Nonetheless, as the study cited by Dr. Peterson noted, there is no question that breast density increases the risk for breast cancer 2-fold. Other studies indicate that women with extremely dense breasts are at a risk for breast cancer of 4 to 6 times that of baseline. Extremely dense breasts do indeed limit mammographic sensitivity. The exact approach and algorithms to screen women with such breast density are being worked out with some of the other modalities that I previously mentioned.

Second, I want to emphasize that despite attempting to estimate risk, it is very important to remember that 75% to 90% of women presenting with breast cancer have absolutely no risk factors at all. To deny those women a screening mammogram on the basis of risk stratification would be ludicrous because you would be missing far more breast cancers.

As far as risk stratifications based on family history, we have said from the outset that this was not within the scope of the discussion. However, there are evidence protocols and algorithms for screening these high risk patients in the references I have cited.

Dr. Oyer: These are excellent points about risk stratification. Given our current state of knowledge, what are your current recommendations?

Dr. Tanna: For women of average risk for breast cancer, I recommend a screening mammogram annually starting at age 40 and continuing until about 7 to 10 years before they would not be able to tolerate any treatment for breast cancer should that develop. So, there is no definite end-point but you should assess the comorbidities that are evident at any given time. If you have a 75-year-old with multiple comorbidities, you can conclude that there is no point in doing screening.

As a side note to that, we do see about 15% of our breast cancers in the over-75 population.

Dr. Peterson: I'm essentially following the USPSTF guidelines.

Dr. Oyer: As the discussion comes to an end, is there a take-home message you want to emphasize? Alan you have already pointed out that pathology and molecular biology will be better future predictors of who can benefit from cancer screening. You have recommended a randomized clinical trial for screening of women aged 40-49 years. Is there anything else?

Dr. Peterson:

1) Physicians need to demand the evidence-based quantitative methodology of all harms and benefits of screening, and the true concept of risk. These were most likely not taught when many of us were in medical school. Educating patients about these newer concepts takes time that many providers don't have. Unfortunately, it is easier to continue what you believe intuitively is correct and simple; just order a mammogram and don't use precious hours delving into the research.
2) All cancer is not deadly. This is a foreign concept to most patients and many physicians. Overdiagnosis is rampant and will continue for the foreseeable future as many community groups and specialists continue to foster screening "at all costs." Future randomized studies will hopefully help us determine those who are truly at higher risk that need earlier or more frequent screening, thus reducing overdiagnosis, false positives, and overtreatment.
3) Treatment and *non*-mammographic breast awareness have recently saved 1/2 - 2/3 of our breast cancer patients. Some studies suggest 15-40% of the decrease in breast cancer mortality is due to screening mammography. Screening needs to continue to improve in a harms/benefit cost effective manner.[14]

Dr. Tanna: While Alan can elect to follow the USPSTF guidelines, the controversy noted here is far from being settled. Since the NEJM Bleyer and Welch article was published, the following groups/Individuals have published "extreme reservations" on the validity of that paper for all the reasons I have stated previously: European Society of Breast Imaging, Society of Surgical Oncology, American Society of Radiation Oncology, American Society of Breast Surgeons, Canadian Association of Radiologists, American Society of Radiology, Society of Breast Imaging, Laszlo Tabar MD, FACR(HON), and Martin J. Yaffee PhD (Senior Scientist, Sunnybrook Research Institute, Director of Smarter Imaging Research Program at Ontario Institute for Cancer Research).

As a result, our recommendations based on ACS guidelines are not changing. There is no doubt that more conclusive research and more broadly accepted recommendations are needed before we change our screening recommendations for women with average risk of Breast Cancer. Women can certainly have this informed discussion with their physicians prior to a screening mammography examination. Again, I must also emphasize that symptomatic patients must be evaluated with the appropriate and accepted modalities I have previously discussed. Their complaints should not be ignored, nor should mammography examination be dismissed in light of this controversy, a phenomenon which we have observed after the 2009 USPSTF recommendations were issued.

Dr. Peterson: The Bleyer paper has certainly created a stir in the specialty "Letters to the Editor" columns and blogs, but it is ultimately supporting the USPSTF guidelines of some 3 years prior. I think it is noteworthy that all of the societies mentioned by Dr. Tanna as having "extreme reservations" about the Bleyer paper represent raiologists, radiation oncologists, or surgeons. None are primary care physicians or oncologists. Thankfully there are multiple other studies that have supported the USPSTF, as the references show. I don't think anyone is ignoring "symptomatic" patients or those with "complaints" as Dr. Tanna implies. I believe that an average risk woman *should* have an informed, unbiased discussion of all benefits and harms before a screening mammogram is ordered."

Dr. Oyer: Thank you gentlemen for such an illuminating discussion.

REFERENCES

1. Oyer RA, Lin K, Sieber P. The Controversial Prostate Specific Antigen (PSA) Test: A Roundtable Discussion of its Indications and Uses. J Lanc Gen Hosp. 2012;7: 101-110.
2. Bonchek LI. On controversial screening for cancer. J Lanc Gen Hosp. 2012; 7(4): 97-99.
3. Tanna NK. Controversies in screening mammography. J Lanc Gen Hosp. 2010; 5(3):80-86.
4. Peterson AS. The debate is over; recent Swedish study shows great survival benefit from mammography between ages 40-49. J Lanc Gen Hosp. 2010; 5:110-111.
5. Swedish Cancer Society and Swedish National Board of Health and Welfare. Breast Cancer screening with mammography in women aged 40-49 years. Intl J. Cancer 1996; 68(6): 693-699.
6. Hagen AI, Kvitsad KA, Maehle L et al. Sensitivity of Breast MRI versus conventional screening in the diagnosis of BRCA–associated breast cancer in a national prospective series. Breast. 2007; 16: 367-374.
7. Lehman CD, Isaacs C, Schnall MD et al. Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institutional breast cancer screening study. Radiology 2007; 244:381-388.
8. Maniero MB, Lourenco A, Mahoney M et al. ACR Appropriateness Criteria Breast Cancer Screening. J Am College Radiology 2013; 10(1): 11-14.
9. Lee CH, Dershaw DD, Kopans D, et al. Breast Cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, Breast MRI, breast Ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol 2010;7:18-27.
10. Humphrey LL, et al. Breast Cancer Screening: A Summary of the Evidence for the U.S. Preventive Services Task Force. Ann Int Med 2002;137: 347-360.
11. http://seer.cancer.gov/
12. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012; 380:1778-1786.
13. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 2012; 367:1998-2005
14. Kaplan HG and Malmgren J. The breast cancer over-diagnosis conundrum: an oncologist's viewpoint. Ann Int Med. 2013; 158: 60-61.
15. Garfinkle L, Boring CC, Heath CC Jr. Changing trends. An overview of breast cancer incidence and mortality. Cancer 1994;74(suppl 1): 222-227.
16. Journal Watch Audio, December 15, 2012.
17. U.S. Preventive Services Task Force Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 17 November 2009;151(10):716-726.
18. U.S. Preventive Services Task Force Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine, 2009;151:738-747.
19. van Ravesteyn NT et al. Tipping the Balance of Benefits and Harms to Favor Screening Mammography Starting at Age 40 Years: A Comparative Modeling Study of Risk. Ann Int Med. 2012; 156: 609-617.
20. Lancet Oncology, 2007, vol 8, pgs 1129-1138.
21. Nelson HD et al. Risk Factors for Breast Cancer for Women Aged 40 to 49 Years; A Systematic Review and Meta-analysis, Ann Internal Med. 2012;156: 635-648.

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