

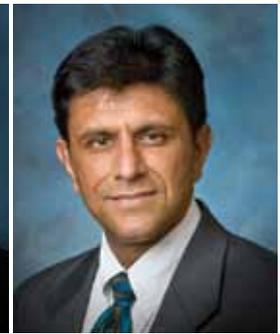
SCREENING MAMMOGRAPHY; AN UPDATE



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EDITOR'S INTRODUCTION:

As noted in my Editor's Page column, there has been a recent upsurge of interest in the changing indications for mammography due to the recent publication of a twenty-five year follow-up of the Canadian National Breast Screening Study.¹ As a result of the very long-term findings, the Canadian Study report concluded: "Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (106/484) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial."

The Canadian study has been sharply and frequently criticized for many years, principally by radiologists (see my Editorial), so its revitalization prompted us to ask the three participants in our previous Roundtable² on mammography (Drs. Randall Oyer—Oncology, Alan Peterson—Family Practice, and Nitin Tanna—Breast Imaging) to contribute short reviews that update their positions on the subject. Herewith their comments:

DR. RANDALL A. OYER:

In my opinion, the three essential areas we need to be concerned about with any cancer screening program are:

1. Avoiding death and disability related to cancer
2. Minimizing unnecessary diagnostic tests which do not translate into benefit for the patient
3. Minimizing over-diagnosis, i.e. treating people for cancer that is not likely to affect health or function

How do two recently published screening studies address these important areas?

The Canadian National Breast Screening Study followed women for 25 years and compared outcomes in women ages 40-59 who did (screened group) or did not (control group) have mammograms once yearly for 5 years. The salient results follow.

25 year survival rates were:

- screened group: 70.6 %
- control group: 66.3%
- mammography group with palpable tumor: 66.3%
- control group with palpable tumor: 62.8 %
- mammography group without palpable tumor: 79.6%

Also:

- 22% of cancers in screened group were considered "over-diagnosis"
- There was one over-diagnosis for every 424 women screened

Welch and Passow³ looked at 9 randomized trials of screening mammography, including the Canadian National Breast Screening Study.⁴ Their salient conclusions are:

For every 1000 women screened annually for 10 years, mammography is estimated to lead to:

- 0.3- 3.2 breast cancer deaths avoided
- 490-670 false positives results requiring additional testing
- 3-14 women over-treated for cancers that are unlikely to affect mortality

What remains to be accomplished?

1. Develop better ways to differentiate women who are likely to benefit from mammography from those who are not.
2. Analyze how mammography screening affects the treatment burden experienced by women diagnosed with breast cancer. That is, do women with cancer diagnosed by mammography require less treatment and thus experience fewer acute and long term side effects. Could this benefit be missed in the analysis if survival is used as the only measure of benefit? This question has not been addressed.

What can we add to our current methods to identify women who are more or less likely to benefit from mammography screening?

- The Nurses' Health Study showed that elevated circulating levels of estradiol and testosterone were both associated with at least a doubling of breast cancer risk in pre-menopausal women.
- Estrone, androstenedione and dihydro-epiandrosterone sulphate levels have been positively associated with a modest increase in breast cancer risk.
- The level of sex hormone binding globulin has been suggested to have a negative association with breast cancer risk.
- The intake of more than 6-12 alcoholic drinks per week (10-19.9 grams of alcohol per day) increases the risk of developing breast cancer by 22%.
- The rate of developing breast cancer is 24% higher in smokers than non-smokers.⁶
- Genetic variants known as single nucleotide polymorphisms (SNPs) increase breast cancer risk. A panel of 10 SNPs added to the Gail model modestly improves its performance.
- Breast density increases the risk of breast cancer.

In my opinion we must do the following:

1. Continue to use mammography as a breast screening tool until we have a better strategy.
2. Incorporate additional risk factors into our models and move beyond age alone to guide our recommendations for breast cancer screening.
3. Counsel women and provide the tools for breast cancer risk reduction.
4. Design studies that will help us understand the extent to which mammography screening lessens treatment burden in those who must be treated for breast cancer.

DR. ALAN S. PETERSON:

I have been asked how I would advise family practitioners to counsel their patients about screening mammography in light of recent scientific literature. This is one of the most emotional and politically charged medical issues of the day.

Basically I have not felt that the recent literature significantly changes my comments from those in our JLGH article in the spring of 2013,² except for one possible amendment.

The Canadian study⁸ will, as always, create tremendous backlash from advocacy groups and mammographers. Governments, research funders, medical practitioners, and scientists may have vested interests in continuing activities that are previously established. I think a personalized risk-related screening algorithm will eventually emerge. A problem is that we have a pre-occupation with screening as opposed to prevention. We all need to exercise, eat more vegetables and less meat, brush and floss our teeth, get adequate rest, stop both smoking and drinking alcohol (especially women with breast cancer risk), and stop drugs and supplements that may increase disease. Obviously we need to also continue to look for preventing the molecular key from turning on uncontrolled cell proliferation.

Recent studies do not decrease but, in fact, increase my belief in the United States Preventive Services Task Force (USPSTF) guidelines, which recommend starting screening mammography at age 50 and continuing every other year. A more recent conference (European Breast Cancer Conference, March 21, 2014) found mammography not helpful for women over 70. Women 70-75 are more likely to die from other causes than from any early stage breast tumors detected by mammographic screening. Those women are also at greater risk for complications of surgery and from side effects of treatments. Screening could result in overtreatment and could decrease the quality of life and ability to function, without lowering the incidence or mortality of breast cancer.

Like much of evolving cancer care, a personalized approach should be used when deciding whether a woman less than 50 years or over 70 years of age should have mammographic screening. Otherwise, I believe the literature supports doing biennial screening starting at age 50 and continuing until age 70. With further study, such as that suggested by Dr. Oyer, a series of known risk parameters (such as genetic predisposition, family history, gynecologic and obstetric history, and other medical and pharmacologic considerations) might be useful in assessing

which females are best able to derive benefit from screening tests like mammography.

An article in *The Annals of Internal Medicine* published online 2/3/14 discusses the purely economic effect of 3 different screening mammography recommendations.

- Annual screening of females 40-84: \$10.1 billion
- Biennial screening of females 50-69: \$2.6 billion
- Biennial screening of females 50-74 and personalized screening based on risk factors/comorbid conditions for women younger than 50 or older than 74 years (USPTF recommendations): \$3.5 billion

The author suggests money saved could be utilized for personal risk-based screening and prevention. Most countries don't screen women for breast cancer. The UK recommends that females be screened every three years starting at age 50. Including costs in decisions about appropriate treatment is an uncomfortable topic but one that can't be ignored. This is, of course, in addition to issues of over-diagnosis, over-treatment, potential harms, false positives, and other issues with mammography that we discussed last year in our article.

The issue will continue to be debated. The American Cancer Society reviews its mammography recommendations this year and the USPSTF has indicated that a panel may revisit its recommendations later this year. Until we truly discover the essence of cell biology and metastasis and its relation to uncontrolled proliferation, all the population-based screening in the world most likely will not provide the answer.

DR. NITIN TANNA (BY DR. BONCHEK):

NOTE: *The press of previous commitments prevented Dr. Tanna from personally authoring his response, but he has asked that I summarize the shortcomings of the Canadian study that are pointed out in references he provided.⁹ He also reminds readers that he discussed the deficiencies of this study as well as those of the USPSTF recommendations in a 2010 article in JLGH.¹⁰ Any statements in quotation marks below are direct quotes from Dr. Tanna's prior article.*

The Canadian study began 25 years ago, so it necessarily used radiological techniques that are badly outdated, yielding mammograms that would be considered unreliable by today's digital standards. Worse, "it was not truly a randomized controlled trial, since patients were assigned to the screening or no-screening groups only after a physical examination of the breasts. Since women with palpable masses were selectively assigned to the screening cohort, it contained 4X as many advanced cancers as the non-screened group. This difference inevitably altered the mortality statistics,

which compromised the parameter by which the effectiveness of screening mammography was assessed. Errors in certification of the cause of death were also raised by the authors in the first study, a fact that was even noted by the authors of the paper. Compliance among the women in these studies was also a problem, as nearly 20% of those assigned to regular screening did not get examinations over a 4-5 year period. Further, many women assigned to the no-screening cohort got screening mammograms outside the study."

The Society of Breast Imaging website also points out the following deficiencies in the techniques and technology of the Canadian study:

- The trial used mammography machines which were not state of the art at the time of the trial.
- The images were compromised by "scatter," which makes the images cloudy and cancers harder to see since they did not employ grids for much of the trial. Grids remove the scatter and make it easier to see cancers.
- Technologists were not taught proper positioning. As such, many women were not properly positioned in the machines, resulting in missed cancers.
- The CNBSS radiologists had no specific significant training in mammographic interpretation.
- The CNBSS own reference physicist stated that ". . . in my work as reference physicist to the NBSS, identified many concerns regarding the quality of mammography carried out in some of the NBSS screening centers. That quality [in the NBSS] was far below state of the art, even for that time (early 1980s)."

In total, only 30% of cancers in the study were detected by mammography, which is considered to be a low detection rate even for that era, confirming the inadequacy of the techniques that were used.

Two final points:

1. If a study is poorly designed and carried out, longer follow-up does not correct its deficiencies;
2. Since these studies (erroneously) found no significant benefit for mammography, their inclusion in any outcomes modeling or meta-analysis skews the results against screening.

Overall, the Society of Breast Imaging feels that the Canadian study is so deeply flawed that it should not influence decisions about patient management in the current era of breast care.

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