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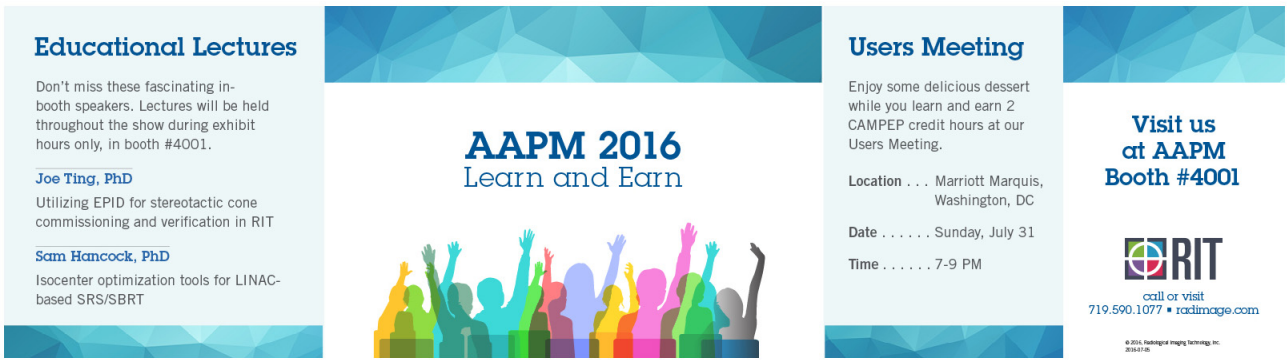

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to the Moderator: William R. Hendee, Medical College of Wisconsin, Milwaukee: whendee@mcw.edu. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

Pre-menopausal women should be actively encouraged to seek screening mammograms

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OVERVIEW

The controversy continues over the merits of screening mammography for pre-menopausal women (women$<$50 years of age). Many persons believe that screening benefits are intuitively obvious, and are well supported by experimental evidence. These individuals endorse screening mammograms for younger women. Others feel that the scientific evidence for screening mammography is inconclusive, and that this uncertainty should be communicated to younger women contemplating mammography. Until now, medical physicists have been relatively silent on the screening issue. But this Point/Counterpoint breaks the silence.

Arguing for the Proposition is Andrew Maidment, Ph.D. Dr. Maidment received his Ph.D. in Medical Biophysics from the University of Toronto in 1993. He is currently Assistant Professor of Radiology, and Chief, Physics Section at the University of Pennsylvania in Philadelphia. He has more than 110 peer-reviewed journal articles, book chapters, proceedings papers and abstracts. He has won several awards including First Place in the 1994 Young Investigators Competition of the International Union for Physical and Engineering Sciences in Medicine. He is active in the ACR and AAPM, including chairing Diagnostic Imaging TG 16, Standards for Noise Power Spectrum Analysis. His research interests include digital mammography, 3-D x ray imaging of the breast, and digital radiography detector physics.

Arguing against the Proposition is Elizabeth Krupinski, Ph.D. Dr. Krupinski received her undergraduate education at Cornell and her Ph.D. at Temple University, both in Experimental Psychology. She has been at the University of Arizona since 1992 in the Departments of Radiology and Psychology. Her interests lie in medical image perception and decision-making, especially in the digital environment. The human-computer interaction is also of interest from the human factors perspective. She is interested in the causes of interpretation error and in developing ways to improve training from an image perception perspective. Dr. Krupinski is also the Associate Director of Evaluation for the Arizona Telemedicine Program.

FOR THE PROPOSITION: Andrew Maidment, Ph.D.

Opening Statement

There is almost complete consensus that routine mammographic screening can reduce the mortality of breast cancer. Recent results indicate mortality can be reduced by 40 to 45%.[1] Controversy continues, however, over whether this reduction is shared by all women or whether it begins after menopause, at approximately 50 years of age in developed countries. This dichotomistic doctrine is fallacious; all women should be actively encouraged to seek screening mammograms starting at age 40.

There is little that distinguishes breast cancer in a woman in her 40s from that in a woman in her 50s. The natural incidence increases only slightly between the two decades.[2]

The etiology, pathology and clinical sequelae are virtually identical. Furthermore, while women 40–49 account for only 16% of breast cancer incidence, they account for 40% of the years of life lost to breast cancer.[3] Thus, women in their 40s will potentially benefit most from screening. The meta-analysis of randomized clinical trials (RCTs) by Humphrey *et al.*[4] indicates that the summary relative risk for women of ages 40–49 is 0.80 (CI 0.67–0.96), compared with a summary relative risk of 0.78 (CI 0.70–0.87) for women older than 50. These estimates correspond to one life saved per 1385 women for the younger group and one life saved per 838 for the older group.[4] Thus, the benefit of routine screening for both groups of women is comparable.

Admittedly, there is not universal agreement on this issue. Notably, the Cochrane Report[5] found no benefit for women aged 40–49. However, the Cochrane Report considered only 2 of 8 applicable RCTs. One of these, the CNBSS study, has been the subject of extensive criticism.[6]

That said, mammography is far from perfect. Mammography lacks sensitivity; some cancers are missed. Mammography also lacks specificity; many healthy women endure negative biopsies, resulting in a high monetary cost, as well as physical and psychological costs. Mammography entails the risk of inducing cancers, but this risk must be weighed against the probable benefits. It is estimated that annual screening from age 40 to 49 will induce fewer than 8 cancers per 100,000 women screened.[7] Thus, nine lives would be saved for each woman who suffers an iatrogenic cancer. Mammography may find indolent cancers. Finally, universal screening guidelines are questionable; for example, consider women with genetic predisposition to cancer (e.g., BRCA-1/2). These are not failings of mammography alone, however; they demonstrate the boundaries of our knowledge of breast cancer, and limitations of current diagnostic and treatment methods.

Mammography may have some flaws, but it is the best screening tool for breast cancer available today. Above the age of 50, it is almost universally accepted that the death rate from breast cancer can be reduced at a monetary, physical and psychological cost that society accepts. There is no evidence to support a different approach for women in their 40s. Finally, early mammograms provide a highly valuable baseline for radiologists attempting to interpret mammograms later in a woman's life. Thus, a variety of considerations strongly support extension of the benefits of routine mammographic screening to this younger population. That is, all women should be actively encouraged to seek screening mammograms starting at age 40.

Rebuttal

Even casual readers of both my own and my colleague's opening statements on this topic will remember Leonard Courtney's famous words ''lies — damn lies — and statistics.''[8] First, I disagree with the assertion that mammography and menopause should be tightly linked. The mean age of menopause in the US is 51, not 45.[9] Menopause is exceptionally rare below the age of 40 or above the age of 59.[9] If menopausal changes had the dominant responsibility for breast cancer incidence, then there should be a stronger correlation with menopause. Yet the strongest correlate of breast cancer risk is age, increasing almost linearly with age from 30 to 75.[9]

Second, the data related to positive-predictive value (PPV) cited by my colleague in this Point/Counterpoint are dated and fail to distinguish prevalence (first) screening from subsequent screenings. Consider for example the Ghent program; PPV = 14.2% for prevalence screens of women in their 40s, while PPV = 28.3% for prevalence screens of women in their 50s. However, PPV = 19.7% and 16.8% in subsequent screens in 40s and 50s, respectively. The increased PPV of the 50s prevalence screen is due to the fact that screening has been started too late for these women; they already have a significant number of readily-detectable cancers. Moreover, the equal values of PPV in subsequent screenings in both age groups clearly indicate that mammography is equally effective for both.

The assertion that young dense-breasted women benefit less from mammography is also questionable. Kerlikowske[10] has shown that sensitivity in women aged 50 and older is affected by breast density (98.4% fatty vs 83.8% dense; $P < 0.01$), yet for women younger than 50 this is not true (81.8% fatty vs 85.4% dense).

Screening will benefit from advances in breast cancer biology, better diagnostic tools and improved treatments. There is little doubt, however, that mammography for women aged 40–49 is not only appropriate, but essential. Likewise, clear, consistent and simple screening guidelines are essential. ''Start annual screening on your 40th birthday'' fulfills this role exactly; it is the perfect birthday gift for any woman.

AGAINST THE PROPOSITION: Elizabeth Krupinski, Ph.D.

Opening Statement

Although the benefits of mammography for early detection and treatment of breast cancer may seem obvious, there is still considerable debate regarding its overall efficacy, who should be screened and at what age.[11,12] The majority of trials (with findings both for and against screening) have been done with women 40 years of age and older. Although the general consensus is that screening mammography is useful for women over 40 (and more so as women get older), the evidence regarding benefits for women under 40 is scarce. Menopause typically occurs between 45 and 50 years of age, with the last two years of perimenopause starting the accelerated decline in estrogen levels. The incidence of breast cancer, to a large extent, parallels menopause onset. Incidence is very low for women in their twenties, increases gradually and plateaus at 45, then increases dramatically after 50. In fact, approximately 50% of breast cancers are diagnosed in women over 65, and recent evidence indicates that since the 1980s breast cancer incidence rates have increased only in women over 50.[12,13] Invasive breast cancer

diagnoses in women over 65 accounts for 45% of all new breast cancer cases, and 45% of all breast cancer deaths are in women over 65.[12]

In terms of sensitivity and specificity, screening mammography is less effective in women with dense breasts, especially younger women.[14,15] The positive predictive value (PPV) ranges from 20% in women under 50 to 60% to 80% in women over fifty.[16,17] The low PPV reflects the higher false positive rate[17] for younger women. Although the psychological effects of false positives are generally short-lived and have few lasting consequences,[12] the immediate experience produces high levels of anxiety, especially since waiting times can be prolonged between initial report and follow-up procedures. In addition to low sensitivity, specificity and PPV in younger women, repeated screening exams starting at a younger age lead to an increased risk of radiation-induced breast cancer.[12,18] This is especially true for women with a family history (i.e., genetic predisposition) of breast cancer, or for women being treated with radiation for other purposes (e.g., radiation treatment, scoliosis progression imaging).

The relative lack of efficacy, and the potential for physical and psychological risks, support the proposition that most premenopausal women should not be encouraged to seek screening mammograms. Younger women who are at risk because of a family history or known genetic predisposition to breast cancer (5–10% of all cancers) should be screened, because their cumulative risk of breast cancer is higher than average.[12] For the average premenopausal woman, a careful analysis of the risk factors associated with breast cancer, and adherence to a healthy lifestyle based on prevention, may be more useful than screening mammography. Although certain risk factors cannot be altered (e.g., age of first menarche, late menopause), there are many others that can be controlled, such as not smoking, having children early in life, increased physical activity, maintaining proper weight, reduced alcohol intake, breastfeeding rather than bottle-feeding, and sticking to a healthy diet.[19] Educating women about these risk-reduction factors, and suggesting other methods of screening that do not involve radiation exposure (e.g., ultrasound, MRI), should be the focus of communication to younger women contemplating the costs and benefits of mammography.

Rebuttal

''Statistics—the only science that enables experts using the same figures to draw different conclusions.'' [20] Reading the statistics on breast cancer screening often leads one to this very conclusion. The Humphrey *et al.*[21] report does indeed report that the relative risk for women aged 40–49 is 0.80, and 0.78 for women older than 50, based on their meta-analysis of eight high profile breast screening trials. This report brings up several other points, however, that lead one to question the strength and generalizability of the conclusions. Most important is the authors' rating of the quality of original studies used in the meta-analysis. Each of the screening trials included in the meta-analysis had important methodological flaws, and seven of the eight studies were rated only fair in terms of study quality. The eighth was rated poor. Also, the authors state that of the seven trials conducted since 1963 that included women aged 40–49, only one actually planned to evaluate breast cancer screening in this group, and none (even the one that specifically included it as a statistical variable) had sufficient statistical power. The lack of power is due mainly to inadequate sample size once data were stratified into age subgroups. There is also some question[22] about when the benefits of screening mammography actually appear in the 40–49 age group in these trials. The potential survival benefit in women aged 40–49 is typically not observed until the trial has progressed for several years. The women included in the studies are now just in the over-50 age group.

In the end, each woman must make a personal decision by trying to understand the overall picture, including an understanding of absolute risk, relative risk and the factors that contribute to breast cancer risk. No studies have been designed that offer guidance on how an individual woman can assess her lifestyle, family history, and environment in the context of available medical evidence to decide when and how often she should be screened. Clearly there are women at higher risk, for whom this decision may be easier. But for women not at obvious risk, the use of the single variable of age (other than gender of course) to determine when screening should begin may not be sufficient. To improve breast cancer screening outcomes, we need to develop better and more accurate models that include as many risk factors as possible for each individual woman.

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