CURRENT ONCOLOGY
PERSPECTIVES IN ONCOLOGY

Breast cancer screening panels continue to confuse the facts and inject their own biases

D.B. Kopans MD*

Additional confusion has been added to the "debate" about breast cancer. Women, their doctors, and the media are being misled, and women will die, unnecessarily, as a result. I recently outlined the scientific errors that I was concerned would be made by the U.S. Preventive Services Task Force (USPSTF) and the International Agency for Research on Cancer (IARC) panels in their reviews of breast cancer screening guidelines[1]. Based on the draft proposal by the USPSTF, and now IARC[2], my concerns have been realized. Because the panels include few (if any) experts in screening, they are unable to sort out the validity of the various analyses involved, and they give credibility to analyses that have major flaws.

One of the other major problems with the panels is that their deliberations are held in secret. If anything should be completely transparent, it should be discussions of health care guidelines. It is my understanding that the IARC panel did not unanimously agree, and that a number of panel members felt that the data supported screening women starting at the age of 40. There should be transparency, and IARC should provide full disclosure, as well as any minority reports.

THE PANELS PROVIDE CONTRADICTORY ANALYSES

At What Age Should Screening Begin?

Now we have two supposedly (not really) "expert" groups reaching different conclusions about the same data. The USPSTF clearly states that screening reduces deaths for women who begin screening at the age of 40 ("The USPSTF found adequate evidence that mammography screening reduces breast cancer mortality in women ages 40 to 74 years"[3]), but the USPSTF would deny women access to screening in their 40s by claiming that "false positives" (recalls from screening for a few extra pictures or an ultrasound) are a major "harm" and that the "most important harm [is] ... overdiagnosis and overtreatment."

On the other hand, and contrary to the actual data, IARC concluded that evidence of a benefit for screening women in their 40s is "limited"[2] and therefore not "sufficient." The organization does not support screening women in their 40s, although it correctly concluded that recalls from screening were not a major issue and that "overdiagnosis" is a minor problem and likely to be 6%–7%, and no more than 10%.

These contradictory analyses of the same data suggest that the "panels" have either an incomplete understanding of the data or other motives in deciding their guidelines. In fact, there are absolutely no data to support the use of the age of 50 as a threshold for screening. The data have always shown that screening reduces deaths for women who start screening at the age of 40[4,5]. The benefit has always been as strong for women 40–49 years of age as for women more than 50 years of age. The age of 50 is a completely manufactured threshold[6]. The recent update of the U.K. Age Trial proves that screening women 40–49 years of age saves lives[7]. That result was accomplished despite the fact that, for incidence screening, the trial used single-view mammography, which is known to miss 20% of cancers[8], and that biopsy failed to be conducted for clustered microcalcifications[9]. Calcifications in the *in situ* portion of a tumour might be the only indication of the presence of an associated small invasive cancer. The Age Trial would likely have saved even more lives of women in their 40s had it used two-view mammography (to which the British are switching) and had it biopsied clustered calcifications[10]. It is time to stop the scientifically unsupportable claim that anything important happens at the age of 50.

There is not a single study in which ungrouped and unaveraged data change abruptly at the age of 50. No parameter of screening changes abruptly at the age of 50[11], and there is no biologic or scientific support for using the age of 50 as a threshold for screening. Anyone claiming that the age of 50 is a legitimate threshold should have to provide ungrouped and unaveraged data to show that a parameter of screening changes abruptly (including lives saved) at the age of 50. It is a myth. There are no such data.

To suggest that data before the age of 50 are "insufficient" is simply ignoring the facts. In addition to the randomized controlled trials[5,12], numerous observational studies show a marked decline in breast cancer deaths for women screened in their 40s[13–18]. The data are equally as strong (if not stronger) for women 40–49 years of age as for older women, and women in their 40s have more years of life to lose.

Even the U.S. National Cancer Institute and its Cancer Intervention and Surveillance Modeling Network show that the most lives are saved by annual screening beginning at the age of 40[19]. The models show that if women in their 30s wait until age 50 and are then screened every 2 years, as many as 100,000 women will die whose lives could have

Correspondence to: Daniel B. Kopans, Breast Imaging Division, Department of Radiology, Massachusetts General Hospital, Avon Comprehensive Breast Center, Suite 240, 15 Parkman Street, Boston, Massachusetts 02114 U.S.A.
E-mail: kopans.daniel@mgh.harvard.edu ■ **DOI:** http://dx.doi.org/10.3747/co.22.2880

been saved by annual screening beginning at the age of 40[20]. Given that the only way to prevent death from breast cancer is to treat it before successful metastatic spread, why would you give cancers an extra year to grow and metastasize by screening every 2 years?

False Positives: Misleading Terminology

The USPSTF has exaggerated the so-called false positives. Women have been led to believe that "false positive" means being told they have cancer when they do not. That understanding is simply false. So-called false positives are nothing more than being recalled from screening for a few extra pictures at a rate that is similar to the recall rate for cervical cancer screening (Pap testing). In nearly all these cases, the women are told that everything is fine. In the United States, the recall rate is approximately 10%. Of 100 women recalled for additional imaging, only 20 are advised to have an image-guided needle biopsy under local anesthesia. The yield of cancer from those biopsies is 20%–40%—a high yield for breast biopsies. In the era before organized screening, when breast biopsies for "lumps" were surgical excisions in the operating room, the yield of cancer was only 15%[21], and the cancers were larger and later-stage.

It is hard to understand how a panel would seek to reduce the anxiety that some women experience on recall by denying women access to screening and, as a result, allowing women to die unnecessarily from breast cancer. What kind of scale was used to "weigh" these benefits and "harms"?

Economic Motivation?

The motivations behind the effort to reduce access to screening are becoming increasingly clear. Many of the government-funded European screening programs have always ignored the scientific support for screening women in their 40s (to reduce costs in national health care systems, I suspect). The IARC is a European agency. Given the unsupportable IARC position concerning women in their 40s, it would appear that economics, and not the scientific evidence, still determines policy.

In the United States, it is now clear that efforts to reduce access to screening are also being driven by the goal of saving money, not lives. A major opponent of screening years ago urged that insurance companies should no longer be graded based on participation by their members in screening[22]. A recent analysis in the *Annals of Internal Medicine* looked at reducing costs by limiting access to screening[23], but neglected to point out the billions of dollars that would be lost by allowing women to die prematurely (and unnecessarily), and thus incurring the high cost of terminal care, premature loss of productivity, and loss to society[24].

So-Called High-Value Screening

Recently Wilt *et al.*[25] proposed "high-value screening," which is simply a euphemism for saving money and not lives. One of the paper's authors was quoted as saying "People need to understand that with this approach, there will be some cancer deaths"[26]. He added, "If we go to a high-value approach rather than a maximal detection approach, we are going to miss some cancers. You have to give in to that"[26].

Claimed Contribution of Improvements in Therapy

The argument has been made that the major decline in breast cancer deaths in the United States since 1990 is attributable to improvements in therapy, and yet not a single study directly shows that when a therapy is introduced into a general population, the death rate goes down in the absence of screening. On the other hand, numerous studies show that screening results in declining deaths[14–19,27–35], separate from access to therapy.

The data clearly show that screening saves lives for women who begin to participate at the age of 40. Women should be provided with accurate information and be allowed to decide for themselves if they wish to participate or not. The use of "guidelines panels" needs some fundamental revisions.

WITH REGARD TO CONCERNS RAISED BY OTHERS ABOUT IARC

It is fascinating that those who are trying to reduce access to screening are raising concerns about IARC's "viewpoint"[2], not concerning women 40–49 years of age, but concerning screening support for women at any age[36]. Those concerns are surprising because every legitimate group that has reviewed the breast cancer screening data since the mid-1990s has agreed that the data clearly show that screening reduces deaths for women 50–74 years of age. When screening has been introduced into the general population, report after report has shown that the death rate declines. The major disagreement over the decades has been whether women should begin screening in their 40s or wait until age 50. It would appear that the critics—such as Dr. Karsten J. Jørgensen, who co-wrote the scientifically flawed Cochrane review "Screening for Breast Cancer with Mammography"[37] with Dr. Peter Gøtzsche—prefer to end all breast cancer screening regardless of age. Gøtzsche has clearly stated that his intention is to end all breast cancer screening[38]. It would appear that this is Jørgensen's goal as well.

According to the commentary in the *British Medical Journal,* Professor Anthony Miller, who headed the Canadian National Breast Screening Study (CNBSS), was most concerned that IARC had overlooked what he claimed were biases in other trials. His concern is ironic given the fact that the CNBSS has indisputably been documented to have violated the fundamental requirements of a randomized controlled trial[39]. Randomized controlled trials rely on blinded random allocation. Nothing can be known about the participants before allocation, and allocation must be completely blinded so that no opportunity arises to intentionally—or inadvertently—compromise random allocation. Any treatment trial that violates those rules would be disqualified, and yet the CNBSS has continued to be used in analyses despite the fact that all of the women who volunteered for the CNBSS had a clinical breast examination before being assigned to the screening arm or the control arm. "Lumps" and axillary adenopathy were identified before women were assigned to one group or the other. Compounding this basic violation was the fact that the coordinators who assigned the women to screening or to control were provided with the results of the clinical

breast examination and assigned the women on open lists so that a line could be skipped to assign an individual to the arm of the coordinator's choosing. This process was even documented by the reviewers who were brought in to try to absolve the CNBSS of allocation bias[40]. The facts are irrefutable: In CNBSS1, a statistically significant excess of advanced cancers was allocated to the screening arm[41]. Of 24 women with advanced breast cancer (4 or more positive axillary lymph nodes), 19 were allocated to the screening group; only 5 were assigned to the "usual care" group. The trial has claimed that this division occurred because mammography finds more of everything, but the explanation is clearly contrived, because 17 of the 19 advanced cancers were found during the clinical breast examination.

More deaths occurred in the screening arm of CNBSS1 for at least 10 years. It was claimed that mammography was leading to earlier deaths. The authors eventually retracted that unsustainable suggestion[42], but they have never provided a cogent explanation of the death rate, nor of how the control group, who received "usual care," had a better than 90% 5-year survival when the 5-year survival in Canada at the time was 75%[43]. The clear and simple explanation is that women destined to die from breast cancer were moved (probably naïvely by the coordinators) from the control arm to the screening group. Such allocation would explain the otherwise inexplicable survival in the control arm, and the excess of deaths in the screening arm. Even ignoring the fact that the mammography in the CNBSS was so poor that the cancers in the screening arms were no smaller than the cancers in the control arms, it is unclear why the CNBSS is allowed to have violated the fundamentals of a randomized controlled trial and still be included in data analyses.

SUMMATION AND APPEAL

It is time for this circus to stop. No one has claimed that screening is the ultimate answer to breast cancer. It does not find all cancers, and some cancers are not found early enough to cure. I have been unable to find a single analysis showing that when a therapy is introduced into a general population, the death rate declines in the absence of screening. And yet numerous studies show that, for women who participate in screening compared with women who do not participate, the death rate goes down even when all have access to improved therapy. In two of the major Harvard teaching hospitals, more than 70% of the women who died from breast cancer were among the 20% who were not participating in screening[44], and yet all had access to modern therapy.

Breast cancer screening is one of the major advances of the last half century in women's health. It would be a shame to return to the death rates of the 1950s based on a misguided effort to save money.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare that I have none.

AUTHOR AFFILIATIONS

*Breast Imaging Division, Department of Radiology, Massachusetts General Hospital, Avon Comprehensive Breast Center, Boston, Massachusetts, U.S.A.

REFERENCES

1. Kopans DB. An open letter to panels that are deciding guidelines for breast cancer screening. *Breast Cancer Res Treat* 2015;151:19–25.
2. Lauby-Secretan B, Scoccianti C, Loomis D, *et al.* on behalf of the International Agency for Research on Cancer Handbook Working Group. Breast-cancer screening—viewpoint of the IARC Working Group. *N Engl J Med* 2015;372:2353–8.
3. U.S. Preventive Services Task Force (USPSTF). Draft Recommendation Statement. Breast Cancer: Screening [Web page]. Rockville, MD: USPSTF Program Office; 2015. [Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementDraft/breast-cancer-screening1; cited 9 June 2015]
4. Shapiro S. Screening: assessment of current studies. *Cancer* 1994;74(suppl):231–8.
5. Duffy SW, Tabár L, Smith RA. The mammographic screening trials: commentary on the recent work by Olsen and Gøtzsche. *CA Cancer J Clin* 2002;52:68–71.
6. Kopans DB. The 2009 US Preventive Services Task Force (USPSTF) guidelines are not supported by science: the scientific support for mammography screening. *Radiol Clin North Am* 2010;48:843–57.
7. Moss SM, Wale C, Smith R, Evans A, Cuckle H, Duffy SW. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age Trial at 17 years' follow-up: a randomised controlled trial. *Lancet Oncol* 2015;:[Epub ahead of print].
8. Blanks RG, Bennett RL, Patnick J, Cush S, Davison C, Moss SM. The effect of changing from one to two views at incident (subsequent) screens in the NHS breast screening programme in England: impact on cancer detection and recall rates. *Clin Radiol* 2005;60:674–80.
9. Evans AJ, Kutt E, Record C, Waller M, Bobrow L, Moss S. Radiological and pathological findings of interval cancers in a multi-centre, randomized, controlled trial of mammographic screening in women from age 40–41 years. *Clin Radiol* 2007;62:348–52.
10. Kopans DB. The UK Age Trial: screening women in their forties. *Lancet Oncol* 2015;:[Epub ahead of print].
11. Kopans DB, Moore RH, McCarthy KA, *et al.* Biasing the interpretation of mammography screening data by age grouping: nothing changes abruptly at age 50. *Breast J* 1998;4:139–45.
12. Hendrick RE, Smith RA, Rutledge JH 3rd, Smart CR. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monogr* 1997;(22):87–92.
13. Jonsson H, Bordás P, Wallin H, Nyström L, Lenner P. Service screening with mammography in Northern Sweden: effects on breast cancer mortality—an update. *J Med Screen* 2007;14:87–93.
14. Hellquist BN, Duffy SW, Abdsaleh S, *et al.* Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. *Cancer* 2011;117:714–22.
15. Paap E, Holland R, den Heeten GJ, *et al.* A remarkable reduction of breast cancer deaths in screened versus unscreened women: a case-referent study. *Cancer Causes Control* 2010;21:1569–73.
16. Hofvind S, Ursin G, Tretli S, Sebuødegård S, Møller B. Breast cancer mortality in participants of the Norwegian Breast Cancer Screening Program. *Cancer* 2013;119:3106–12.
17. Coldman A, Phillips N, Warren L, Kan L. Breast cancer mortality after screening mammography in British Columbia women. *Int J Cancer* 2007;120:1076–80.

18. Coldman A, Phillips N, Wilson C, *et al.* Pan-Canadian study of mammography screening and mortality from breast cancer. *J Natl Cancer Inst* 2014;106:pii:dju261.
19. Mandelblatt JS, Cronin KA, Bailey S, *et al.* on behalf of the Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med* 2009;151:738–47.
20. Hendrick RE, Helvie MA. United States Preventive Services Task Force screening mammography recommendations: science ignored. *AJR Am J Roentgenol* 2011;196:W112–16.
21. Spivey GH, Perry BW, Clark VA, Coulson AH, Coulson WF. Predicting the risk of cancer at the time of breast biopsy. Variation in the benign to malignant ratio. *Am Surg* 1982;48:326–32.
22. Welch HG. Screening mammography—a long run for a short slide? *N Engl J Med* 2010;363:1276–8.
23. O'Donoghue C, Eklund M, Ozanne EM, Esserman LJ. Aggregate cost of mammography screening in the United States: comparison of current practice and advocated guidelines. *Ann Intern Med* 2014;160:145.
24. Helvie MA. Aggregate cost of mammography screening in the United States. *Ann Intern Med* 2014;161:304–5.
25. Wilt TJ, Harris RP, Qaseem A on behalf of the High Value Care Task Force of the American College of Physicians. Screening for cancer: advice for high-value care from the American College of Physicians. *Ann Intern Med* 2015;162:718–25.
26. Lowry F. ACP Offers Advice for "Wiser" Cancer Screening [online news article]. Medscape Multispecialty from WebMD; 18 May 2015. [Available at: http://www.medscape.com/viewarticle/844889 (free registration required); cited 21 May 2015]
27. Tabár L, Vitak B, Chen HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001;91:1724–31.
28. Duffy SW, Tabár L, Chen HH, *et al.* The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties. *Cancer* 2002;95:458–69.
29. Otto SJ, Fracheboud J, Looman CW, *et al.* on behalf of the National Evaluation Team for Breast Cancer Screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003;361:1411–17.
30. van Schoor G, Moss SM, Otten JD, *et al.* Increasingly strong reduction in breast cancer mortality due to screening. *Br J Cancer* 2011;104:910–14.
31. Otto SJ, Fracheboud J, Verbeek AL, *et al.* on behalf of the National Evaluation Team for Breast Cancer Screening. Mammography screening and risk of breast cancer death: a population-based case–control study. *Cancer Epidemiol Biomarkers Prev* 2012;21:66–73.
32. Swedish Organised Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 2006;15:45–51.
33. Kopans DB. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2002;94:580–3.
34. Broeders M, Moss S, Nyström L, *et al.* on behalf of the EUROSCREEN Working Group. The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. *J Med Screen* 2012;19(suppl 1):14–25.
35. Sigurdsson K, Olafsdóttir EJ. Population-based service mammography screening: the Icelandic experience. *Breast Cancer (Dove Med Press)* 2013;5:17–25.
36. Mayor S. Experts question IARC report saying benefits of mammography in older women outweigh risks. *BMJ* 2015;350:h3156.
37 Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013;6:CD001877.
38. Gøtzsche PC. Time to stop mammography screening? *CMAJ* 2011;183:1957–8.
39. Kopans DB, Feig SA. The Canadian National Breast Screening Study: a critical review. *AJR Am J Roentgenol* 1993;161:755–60.
40. Bailar JC 3rd, MacMahon B. Randomization in the Canadian National Breast Screening Study: a review for evidence of subversion. *CMAJ* 1997;156:193–9.
41. Tarone RE. The excess of patients with advanced breast cancer in young women screened with mammography in the Canadian National Breast Screening Study. *Cancer* 1995;75:997–1003.
42. Merz B. Author of Canadian Breast Cancer Study retracts warnings. *J Natl Cancer Inst* 1992;84:832–4.
43. Kopans DB. Screening for breast cancer and mortality reduction among women 40–49 years of age. *Cancer* 1994;74(suppl):311–22.
44. Webb ML, Cady B, Michaelson JS, *et al.* A failure analysis of invasive breast cancer: most deaths from disease occur in women not regularly screened. *Cancer* 2014;120:2839–46.