Does Screening for Breast Cancer with Five Screening Modalities in Average-Risk Women Reduce Mortality from Breast Cancer?

Steven Latosinsky, MD, Ralph George, MD, Hiram S Cody III, MD, for Members of the Evidence-Based Reviews in Surgery Group

The term *evidence-based medicine* was first coined by Sackett and colleagues[1] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility, and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics, as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program titled, "Evidence-Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserve discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence-Based Reviews in Surgery through the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews, which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS website or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in *the Canadian Journal of Surgery*, 4 in the *Journal of the American College of Surgeons*, and 4 in *Diseases of Colon and Rectum* each year.

REFERENCE

1. Evidence-Based Medicine Working Group. Evidence-based medicine. JAMA 1992;268:2420–2425.

SELECTED ARTICLE

US Preventive Services Task Force. Screening for breast cancer: US Preventive Task Force recommendation statement

Ann Intern Med 2009;151:716–726.

Objective: To determine if screening with 1) film mammography, 2) clinical breast examination, 3) breast self examination, 4) digital mammography, and 5) MRI in average risk women 40 years or older reduces mortality from breast cancer.

Data Source: Data from Breast Cancer Surveillance consortium and the Cancer Intervention Surveillance Modeling Network (CISNET) Breast Cancer Modeling Group.

ISSN 1072-7515/13/$36.00
http://dx.doi.org/10.1016/j.jamcollsurg.2013.03.010

Data Extraction: Systematic review of 6 selected questions relating to the benefits and harm of screening and a decision analysis that used population modeling techniques to compare the expected health outcomes and resource requirements of starting and ending mammography screening at different ages and using annual vs biennial screening intervals.

Results: The US Preventive Services Task Force (USPSTF) recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and should take into account patient context, including the patient's values regarding specific benefits and harms (Grade C recommendation).

The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years (Grade B recommendation).

The UPSTF recommends against clinicians teaching women how to perform breast self-examination (Grade D recommendation).

Conclusion: The US Preventive Services Task Force (USPSTF) concludes that current evidence is insufficient to assess additional benefits and harms for screening mammography in women 75 years or older, clinical breast examination beyond screening mammography in women 40 years older, and digital mammography or MRI instead of film mammography as screening modalities for breast cancer (I statement).

Commentary: The 2009 US Preventive Services Task Force[1] (USPSTF) update recommended against routine screening mammography in women aged 40 to 49 and instead of annual recommended biennial screening of women aged 50 to 74. The basis for their changes stems from the perceived harms of screening, particularly in the 40 to 49 year age group. In response to a firestorm of protest from the media, patients, physicians, advocates, and national organizations (the American Cancer Society and others), on December 4, 2009 the USPSTF issued an addendum in which they advised that "the decision to begin regular biennial screening mammography" before age 50 should be individualized, based on "the patient's values regarding specific benefits and harms." The guidelines of most American organizations continue to recommend annual mammography starting at age 40. The Canadian Task Force on Preventive Health Care was even less enthusiastic about screening mammography, suggesting that screening women aged 50 to 74 biennially should also be individualized and that the interval could be every 2 to 3 years.[2] It all seems a bit confusing. This review will focus on the evidence that informs us on these screening mammography recommendations. The USPSTF paper also looked at other screening maneuvers, which will not be covered here.

The 2002 USPSTF recommendations[3] were based on a meta-analysis of 8 randomized controlled trials that showed a reduced relative risk (RR) of breast cancer death among all women invited to screening (RR 0.84), a comparable risk reduction for women under age 50 (RR 0.85), and that 1,224 women over 50 years of age would have to be invited to screening or 1,792 under age 50 to prevent 1 breast cancer death. These benefits accrued from multiple rounds of screening over many years in the trials. The USPSTF noted the risks and costs of screening, but concluded by recommending mammography for women age 40 and older every 1 to 2 years.

The 2009 guideline is largely qualitative; however, in order to update the recommendations, the USPSTF commissioned 2 quantitative analyses that were published at the same time. They attempt to inform on the balance between mortality reductions in screening mammography, specifically, initiation and cessation ages and frequency of tests (annually or biennially), and harms. The studies used an explicit and sensible process to identify, select, and combine evidence.

The first study was a systematic review by Nelson and colleagues,[4] which addressed 6 selected questions relating to the benefits and harms of screening. The review included additional follow-up of the original trials and incorporated the results of 2 other trials: the Gothenburg and UK Age trials. Specific questions addressed the effectiveness of mammography screening in decreasing breast cancer mortality among average-risk women aged 40 to 49 years and 70 years or older. The harms of screening mammography were also informed by a review and analysis of real patterns of care using clinical data provided by the Breast Cancer Surveillance Consortium.

The second study was a decision analysis by Mandelblatt and associates,[5] which used population modeling techniques to compare the expected health outcomes and resource requirements of starting and ending mammographic screening at different ages and using annual vs biennial screening intervals. They combined the results of 6 different models at 6 different centers. The resulting conclusions about the ranking of screening strategies were very robust among models, providing greater credibility than inferences based on a single model.

The primary benefit in cancer screening is mortality reduction, which can be reported in several different metrics. The study by Nelson and colleagues[4] commendably included relative mortality reduction, life years gained, and number needed to invite to screen to save a life.

A 15% relative risk reduction in breast cancer mortality sounds reasonable. However, the benefits of a "looking for a needle in a haystack" approach of screening in average risk individuals is better captured by a number needed to treat type metric: 1,792 women between the ages of 40 and 49 need to be invited to screen annually over many years to prevent 1 death from breast cancer. In calculating the mortality benefit, there is heated debate about whether all women invited to screen, as used in this study, or only women who are actually screened should be considered. The former provides outcomes that underestimate the benefit because not all women randomized to the screened group participate; the latter is problematic due to volunteer bias resulting in an overestimate of the benefit. A final issue to consider in reporting benefits is that most cancer screening studies use cancer-specific survival as their primary outcome rather than overall survival. It is conceivable that screening improves cancer-specific mortality but does not translate into an overall survival benefit. An interesting and controversial meta-analysis by Olsen and Gotzsche[6] showed no overall survival benefit in breast cancer screening studies; the benefit in breast cancer mortality from screening was negated by an increase in cardiac mortality related to radiotherapy. Using overall survival as the endpoint would require prohibitively large sample sizes in screening studies.

The harms of screening need to be considered as well. Overdiagnosis, the diagnosis of a cancer that would never cause symptoms or death, was not reported in this study. A footnote in the article by Mandelblatt and coworkers[5] mentioned that they considered this harm, but the numbers were believed to be too unreliable to report. Cost effectiveness is not part of the mandate of the USPSTF. Although breast cancer screening is cost effective, it is not cost saving,[7] and therefore could be seen as harm in terms of resource allocation. Information from the 2 commissioned studies helped to clarify the tradeoff of benefits (mortality reduction) and harms (number of screening mammograms, false positives, and unnecessary biopsies) because they varied by age of initiation and termination of screening and by screening interval. According to the Mandelblatt and colleagues'[5] analysis, a large proportion of the benefit (81%) of screening mammography is maintained by biennial screening. Changing from annual to biennial screening is likely to reduce the harm of mammography screening (false positive results and unnecessary biopsies) by nearly half. If the new recommendations are followed, screening 1,000 women aged 50 to 69 biannually would result in 8,944 mammograms, 780 false positives, and 55 unnecessary biopsies and avert 5.4 cancer deaths. Starting at age 40 years and screening annually would result in 3 additional cancer deaths averted but 3 times the activity as described. Similarly, Nelson and coauthors[4] reported that the number of mammograms, false positives, and biopsies required to diagnose a single cancer in the 40 to 49 age group requires almost twice as much activity as in any other breast screening age group to diagnose a cancer.

Although updated trial information and 2 new trials were used in the reanalysis, the trials examining screening for breast cancer are old and may not account for important recent developments. Advocates of screening might argue that current mammographic techniques are superior to those used in the trials so mortality outcomes should be better. Opponents of screening argue that the improvements in breast cancer survival on a population basis seen since the implementation of screening programs are largely related to improvements in systemic therapy, which came after screening was implemented, and we should abandon screening.[8,9]

Despite strong opinions regarding the benefits of breast cancer screening, there are no Grade A recommendations given to any of the breast cancer screening maneuvers, where there is high certainty that the net benefit is substantial. Overall, the findings of the USPSTF are evidence-based and the rationale to inform their recommendations is easy to follow. Their concluding recommendations and grade (strength of recommendation) regarding screening mammography are:

The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. This is a Grade B recommendation because there is moderate certainty that the net benefit is moderate and the service should be offered/provided.

The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms. This is a Grade C recommendation because there is moderate certainty that the net benefit is small, and the service should be offered/provided only if other considerations support it in an individual patient.

The USPSTF-commissioned studies and 2009 update laid a new foundation over which breast cancer screening is debated. This is a useful guideline and articulates potential benefits and harms of screening in concrete numbers that can be discussed with patients. Although the concept of early detection with screening is seen by many as a "no-brainer," the balance between harmful and beneficial effects in cancer screening is actually quite delicate. The USPSTF has done an excellent job of finding that balance. The recommendations are reasonable for clinical practice.

The Evidence-Based Reviews in Surgery Group Comprises:

Members of the EBRS Steering Committee

Nancy N Baxter MD, FACS, Toronto, ON, Canada
Karen J Brasel MD, FACS, Milwaukee, WI
Carl J Brown MD, Vancouver, BC, Canada
Prosanto K Chaudhury MD, Montreal, QC, Canada
Celia M Divino MD, FACS, New York, NY
Elijah Dixon MD, FACS, Calgary AB, Canada
G William N Fitzgerald MD, St Anthony, NL, Canada
S Morad Hameed MD, FACS, Vancouver, BC, Canada
Harry J Henteleff MD, FACS, Halifax, NS, Canada
Tyler G Hughes MD, FACS, McPherson, KS
Lillian S Kao MD, FACS Houston, TX
Andrew W Kirkpatrick MD, FACS, Calgary, AB, Canada
Steven Latosinsky MD, London, ON, Canada
Tara M Mastracci MD, Cleveland, OH
Robin S McLeod MD, FACS, Toronto, ON, Canada
Arden M Morris MD, FACS, Ann Arbor, MI
Timothy M Pawlik MD, FACS, Baltimore, MD
Larissa K Temple MD, FACS, New York, NY
Marg McKenzie RN, Toronto, ON, Canada

REFERENCES

1. U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2009;151:716–726.
2. Tonelli M, Gorber SC, Joffres M, et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. CMAJ 2011;183:1991–2001.
3. U.S. Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. Ann Intern Med 2002;137: 344–346.
4. Nelson HD, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727–742.
5. Mandelblatt JS, Cronin KA, Bailey S, G et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med 2009; 151:738–747.
6. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. Lancet 2001;358:1340–1342.
7. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst 2006; 98:774–782.
8. Welch HG. Screening mammography—a long run for a short slide? N Engl J Med 2010;363:1276–1278.
9. Gotzsche PC. Time to stop mammography screening? CMAJ 2011;183:1957–1958.