

CJS debate: Is mammography useful in average-risk screening for breast cancer?

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SUMMARY

Given the recent debate over breast cancer screening that was reignited by the 25-year follow-up data from the Canadian National Breast Screening Study, the *Canadian Journal of Surgery* commissioned a group of Canadian experts to debate the value of screening mammography. We discuss the Canadian study and summarize the arguments in favour of and against screening mammography for average-risk patients. We also provide summary recommendations for the use of mammography.

The recent publication of the 25-year follow-up data from the Canadian National Breast Screening Studies (CNBSS) has once again stirred the debate over breast cancer screening.¹ The CNBSS recruited almost 90 000 Canadian women in 6 provinces to 2 studies between 1980 and 1988. Women aged 40–49 years were randomized to physical breast exam and mammographic screening versus usual care (observation), while women aged 50–59 years were randomized to physical breast exam and mammographic screening versus physical breast exam screening. All women were seen at recruitment for a physical breast exam and were taught how to do a breast self-exam. Women were randomized independent of the clinical findings, and those who were randomized to mammographic screening had a mammogram at the time of recruitment. The usual care group aged 40–49 years was no longer seen, while the remaining screened groups were seen for 4 additional rounds of annual screening. The current CNBSS publication combined the 2 age groups in the analysis.

Two take-home messages were highlighted: there was no difference in survival among mammographically screened women and the control cohort, and screening mammography resulted in harm by overdiagnosing cancers in 22% of women.¹ The *Canadian Journal of Surgery* commissioned a group of Canadian experts to debate the implications of this study on mammography screening and challenged them to provide advice to the average-risk woman.

STRENGTHS OF THE CNBSS AND RESULTANT ARGUMENTS AGAINST MAMMOGRAPHIC SCREENING

The CNBSS by Miller and colleagues¹ is 1 of 8 randomized controlled trials^{1–8} evaluating mammography screening, each of which has its own methodological limitations. For this reason, CNBSS sought to overcome these using its individual patient-level randomization schema.

The CNBSS found that annual mammography in women aged 40–59 years does not reduce mortality from breast cancer beyond clinical breast exam or usual care.¹ Further analysis showed that screening mammograms picked up more cancers at a smaller size than did physical examination. The cancers found in the mammography-screened group, especially

those that were nonpalpable, had a much better prognosis than those found in the group that did not receive mammograms. However, it is important to remember that subgroup analyses using survival statistics are subject to lead-time bias, length bias and overdiagnosis. Miller and colleagues¹ have correctly reported breast cancer-specific mortality as the primary outcome.

Miller and colleagues¹ determined that the rate of overdiagnosis in the mammographically screened group was 22%. This represents the difference in mean number of cancers diagnosed in the screened versus unscreened cohorts over the 5-year intervention period. Overdiagnosis refers to “the possibility that a screen-detected cancer might not otherwise become clinically apparent during the lifetime of the woman.”²¹ Detection of these cancers turns women into patients, leads to unnecessary treatment and adversely affects quality of life. The CNBSS is one of the ideal studies to address this critical question.⁹ Of note, this estimate does not include ductal carcinoma in situ (DCIS), the incidence of which has increased 500% with the introduction of screening mammography and which now represents approximately 20% of breast cancers.¹⁰ The benefit of screening mammography is in finding smaller tumours that need less treatment (mastectomy or chemotherapy) for women whose cancers are screen-diagnosed. However, if this applies to fewer women than those who are overtreated for their screen-detected malignancies that might never have become clinically symptomatic, the benefits of screening should be questioned.

The radiology literature is harsh in its criticism of the latest CNBSS publication: “... an incredibly misleading analysis based on the deeply flawed and widely discredited Canadian National Breast Screening Study.”^{11,12} Much has been made of concerns that physical examination carried out before randomization may have resulted in an excess of patients with palpable cancers being assigned to the mammography arm of the CNBSS. Careful review of the literature shows that their concerns regarding the randomization have been addressed¹³ and are not shared by multiple expert panels from the various systemic reviews on mammographic screening.^{9,14-16} In fact, if anything, reviewers found that randomization was more fair and transparent in the CNBSS than in any of the other trials.^{14,16} Criticism of the quality of the imaging has also been addressed.¹⁷ Poor-quality mammograms represented a very small fraction of those in the study.¹⁸ Only 1 other randomized study has some form of mammographic quality documentation.¹⁹ Most other studies did 1- rather than 2-view mammography and/or had greater screening intervals of up to 3 years.

All of the randomized trials on mammographic screening have methodological issues that challenge their internal validity,^{9,14,16} while the time that has passed since

they were conducted challenges our ability to compare them to current practice. Screening advocates argue that current mammographic images are superior, so benefits should be greater. Screening opponents argue that improvements in breast cancer survival are associated with systemic therapy, which came into widespread use at the same time as screening.^{20,21}

If one doesn't accept the evidence from the CNBSS, what benefits and harms do exist? Recognizing these and other methodological issues, several expert panels have performed systematic reviews to assist in policy decisions. The Canadian Task Force on Preventive Health¹⁴ estimated that the relative risk reduction for breast cancer mortality in women aged 50–69 years who were screened for 11 years was 21%. Estimates from the Independent UK Panel on Breast Cancer Screening⁹ and the United States Preventive Task Force¹⁵ were similar at 19% and 20%, respectively. A 20% reduction in breast cancer mortality sounds good, but it is helpful to keep the absolute numbers of patients that this represents in mind. Extrapolating to a lifetime of screening for women aged 50–69 years, the UK Panel estimated that inviting 230 women to screen over a period of 20 years would result in 1 breast cancer death averted and 3 women overdiagnosed.⁹ These benefits (improved survival) are much smaller and the harms (biopsies and treatments undertaken) are larger than most women and physicians imagine.

The delicate balance of risks and benefits explains why none of the expert panels have strongly recommended screening mammography. For women aged 50–69 years, the Canadian Task Force gives screening with mammography a weak recommendation with evidence of moderate quality,²² while the US Task Force gives a grade B recommendation owing to the moderate certainty that the net benefit is moderate.²³ Increasingly, consensus statements stress the importance of clear communication with individual women about the harms and benefits of screening.

LIMITATIONS OF THE CNBSS AND RESULTANT ARGUMENTS IN FAVOUR OF SCREENING MAMMOGRAPHY

The CNBSS is a randomized study that reported no difference in mortality attributed to screening mammography;²² however, it is important to look only at outcomes from cancers diagnosed during the study period, since breast cancers diagnosed during the decades following the 5-year intervention period cannot and should not be attributed to any perceived benefit from brief mammography screening. When comparing cancer-specific mortality (or conversely, survival) from cancers diagnosed in both groups during the 5-year mammography study period, there was a statistically significant 25-year survival for women in the mammography arm

of 70.6% versus 62.8% in the control arm ($p = 0.02$). When comparing women for whom the mammogram diagnosed a nonpalpable tumour (the intent of routine screening mammography), the survival was 79.6% versus 62.8% ($p < 0.001$). This study therefore found a statistically significant improvement in survival among women with mammographically versus palpably detected cancers of greater than 27%.

It is accepted that tumour size is correlated with clinical outcome,^{11,22} supported by the finding that nonpalpable tumours in this study were associated with a significantly improved survival. The mean tumour size identified in this study was 2.1 cm for clinically palpated cancers versus 1.9 cm in the mammography cohort. With the advent of digital imaging, it is expected that the size of image-detected cancers will become smaller over time. The rationale for advocating any screening test is to identify disease in its earliest stage,²⁰ presuming that an early diagnosis interrupts disease progression before it becomes advanced or metastatic. Reduced tumour size at diagnosis results in fewer patients requiring chemotherapy and mastectomy, a clinically meaningful outcome for these patients.

Although the CNBSS methodology is likely one of the fairest designs of any mammography trial, the randomization schema remains one of its methodological shortcomings.²⁴ Patients underwent a breast examination by a study nurse, and therefore both would have been aware of the findings from this examination. They were then randomized at each centre to either the treatment or the control arm.¹ Imaging researchers directly involved in the study have described the randomization schema as “open book sequential registration” design entered manually by the nurse locally in a log book, and therefore subject to bias due to the physical examination (M. Yaffe, Cambridge, Canada, personal communication, 2015). The authors recognized and addressed this bias in favour of putting more palpable breast cancers into the mammography arm by excluding the first year of breast cancers, since almost 50% more cancers were diagnosed in the mammography arm than the control arm. This cannot be attributed to chance alone. Unfortunately there was no adjustment for cancers diagnosed in the second year (prevalent cancers not identified by poor quality analogue mammograms during the first year), where 23% more cancers were identified in the mammography arm — again, much more than would be expected by chance alone. By discounting the unequal distribution of prevalent cancers in years 1 and 2, the difference between treatment arms remained stable at 15% more cancers per year diagnosed in the mammography screening cohort than the control cohort (years 3–5).

A second source of criticism of this study was that mammograms were of poor quality.^{11,25} Although the CNBSS authors mentioned that mammogram quality was appro-

priate for that time period, imaging scientists involved in this study have criticized the quality of the images, even for the time period of the study.^{26,27}

While it is widely accepted that some early breast cancers identified by screening imaging may represent a subset of disease that would not otherwise progress or result in clinically relevant disease (resulting in overdiagnosis), we remain unable to identify which patients belong to this group. Overdiagnosis rates can be calculated in screening tests only when enough follow-up time has occurred to allow any clinically relevant cancers to be clinically detected.¹ Miller and colleagues¹ calculated an overdiagnosis rate of 22% at the end of the 5-year study period, which was seen to persist at 15 years as an annual rate of overdiagnosis; however, without following these individual cases for several years, it is difficult to confirm which of these cases might become clinically relevant in subsequent years or decades. In this study, this rate could be recalculated to adjust for bias in the mammography arm to 15% (the mean difference in the number of cancers diagnosed between the screened and unscreened cohorts when the unequally distributed prevalent cancers diagnosed during the first 2 years are not counted), not 22% as quoted by CNBSS. This risk of overdiagnosis needs to be contrasted to the 27% improvement in breast cancer-specific survival in the mammographically detected cancer cohort of average-risk women. The solution to this dilemma is not to eliminate screening, with its associated improved survival for women overall, in order to avoid overdiagnosing a small proportion of them, but rather to continue to engage in clinical trials to determine better methods of stratifying patients who can be followed by active surveillance, as has been the method adopted for prostate cancer patients.

WHAT CAN WE AGREE ON?

There have been 8 randomized controlled trials^{1–8} evaluating screening mammography, including the CNBSS,¹ 4 of which were from Sweden.^{3,4,6,7} Except for the HIP trial⁵ (1963) and the AGE trial⁸ (1991), like the CNBSS, all were initiated in the 1970s and 1980s. Major methodological differences in study design included unselected populations versus prescreened volunteers, age groups that were screened, true versus quasirandomization, 1- versus 2-view mammography, the use of physical examination versus usual care (observation) as a control, screening interval range from 12 to 33 months, the number of screening rounds from 2 to 9 and the duration of follow-up reported between 10 to 25 years.^{15,25} The CNBSS was designed purposefully to overcome as many potential limitations in prior studies as possible.

The forgoing arguments highlight the divergent views that exist regarding breast screening. Mammography

screening at any age is a tradeoff of benefits and harms. For a moment let's consider what is agreed upon.

No jurisdiction, agency or society recommends screening average-risk women before the age of 40 years. There is little support for screening average-risk women between the ages of 40 and 49 years. While the US Preventative Services Task Force—commissioned meta-analysis¹⁵ suggested a small survival advantage for women aged 40–49 years, the advantage is offset by an excessive number needed to screen, call-back rates, negative biopsies, and the potential for overdiagnosis. This same 40–49 age group was a large part of the Baines cohort in the CNBSS 25-year update,¹ and neither the Canadian Task Force¹¹ nor the Independent UK Panel⁹ recommends screening in this age group.

Both Task Forces and the Independent UK Panel endorse, with minor variations, screening for average-risk women aged 50–69 years owing to fewer callbacks and a more reasonable number needed to screen to prevent a breast cancer death. The Canadian Task Force emphasizes that the absolute mortality benefits are small, and therefore a greater effort needs to be made to provide women with information about the harms versus benefits in this decision and not just provide encouragement to screen. The UK Independent Panel also discusses the need for clear communication of these harms and benefits. In clinical practice, women can be directed to either the decision aid for breast cancer screening from Health Canada²⁸ or posters from the Canadian Task Force.²⁹

There is little support for screening average-risk women older than 74 years. Competing morbidities would increase the harms of screening and make it difficult for screening mammography to provide a survival advantage among older women. However, this group has not been adequately studied.

In North America, the Canadian Preventative Screening Task Force,²² Canadian Cancer Society,³⁰ and the latest 2015 draft recommendations from the US Preventative Services Task Force³¹ all support the recommendations outlined here. Currently only the National Comprehensive Cancer Network (NCCN) and American Cancer Society³² continue to recommend annual screening for all average-risk women beginning at age 40 years.

It is unlikely that breast cancer screening programs will disappear soon, based on the CNBSS update. Heightened awareness of the issues it raises about the value of screening should, however, translate into changes in screening practices. Screening programs should reassess the aggressiveness of their recruitment strategies and uptake targets and make greater efforts to provide informed choice. Screening outside the age guidelines of 50–74 years should decrease. Future research could focus on better stratification of women who might benefit from screening.

Finally, based on our experience with screening mammography, we should avoid systematic implementation of other breast screening modalities (e.g., screening ultrasonography and magnetic resonance imaging) unless rigorously evaluated in a prospective fashion.

RECOMMENDATION

For women at average-risk for breast cancer, screening mammography is

- not recommended before age 40 years,
- not recommended between ages 40 and 49 years,
- recommended between ages 50 and 74 years, and
- not recommended after the age of 74 years unless more evidence becomes available.

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References

1. Miller AB, Wall C, Baines CJ, et al. Twenty-five year follow-up for breast cancer incidence and mortality of the Canadian national breast screening study: randomised screening trial. *BMJ* 2014;348:g366 10.1136/bmj.g366.
2. Alexander FE. The Edinburgh randomized trial of breast cancer screening. *J Natl Cancer Inst Monogr* 1997;22:31-5.
3. Bjurstam N, Björneld L, Warwick J, et al. The Gothenburg breast screening trial. *Cancer* 2003;97:2387-96.
4. Andersson I, Janzon L, Sigfusson BF, et al. Mammographic breast cancer screening — a randomized trial in Malmö, Sweden. *Maturitas* 1985;7:21-9.
5. Shapiro S. Periodic screening for breast cancer: the HIP randomized controlled trial. Health Insurance Plan. *J Natl Cancer Inst Monogr* 1997;22:27-30.
6. Frisell J, Eklund G, Hellström L, et al. Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. *Breast Cancer Res Treat* 1987;9:219-25.
7. Duffy SW, Tabar L, Fagerberg G, et al. Breast screening, prognostic factors and survival — results from the Swedish two county study. *Br J Cancer* 1991;64:1133-8.
8. Moss SM, Cuckle H, Evans A, et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006;368:2053-60.
9. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778-1786.
10. Kerlikowske K. Epidemiology of ductal carcinoma in situ. *J Natl Cancer Inst Monogr* 2010;2010:139-41.
11. American College of Radiology. BMJ article on breast cancer screening effectiveness incredibly flawed and misleading. Available: www.acr.org/News-Publications/News/News-Articles/2014/ACR/BMJ-Article-on-Breast-Cancer-Screening-Effectiveness-Incredibly-Flawed-and-Misleading (accessed 2014 Apr. 8).
12. Canadian Association of Radiology. National association of radiologists

- continues to support the use of mammograms regardless of recent report. Available: www.car.ca/uploads/News%20Publications/CAR_Statement_Mammography_Support_20140213.pdf (accessed 2014 Apr. 18).
13. Bailar JC III, MacMahon B. Randomization in the Canadian national breast screening study: a review for evidence of subversion. *CMAJ* 1997;156:193-9.
 14. Canadian Task Force on Preventive Health Care. Breast cancer screening systematic review. Available: <http://canadiantaskforce.ca/wp-content/uploads/2012/09/Systematic-review.pdf?414ed1> (accessed 2014 Apr. 18).
 15. 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;151:727-37.
 16. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013;6:CD001877
 17. Baines CJ, Miller AB, Kopans DB, et al. Canadian national breast screening study: assessment of technical quality by external review. *AJR Am J Roentgenol* 1990;155:743-7, discussion 748-9.
 18. Miller AB. Canadian national breast screening study: response. *CMAJ* 1993;149:1374-5.
 19. Fletcher SW, Black W, Harris R, et al. Report of the international workshop on screening for breast cancer. *J Natl Cancer Inst* 1993;85:1644-56.
 20. Gotzsche PC. Time to stop mammography screening? *CMAJ* 2011;183:1957-1958.
 21. Welch HG. Screening mammography — A long run for a short slide? *N Engl J Med* 2010;363:1276-1278.
 22. Canadian Task Force on Preventive Health Care, Tonelli M, Connor Gorber S, et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ* 2011;183:1991-2001.
 23. US Preventive Services Task Force. Screening for breast cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2009;151:716-26.
 24. Swift D. Will better treatment phase out breast screening? *The Medical Post* 2014;March 11:10-11.
 25. Kopans D. The Canadian screening program: a different perspective. *AJR Am J Roentgenol* 1990;155:748-9.
 26. Yaffe M. Correction: Canada study. *J Natl Cancer Inst* 1993;85:94.
 27. Yaffe M. The facts about breast cancer screening and the Canadian national breast screening study (CNBSS). Available: www.mammographyed.com/Resources/15266/FileRepository/Canadian%20Research%20Feedback/Yaffe_RevisedCNBSS_Report_2014.pdf (accessed 2014 Apr. 8).
 28. A decision aid for breast cancer screening in Canada. Available: www.phac-aspc.gc.ca/cd-mc/pdf/Information_on_Mammography-eng.pdf (accessed 2014 Apr. 22).
 29. Canadian Task Force on Preventive Health Care. Breast cancer screening risks vs. benefits poster: for ages 50-69. Available: http://canadiantaskforce.ca/wp-content/uploads/2012/10/versionf4_5069.pdf?414ed1 (accessed 2014 Apr. 18).
 30. Screening for breast cancer. Canadian Cancer Society. Available: www.cancer.ca/en/cancer-information/cancer-type/breast/screening/?region=on (accessed 2015 Apr. 20).
 31. US Preventative Services Task Force 2015 draft recommendations. Available: www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementDraft/breast-cancer-screening1 (accessed 2015 Apr. 30).
 32. American Cancer Society recommendations for early breast cancer detection in women without breast symptoms. American Cancer Society. Available: www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-recs (accessed 2015 Apr. 20).