By Dr M Brackstone

Debating the value of mammography screening in average risk women following the publication of 25-year follow-up in the Canadian National Breast Screening Study

INTRODUCTION

On the heels of a change in breast cancer screening recommendations for average risk women by the Canadian Task Force on Preventive Health Care in 2011, reducing the recommended screening interval to once every two years from ages 50-74 [1], the debate regarding the benefits of screening mammography in Canada reignited. The Canadian National Breast Screening Study (CNBSS) was published in 2014 by Miller *et al.* [2] which, rather than clarifying the issue, prompted further debate. Physicians seem more divided than ever regarding the interpretation of this study and whether it supports or refutes the value of screening mammography for average risk women [3].

SUMMARY OF THE CANADIAN NATIONAL BREAST SCREENING STUDY

The CNBSS was a Canadian multi-centered randomized clinical trial conducted in 15 screening centres in six provinces across Canada from 1980-1988. A total of 89,835 women participated, into two separate studies that were later merged for this 25-year publication. The first study involved almost 50,000 women aged 40-49, who underwent a physical examination by a study nurse and were then randomized to 'usual care' (meaning no formalized screening) or 'mammography' (meaning annual mammogram plus physical examination for five years). The second study involved almost 40,000 women aged 50-59, who likewise underwent a physical examination by a study nurse and were then randomized to 'physical examination' (annual physical examination only for five years) or 'mammography' (annual mammography and physical examination for five years). Following the five years of screening, the women were returned to usual care with their physicians and were not seen again.

One of eight randomized controlled trials evaluating mammography screening, the CNBSS is probably one of those with the most rigorous design, with individual level randomization and comprehensive follow-up. Whether any breast screening was performed in any of the women following the five year period was not known.

During the five-year screening period, 1190 breast cancers were detected in both age cohorts (666 in the mammography arm and 524 in the control arm). Of note, an additional 5193 breast cancers were diagnosed in the 20 subsequent years without screening (2584 in the mammography arm and 2609 in the control arm). After 25 years, there was no significant difference in overall cumulative breast cancer-specific mortality between the screened and control arms. There was, however, a significant reduction in breast cancer-specific mortality associated with mammography screening in the first year (prevalent cancers) but not in the subsequent years 2-5 (incident cancers). When comparing survival rates, there was a significant difference in the 25-year survival for women with breast cancer detected in the mammography arm compared with the control arm (70.6% versus 62.8%). This difference is more pronounced when comparing the non-palpable cancers diagnosed in the mammography arm (79.6% versus 62.8%) with a significant improvement in survival in non-palpable versus palpable cancers, which many would feel represents the intended benefit of screening prior to palpability.

A number of concerns regarding the design of the study and potential limitations of its findings were vigorously debated among breast imagers, surgeons and policy makers. Although the 'open book sequential randomization' was done locally by each site coordinator, there were

The author:
Muriel Brackstone MD, PhD, FRCSC
Surgical Oncologist & General Surgeon
London Regional Cancer Program
Director, London Breast Care Clinic
Director, London Tumour Biobank
Associate Professor, Depts of Surgery & Oncology
Western University, London ON CANADA
email: muriel.brackstone@lhsc.on.ca

concerns raised that the process was not independent of the physical examination, since in the first year there were almost 50% more cancers diagnosed in the mammography arm versus the control arm, which cannot be attributed to chance alone. There were 23% more cancers diagnosed in the mammography arm in year 2, and then cancer diagnosis rates stabilized at 15% more cancers per year in the mammography arm versus the control arm. This difference in diagnosis may in part represent what some term 'over-diagnosis' and others call 'over-detection' of clinically irrelevant cancers [4].

Although tumors diagnosed in the mammography arm were smaller than in the control cohort (1.9 cm versus 2.1 cm, with no significant difference in lymph node positivity rates between the two arms), the quality of mammograms have significantly improved since the 1980s, particularly with the advent of digital mammography. It is accepted that tumor size is correlated with clinical outcome, not only in survival but also in reduced treatment (less need for mastectomy and lower rates of chemotherapy). It has been argued that digital mammography will reduce the size of image-detected cancers even further, perhaps providing additional benefits not captured by this study [4]. Given that sixty-eight percent of all cancers diagnosed were palpable, the benefits of screening could therefore only have been truly evaluated in the remaining one third of cancers, and that the technical limitations at the time of the study prohibited an effective evaluation of the imaging modality currently in use [5].

CONCLUSIONS

The balance between improving early detection and diagnosis of clinically meaningful breast cancers and risking over-detection of clinically irrelevant cancers continues to elude us, and neither one should fully trump the other. Ideally, improved imaging, genomic or phenotypic signatures need to be developed to differentiate high from low risk cancers so that patients can be treated accordingly. It is likely that the treatment of breast cancer in the future will mimic that of prostate cancer with the adoption of watchful waiting for low risk cancers. In the interim, a discussion with patients about the risks and benefits of screening mammography continues to be important and should be individualized.

SUMMARY RECOMMENDATIONS FOR BREAST SCREENING

Authors of the CNBSS argued that a 5-year screening intervention failed to significantly impact on breast cancer-specific mortality at 25 years and should therefore be abandoned in average risk women. Perhaps given the limitations outlined above, the Canadian Preventative Task Force guidelines have not changed. A polarization has developed in the medical literature however, with surgical oncologists who treat these patients endorsing annual screening beginning at the age of 40 [6]. This is in recognition of what is felt to be a smaller but persistent improvement in breast cancer-specific survival among screened versus unscreened women aged 40-49, even if not cost-effective and associated with a higher number needed to treat. In contrast, policy advocates have quoted the CNBSS study as evidence that such universal population-based screening is associated with significant harms such as false positive findings, over-diagnosis, unnecessary treatment and psychological distress and should therefore be abandoned [7].

The recommendation of the Canadian Task Force on Preventive Health Care, reducing the recommended screening interval to once every two years from ages 50-74 has re-ignited the debate in Canada regarding the benefits of screening mammography. .

On the whole, our debate [3] determined that the evidence from the CNBSS study did not impact the current Canadian guidelines (offering screening mammography to average risk women starting at the age of 50 and every 2 years until age 74), which should be continued in the absence of better stratification for low and high risk among these early detected cancers.

REFERENCES

[1] 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).

[2] 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.

[3] Brackstone M, Latosinsky S, Saettler E, George R. CJS debate: Is mammography useful in average-risk screening for breast cancer? Can J Surg 2015; DOI: 10.1503/cjs.017514.

[4] 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).

[5] Heywang-Kobrunner SH, Shreer I, Hacker A, Noftz MR, Katalinic A. Conclusions for mammography screening after 25-year follow-up of the Canadian National Breast Screening Study (CNBSS). Eur. Radiol. 2015 May 28 [epub ahead of print].

[6] Van Zee KJ, Hansen NM, Barrio AV, Connor CS, Danforth DN, Euhus DM, Kulkami SA, McCready DR, McLaughlin S, Wilke LG. Commentary on the Canadian National Breast Screening Study. Ann Surg Oncol. 2014; 21(13):4397-4398.

[7] Kearney AJ. Viewpoint: Is it time to reconsider policy for population-based mammography screening. J. Public Health Policy. 2015;36(3):259-269.