CJS Debate: Mammography is useful in average risk screening for breast cancer

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Abstract: Given recent debate over breast cancer screening 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. This manuscript summarizes the arguments in favour of and against screening mammography for average risk patients. Summary recommendations for the use of mammography are provided.

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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 with the media emphasizing 2 take-home messages: 1) there was no difference in survival among mammographically screened women when compared with the control cohort and 2) screening mammography resulted in harm by over-diagnosing cancers in 22% of women [1]. The Canadian Journal of Surgery commissioned a group of Canadian experts to debate the issue and challenged them to provide advice to the average-risk woman.

Arguments in favour of screening mammography

One of the fatal flaws repeatedly quoted in studies evaluating screening tests, particularly mammography, is that "If screening does not reduce the occurrence of advanced cancers, it does not work."[2] This qualifying statement refers to patients presenting with large primary breast tumours (locally advanced non-metastatic breast cancer) and presumes that the development of advanced breast cancer is a linear progression of early disease, which grows in compliance with tumour growth kinetics.[3] If this were the case, early disease should be visible on a screening imaging test years before its presentation as a larger mass. There is no clinical evidence to support this presumption. More likely is that locally advanced breast cancer represents a subset of heterogenous diseases, as evidenced by their frequent presentation as 'interval cancers' and rapid growth in size. Locally advanced breast cancers represent up to 15% of all breast cancers and the inability of a screening program to reduce the incidence of these cancers does not equate to a failure of the screening tool to identify early breast cancers.

This study represents the first randomized controlled trial to report a lack of survival attributed to screening mammograph,[4] however the data presented by this study does not support this conclusion.

The average life expectancy of a 50 year-old woman at the time this study was conducted (early 1980s) was 81.[5] Twenty-five year follow-up of this study means that many women in this study would be in their mid 80s, where the majority of their age cohort would have already died, however when looking only at survival from cancers diagnosed during the 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 non-palpable tumour (the intent of routine screening mammography), the survival was 79.6% vs 62.8%

($p < 0.0001$). This study found a statistically significant improvement in survival among mammographically versus palpably detected cancers of greater than 27%.

One of the main criticisms of this study was that mammograms were of poor quality.[6,7] Even the imaging scientists involved in this study during the active phase of this study have criticized the quality of these images, even for the time period of the study.[8,9]

It remains accepted that tumour size is correlated with clinical outcome,[4,7] supported by the finding that non-palpable 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 1.91 cm in the mammography cohort, however currently approximately 30% of tumours diagnosed are now less than 1 cm,[10] The reduced tumour size at diagnosis results in fewer patients requiring chemotherapy and mastectomy, which should also be considered a clinically meaningful outcome for patients.

One of the most challenging methodological flaws of this study was the randomization schema,[11] 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 to either treatment arm. 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, where there was almost 50% more cancers diagnosed in the mammography arm versus 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 analog mammograms during the first year), where 23% more cancers were identified in the mammography arm. By

discounting the unequal distribution of prevalent cancers, the difference between treatment arms is actually stable at 15% per year (years 3–5).

The 'over-diagnosis' referred to in this study is calculated by the authors as the increased number of cancers diagnosed in the mammography arm compared with the control arm. However, if mammograms are identifying cancers earlier in time than in the control arm, one should look at the differences in years 6–10, where there were 8% more cancers diagnosed in the control arm. This excess in cancers diagnosed in the control arm can only be attributed to cancers not already diagnosed in the mammography arm, therefore the absolute 'over-diagnosis' resulting from mammography cannot be attributed to any more than 15% – 8% = 7%.

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, we remain unable to identify which patients belong to this group. The solution to this dilemma is not to eliminate screening with its associated improved survival for all average-risk women in order to avoid over-diagnosing a small proportion of these, 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.

Arguments against mammographic screening

The CNBSS found that annual mammography in women aged 40–59 does not reduce mortality from breast cancer beyond clinical breast exam or usual care. The message has not changed from previous publications of the CNBSS with shorter follow-up starting in 1992.[12-14] Miller and colleagues have correctly reported breast cancer specific mortality as the primary outcome. They also provide descriptive sub-analyses, including

comparisons of mammographically detected versus palpable cancers and cancers detected only during the study period, which should not be over interpreted as they are subject to lead-time bias, length bias and over-diagnosis.

What is new is that there is now sufficient follow-up to determine that the rate of over-diagnosis in the mammographically screened group is 22%. Over-diagnosis is the finding of "disease" that will never cause symptoms or death during a patient's lifetime. Detection of these cancers turns women into patients, leads to unnecessary treatment and adversely affects quality of life. There are various methods for expressing over-diagnosis depending on the question of interest, which explains some of the variation in estimates. The CNBSS is one of the ideal studies to address this critical question.[15]

The Canadian Association of Radiology[7] endorses the American College of Radiology's unfortunate comments regarding the CNBSS; "… (the recent publication) is an incredibly misleading analysis based on the deeply flawed and widely discredited Canadian National Breast Screening Study."[16] Careful review of the literature shows that their concerns regarding the randomization have been addressed[17] and are not shared by multiple expert panels from the various systemic reviews on mammographic screening [15, 18,19,20]. In fact, if anything reviewers found that randomization was fairer and more transparent in the CNBSS than in any of the other trials.[18,20] Criticism of the quality of the imaging has also been addressed.[21] Poor quality mammograms represented a very small fraction of those in the study.[22] Only one other randomized study has some form of mammographic quality documentation.[23] Most other studies did one 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,[15,18,20] 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 due to systemic therapy, which came into widespread use at the same time as screening.[2,24]

If you don't believe 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 Health[18] estimated that the relative risk reduction for breast cancer mortality in women aged 50–69 screened for 11 years was 21%. Estimates from the Independent UK Panel on Breast Cancer Screening[15] and the United States Preventive Task Force[19] were similar at 19% and 20% respectively. A 20% reduction in breast cancer mortality sounds good, but screening a healthy population for cancer is a bit like looking for a needle in a haystack. The Canadian Task Force estimates that if 720 women screened for 11 years one breast cancer death would be prevented. Of those, 204 would have a false-positive mammography result, 26 would have an unnecessary biopsy and at least 4 would be over-diagnosed. Extrapolating to a lifetime of screening for women 50–69 the UK Panel estimated that inviting 230 women to screen over 20 years would result in 1 breast cancer death averted and 3 women over-diagnosed.[15] These benefits are much smaller and the harms 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 50–69 the Canadian Task Force gives screening with mammography a weak recommendation with evidence of moderate quality, [4] while the US Task Force gives a grade B recommendation due to the moderate certainty that the net benefit is moderate.[25] Increasingly, consensus

statements stress the importance of clear communication with individual women about the harms and benefits of screening.

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. The decision aid for breast cancer screening from Health Canada[26] and posters from the Canadian Task Force[27] are a good start. Screening outside the age guidelines 50–74 should decrease. Finally, the less than spectacular results of screening mammography should call for more rigorous evaluation of other techniques like screening ultrasound and MRI before their widespread implementation.

Summary

The forgoing arguments highlight the divergent views that exist regarding breast screening. 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. Most recommend screening only from the age of 50.

The Canadian Task Force on Preventative Health Care (CTFPHC),[4] the US Preventative Services Task Force (USPSTF),[19] and the UK Independent Panel on Breast Cancer Screening[5] all endorse with minor variations screening for average risk women ages 50–69.

While the USPSTF commissioned meta-analysis suggested a small survival advantage for women age 40–49, most accept that advantage is negated by an excessive

number of women needed to treat (NNT), higher call back rates, negative biopsies, and the potential for over diagnosis.

This same 40–49 age group was a large part of the Baines cohort in the CNBSS 25 year update,[1] and represents the age group that neither of the Task Forces or the UK independent panel recommends for screening.

The task forces (Canadian and US) as well as the UK independent panel prudently focus on the cohorts with fewer callbacks (ie lower false positive rates) and more reasonable NNT's for their screening recommendations.

In summary, mammography screening recommendations for average risk women arising from arguments raised by this expert panel is provided below.

Recommendation:

1. Screening average risk women below age 40 and between age 40–49 with mammography is not recommended on the basis of an excessive NNT, high call back rates, negative biopsies, and potential over treatment. Physical examination alone is recommended.
2. Screening age 50–69 is recommended for average risk women at the current recommended interval of 2 years. They too will experience some of the negative effects mention above, but most expert panels accept the benefits outweigh the risks for this population. Women need to understand the risks as well as the benefits.
3. Screening older patients has less data from which to reach a conclusion. Competing morbidities and causes of death have made it difficult to demonstrate a clear survival advantage among older populations. Screening tailored to the individual is recommended.

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