COMMENTARY

Optimizing Canadian Breast Cancer Screening Strategies: A Perspective for Action

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ABSTRACT

While controversies regarding optimal breast cancer screening modalities, screening start and end ages, and screening frequencies continue to exist, additional population-based randomized trials are unlikely to be initiated to examine these concerns. Simulation models have been used to evaluate the efficacy and effectiveness of various breast cancer screening strategies, however these models were all developed using US data. Currently, there is a need to examine the optimal screening and treatment policies in the Canadian context. In this commentary, we discuss the current controversies pertaining to breast cancer screening, and describe the fundamental components of a simulation model, which can be used to inform breast cancer screening and treatment policies.

Key words: Breast cancer; screening controversies; screening strategies; simulation; model components

La traduction du résumé se trouve à la fin de l'article.

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In 2011, an estimated 23,400 Canadian women developed breast cancer and approximately 5,100 women died of the disease, making breast cancer the second most commonly occurring cancer and the second leading cause of cancer mortality (second to lung cancer) among Canadian women.[1] Several randomized trials and meta-analyses have demonstrated that screening for breast cancer is associated with a reduction in breast cancer mortality for women aged 40 to 74 years;[2-6] however, results from other randomized trials[7] and meta-analyses[8-10] did not reach statistical significance. Thus, controversy regarding the benefit of screening and optimal screening strategies continues to exist.

Screening controversies

Concerning screening efficacy, several Swedish trials have examined the impact of mammography on mortality reduction in comparison to no screening, and found that mammographic screening was associated with a statistically significant reduction in breast cancer mortality among women aged 40 to 74 years, ranging from 21 to 31%.[7,11] However, a study that examined the benefit of mammography in addition to other screening strategies (e.g., physical breast examination) found that the addition of mammography had no impact on breast cancer mortality,[12] raising questions regarding the optimal screening instrument.

Moreover, although results from the Swedish trials mentioned above demonstrated a borderline statistically significant 20% reduction in breast cancer mortality among women aged 40 to 49 years,[7] the results of trials that were designed specifically to examine the benefit of mammography among younger women provide less optimistic results. The UK Age Trial[13] recruited women 39-42 years of age and found that mammography was associated with a non-statistically significant 17% reduction in breast cancer mortality after 10 years of follow-up. Similarly, the CNBSS I* trial,[14] which randomized women aged 40-49 years either to receive annual mammography and physical breast examination, or to receive a single physical breast examination and instruction on how to conduct self-breast examination, found no reduction in breast cancer mortality after 11 to 16 years of follow-up.

Finally, there is also uncertainty regarding screening frequency. This is demonstrated by recent changes to guidelines made by the Canadian Task Force on Preventive Health Care (CTFPHC), which changed its recommendation that average-risk women 50-69 years of age should receive mammography annually, to a recommendation that women 50-74 years of age should only receive mammography every 2 to 3 years.[15]

As a result of the doubts concerning key aspects of breast cancer screening policies, optimal screening strategies continue to remain a topic of considerable debate, and an extremely important public health issue. However, as it is unlikely that additional randomized trials will be initiated to address remaining gaps in knowledge (due to financial constraints, and the time that such trials would take to reach an outcome), simulation studies provide an important tool for examining questions concerning both the efficacy of screening instruments, and optimal screening strategies pertaining to start and end ages and screening frequency for Canadian women.

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Simulation model as a decision-informing tool

Several simulation studies have been initiated to examine these questions (e.g., those conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET)[16-21]), however these models were all based on US data, and accordingly there is currently a paucity of research that has examined the optimal screening and treatment policies in the Canadian context. The studies conducted by the CISNET collaboration,[16-21] however, provide valuable insight regarding ways in which simulation can be used to elucidate gaps in knowledge pertaining to Canadian screening policies. Common components considered by the CISNET models and simulation studies conducted by other researchers[22] include population, natural history, screening and treatment components. If a cost-effectiveness analysis is the objective, financial considerations are also taken into account. The remainder of this commentary will highlight important considerations for each of these components, which may help inform methodological considerations for possible simulation studies using Canadian estimates.

Model components

Population Component

This component determines how the model builds the initial cohort of women, and how they will be followed over time. Considerations within this component include whether to simulate a birth cohort or a cohort of adult women; the size of the population of women to be simulated; the age group of women for whom outcomes will be generated; the length of time they will be followed; and whether a closed population, or a dynamic population incorporating new births, deaths and immigration/emigration, will be simulated. Finally, the decision to account for regional demographic differences between provinces will also need to be considered. Previous models have used varying approaches, and decisions will largely be based on available data sources.

Natural History Component

This component determines how the biological nature of breast cancer will be modeled. Considerations within this component include whether to model ductal carcinoma in-situ (DCIS), or restrict outcomes to invasive breast cancer only. Next, the staging system used will need to be considered. The simplest model is the four-stage model of no detectable breast cancer, preclinical phase, clinical phase, and death from breast cancer (one can also include death from other causes, creating a 5-stage model). Other researchers have opted to use the SEER† staging TNM system‡ of in-situ, local, regional, or distant,[18,20,21] while still others[22] chose to stage breast cancer according to the American Joint Committee on Cancer staging (AJCC) system of 0 (in-situ), I, II, III, IV. Furthermore, it is important to note that all of the CISNET models included estimates according to estrogen receptor (ER) status. This is based on the understanding that ER status will influence treatment determination, as only ER-positive women will be administered hormonal therapy. However, while Canadian breast cancer incidence estimates by ER status are not available, it may be appropriate to assume SEER estimates will closely reflect Canadian estimates.

† SEER=Surveillance Epidemiology and End Results.

‡ TNM staging system=Based on extent of the tumour (T), whether cancer cells have spread to nearby lymph nodes (N), and whether distant metastasis (M) has occurred.

Screening Component

This component determines the start and end ages at which women will receive screening, along with the screening interval. The details of the screening policy will be dependent on the research question under consideration. Based on the gaps in knowledge described above, important research questions to be examined include optimal screening start and end ages, screening intervals, and the benefits of stratifying screening strategies by age. Furthermore, the efficacy of various screening instruments can be examined, along with the benefits of dual screening modalities (e.g., physical breast examination in addition to mammography). However, regardless of which screening strategy is selected for modeling, screening adherence should be taken into consideration. Previous studies have used various estimates of adherence ranging from actual adherence rates to assuming 100% screening and treatment adherence. This will influence whether the actual or potential efficacy of the strategy in question is being examined. Furthermore, test sensitivity and specificity should also be taken into consideration. The simplest approach is that used by Hunter et al. (2004), who used fixed sensitivity and specificity estimates of 88% and 96%, respectively (based on data from the organized breast cancer screening program).[22] However, this does not take into account that mammography sensitivity is age- and tumour size/stage-dependent. Accordingly, a more robust approach would be to use the strategy adopted by Ahern and Shen (2009),[23] who modeled mammography sensitivity according to age and tumour size using a logit model, where the coefficients were determined using published estimates.[24]

Treatment Component

This component determines how treatment for women who are diagnosed with breast cancer will be administered. Although not all models include a treatment component (i.e., those interested in examining the effectiveness of a screening policy assuming 100% adherence to treatment), taking into consideration that screening can only reduce mortality when a true-positive result is followed by timely effective treatment, all of the CISNET models examined the effectiveness of various screening strategies in addition to the administration of adjuvant therapy (tamoxifen, chemotherapy, or both; administration of therapy was age-, stage- and ER status-dependent). The benefits of treatment in the CISNET models were based on published hazard ratios provided by the Early Breast Cancer Trialists' Collaborative Group.[25-27]

Financial Consideration

A cost-effectiveness analysis (versus examining the efficacy of screening in reducing morbidity and mortality exclusively) determines whether financial considerations should be limited to direct cost only (i.e., costs associated with screening, diagnosis and treatment), or whether indirect costs should be included as well (e.g., costs associated with false-positive or negative results, lost wages, etc.). Moreover, previous simulation studies have discounted costs of 4-6%, based on the understanding that we prefer to gain benefits sooner and incur costs later.

Measure of Benefit

Finally, the measure of benefit will also need to be determined. Although Quality-Adjusted Life Years (QALY) gained appears to be

a commonly used measure,[28-30] since the goal of screening is to reduce breast cancer mortality, some authors argue that the outcome measured should correspond to the goal of the intervention (i.e., mortality reduction or life-years gained).[31] Conversely, others argue that death from all causes should be the outcome measured.[10] This is based on the understanding that some diagnostic and treatment exposures, such as radiation, may contribute to increased mortality.

CONCLUSION

Although efficacy of screening is best examined using large-scale population-based clinical trials, such trials often require long follow-up periods, and accordingly results can be difficult to interpret (due to improvements in technology, and changes in screening modalities). Simulation represents a promising tool in examining the efficacy of a given screening instrument, while avoiding many problems concerning validity commonly faced by clinical trials. In addition, simulation can be used as an important potential tool to inform policies concerning optimal screening modalities, screening start and end ages, and screening frequencies in the Canadian context. Finally, simulation can also be used to conduct cost-effectiveness analyses to enhance the efficient use of limited public health resources.

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RÉSUMÉ

Des controverses persistent au sujet des modalités optimales de dépistage du cancer du sein, de l'âge de début et de fin du dépistage, et de la fréquence du dépistage, mais on a peu tendance à lancer d'autres essais aléatoires en population pour examiner ces questions. Des modèles de simulation ont été utilisés pour évaluer l'utilité et l'efficacité de diverses stratégies de dépistage du cancer du sein, mais ces modèles ont tous été élaborés à l'aide de données des États-Unis. Il faudrait aujourd'hui examiner les politiques de dépistage et de traitement optimales dans un contexte canadien. Dans notre commentaire, nous expliquons les controverses actuelles afférentes au dépistage du cancer du sein et nous décrivons les composants fondamentaux d'un modèle de simulation pouvant servir à éclairer les politiques de dépistage et de traitement du cancer du sein.

Mots clés : tumeurs du sein; controverses et dissensions (dépistage); stratégies de dépistage; simulation; composants de modèle