TITLE: Detection at All Costs: Is Breast Cancer Screening Always Better?

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ABSTRACT

Cancer treatment and prevention is a continuously evolving field. Canadian guidelines suggest that women of average breast cancer risk receive mammography screening regularly. Screening seems an intuitive approach to diagnosing cancer in its early and curable stages. However, repeat cancer screening is not without drawbacks; as the intensity and frequency of cancer screening increases, so do the consequences of overdiagnosis, including avoidable testing and treatment, pain, stress, unwillingness to participate in future testing, and healthcare spending. Therefore, achieving optimal screening outcomes requires an accurate understanding of the costs and benefits associated with this procedure. By empowering patients to make informed decisions regarding cancer screening, one potential strategy to improve patient care is to improve communication and decision-making between physicians and patients. Other strategies to achieve better screening include targeted screening programs for high-risk patients that rely on different screening modalities.

INTRODUCTION

Cancer is the leading cause of death in Canada and the second leading cause of death worldwide.^{1,2} One in two Canadians will develop cancer in their lifetime, and one in four is expected to die of cancer.¹ The Canadian Task Force on Preventative Health Care and Cancer Care Ontario breast cancer screening recommendations are designed to reflect the best available evidence of the harms and benefits of cancer screening.^{3,4} However, there may be significant drawbacks associated with intensive screening protocols. Furthermore, breast cancer detection may not always influence patient outcomes and illness trajectory. It is, therefore, important to

consider the impact of routine breast cancer screening on patient well-being and outcomes, and whether earlier cancer detection always better.

SECTION 1: WHAT CONSTITUTES OPTIMAL CANCER SCREENING?

Despite improvements in medicine's understanding of prevention disease management, cancer screening continues to represent a challenge. According to the World Health Organization (WHO), the principles of an effective screening program include that (a) the target disease is common and highly correlated with health compromise (as measured by morbidity and mortality), (b) follow-up treatment options are effective and available, and (c) screening procedures are safe, simple, and reasonably inexpensive.² However, there is no definite cut-off for determining which patients should be screened and which should not.⁵ Developing cancer screening best practices is an ongoing process, as reflected by changes to cancer screening guidelines and differences in breast cancer screening recommendations provincially, nationally, and internationally.^{3,4,6}

When designing screening programs, clinicians must determine an acceptable false-positive rate, and balance the benefits and anticipated harms of cancer screening. Harris et al. describe a framework for conceptualizing the interplay between cancer screening intensity and cost-benefit.⁷ High-value screening occurs when there is a balance between harm (e.g., psychological harm, physical harm, opportunity-costs, and financial strains), benefits (decreased morbidity and mortality), and costs.⁷ An optimal, "Goldilocks" zone of high-value testing occurs with the optimal screening intensity.⁷ Below this optimal value, the costs exceed any meaningful benefit because the amount of population screened and intensity of screening are low.⁷ Above

this optimal value, there is a disproportionate increase in harms and costs with diminishing returns in terms of patient outcomes.⁷

SECTION 2: WHAT IS THE IMPACT OF BREAST CANCER SCREENING ON PATIENT OUTCOMES?

Obtaining a positive screening test is only one part of a detailed diagnostic algorithm.⁷ Following a screening test, some patients will have positive results, others negative results, and still others will be informed of incidental findings that require clinical work-up. Those with positive tests will have further work-up including imaging and diagnostic breast cancer biopsy. Furthermore, tests may yield indeterminate results, requiring that patients follow a surveillance program.⁷

As discussed in Nelson and colleagues' systematic review, studies indicate that the 10-year cumulative likelihood of receiving a false positive breast cancer result with biannual screening beginning at age 50 is as high as 42%.⁸ In other words, 4 out of every 10 low-risk patients who attend regular screening appointments according to Ontario's breast cancer screening guidelines will receive a false positive mammography result by age 60.^{4,8} False positive breast cancer screening results may lead to significant psychological stress for patients.⁸ Indeed, those patients who receive false-positives are at increased risk of developing symptoms consistent with subclinical depression, breast cancer specific anxiety, and worries that impact daily functioning.⁸ Furthermore, patients who receive false positives may be less likely to return for routine screening in the future.⁸ From this standpoint, a cohort of patients engaging in regular breast cancer screening appointments would be anticipated to decrease in size with an increasing frequency of screening, since the likelihood of having a negative reaction to a false positive test

result would increase during the same time. While the generalizability of data is limited by study diversity and self-report measures, this data ultimately highlights that the psychological impacts of routine breast cancer screening require thoughtful consideration.

Some evidence suggests that patients with disease that progresses either very quickly or very slowly are relatively unlikely to benefit from earlier detection.⁷ For instance, it is estimated that only 8 out of every 122 patients diagnosed with early-stage breast cancer via mammography will ever develop advanced disease in the absence of treatment.⁹ In this case, patients are deemed overdiagnosed because their positive test does not modify the disease trajectory. Overdiagnosis is an inevitability of cancer screening since there is no way to know in advance whether or not a patient's true positive test will correlate with a very mild disease progression. Indeed, up to 1 in 3 cases of breast cancer diagnoses screened with mammography is considered an overdiagnosis.⁹ Reducing overdiagnosis is an ongoing concern for breast cancer researchers.^{9,10}

One might intuit that these drawbacks, while unfortunate, are outweighed by a significant decrease in cancer mortality. However, this may not necessarily be the case. Though there has been a 34% reduction in breast cancer mortality from 1975 to 2010, Narod et al. posit that improvements to breast cancer prevention and screening may have little to do with this.¹⁰ If prevention contributed significantly, one would expect to see decreased incidence. If screening contributed significantly, one would expect to see decreased rates of more advanced cancers. However, Surveillance, Epidemiology, and End Results data from almost 3,000,000 women with invasive breast cancer show that neither of these have occurred; instead, the incidence of early-stage breast cancer has increased and has not been associated with a decrease in the incidence of advanced cancer.^{9,10} That is to say, research does not suggest that breast cancer screening has successfully caught the disease during earlier and more curable stages.⁹ Instead, this suggests

decreased case-fatality through improvements to cancer treatment, such as adjuvant chemotherapy, has been responsible for improved mortality.¹⁰ This is in agreement with the Canadian National Breast Cancer Screening study, which randomly assigned 89,835 women to receive either annual mammography screening or no mammography over five years, and followed patients for up to 25 years.¹¹ Researchers concluded that mammography screening had no significant impact on patient mortality as compared with regular physical examination.¹¹ Furthermore, a Cochrane review has concluded that only one out of every 2,000 women screened by mammography for 10 years will avoid a cancer-related death, while 10 women will be overdiagnosed and undergo unnecessary treatments, and 200 will receive false-positive results and endure the accompanying consequences.¹²

SECTION 3: HOW CAN WE ACHIEVE BETTER CANCER SCREENING?

As discussed in Section 2, the goal of large-scale organized cancer screening programs ought to be to deliver the optimal, value-based intensity and frequency of cancer screening.⁷ Similar to determining patient preferences in end-of-life intensive care unit care, it is imperative that clinicians strive to deliver preventative screening that is patient-centered and non-harmful.¹³ However, physicians are under constant pressure to order more and sometimes needless investigations. There is a multitude of factors that influence cancer screening decision-making, including public misinformation (ex. “earlier screening and cancer detection is always better”), lack of physician knowledge of the benefits and harms of cancer screening, perceived physician responsibilities (ex. the belief that action is always superior to inaction), and malpractice apprehensions.⁷ Furthermore, social attitudes may influence patient decision-making, since media messaging about screening may give patients the impression that screening as a health

practice is an individual and medicosocial responsibility. Indeed, almost 80% of the public would characterize a 55-year-old patient of average risk who doesn't undergo routine mammography as irresponsible.¹⁴ Under such pressures, it is no wonder that physicians may employ screening tests to detect all cancers rather than adopt a value-based approach.

Cancer Care Ontario recommends that women aged 50-74 receive biennial cancer screening.⁴ The undiscounted lifetime cost of this screening per 1,000 women aged 50-69 is estimated at \$6.1 million.¹⁵ Recent Canadian estimates suggest that biennial breast screening costs \$38,142 per quality-adjusted life-year (QALY) gained for women aged 50-69.¹⁵ Though a cost per QALY between \$20,000 and \$100,000 of healthcare spending is considered moderately cost-effective in developed countries such as Canada,¹⁶ even a marginal decrease in the number of screening tests could translate into a meaningful savings of healthcare resources.

The Gail Model is a clinically-validated screening tool designed to estimate a patient's annual and lifetime risk of developing breast cancer.¹⁷ By relying on demographic variables including age, race, the onset of menses, number of first-degree relatives with breast cancer, and previous biopsy results, the model allows clinicians and patients to tailor screening protocols according to individual-level risk assessments.¹⁷ An intuitive conjecture using this tool would be to stratify patients into risk groups and screen only patients with the highest risk. However, as discussed by the WHO, screening just the high-risk subset of a larger population is rarely supportable.¹ This makes sense when considering that most forms of cancer are sporadic, and hereditary and familial cancers represent only 30% of breast cancer cases.¹⁸ That is, a program targeting only high-risk patients would mean that 70% of patients who develop breast cancer would be ineligible for screening.

One significant limitation of the Gail Model is that it specifically excludes women in the highest risk group of developing breast cancer; that is, women with a previous diagnosis of breast cancer, and patients with genetic variations in tumor suppressor genes or syndromes implicated in breast cancer development.¹⁷ These patients would most benefit from risk-reducing mastectomy or a more intensive screening protocol involving more frequent and earlier mammography combined with MRI imaging.¹⁹ However, this approach is not without its drawbacks; researchers have drawn attention to the radiation exposure risks particularly involved with early and repeated breast cancer screening.²⁰ Specifically, early and repeated mammography offered to high-risk patients may play a role in increasing the likelihood of developing radiation-induced breast cancer.²⁰ Researchers recommend that once there is a better understanding of the impacts of ionizing radiation from screening modalities on the development of breast cancer, incorporating this data into guidelines will assist clinicians in supporting these high-risk patients.²⁰

Other patient groups at increased risk of developing breast cancer, including those with high-density breast tissue, also benefit from alternative screening modalities.²¹ This seems logical considering that women with more radiopaque stromal or epithelial tissue are at an increased risk of receiving false negative mammography results, yet are more likely to develop cancer.²¹ Promising evidence suggests that these patients may benefit from alternative breast cancer screening modalities, including MRI, US, and digital breast tomosynthesis, which takes several low-dose mammograms in order to reconstruct tissues with lesser superimposition between different planes of breast tissue.^{21, 22}

Given the influence of social, cultural, professional, legal, and commercial interests in decision-making, perhaps it is time to revisit the traditional concept of the doctor-patient

therapeutic relationship and the potential for improved patient-physician communication.

According to the Canadian Medical Protective Association (CMPA), patients need to be sufficiently informed about the nature, anticipated outcomes, significant risks, and alternatives to an investigation or treatment.²³ The informative model of the patient-physician relationship described by Emanuel & Emanuel involves the clinician sharing the risks and benefits of an intervention and then allowing the patient to make decisions independent of the clinician's input. While suitable in clinical situations where the medical evidence is clear and unambiguous, this model may not be appropriate in the context of cancer screening, wherein patients have discernable options, and their values and preferences can have a meaningful impact on what constitutes optimal patient-centered care.²⁴ Instead, shared decision-making serves as an evidence-based alternative shown to improve patient satisfaction with healthcare delivery.²⁵ Shared decision-making refers to the bidirectional flow of information wherein physicians assist patients in evaluating options and deciding on care based on patient values and concerns.²⁴ In the context of breast cancer screening, shared decision-making involves the clinician taking a thorough family history and using risk assessment tools to understand patients' health, and inviting patients to share their feelings regarding the risks of being diagnosed with cancer after foregoing mammography, as well as overtreatment.²⁶ By helping patients explore their understanding and feelings about the risks and benefits of breast cancer screening, physicians can assist their patients in making informed decisions and knowing what to expect from screening should they decide to pursue it. However, there are barriers to implementing shared decision-making into the clinical practice, including time constraints and available quality indicators that emphasize the rate of mammography screening rather than the quality of conversations between patient and physician.²⁶

CONCLUSION

Cancer presentation and diagnosis continues to represent a diagnostic puzzle. Effectively addressing this problem is further complicated when clinicians and policymakers are tasked with making fiscally responsible decisions without compromising patient care. To ensure that patients make decisions consistent with their values, physicians should strive to help patients develop a clearer understanding of the risks and benefits. The use of alternative screening modalities and discussion styles may also contribute to improved patient care and outcomes. It is recommended that clinicians and researchers continue to fine-tune breast cancer screening protocols to reflect the value-based approach to cancer screening.

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