Definitions/curroncol-logo-eps-converted-to.pdf

MDPI

Article

Trade-offs of Breast Cancer Screening Scenarios in Canada: A Microsimulation Modeling Study

Hamed Milani [1,*], Marco Bijvank [1], Hossein Piri [1] and Darren Brenner [2,3]

[1] Operations and Supply Chain Management Area, Haskayne School of Business, University of Calgary.
[2] Department of Oncology, Cumming School of Medicine, University of Calgary.
[3] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary.
* Correspondence: hamed.milani@ucalgary.ca

Abstract:

Objective: To evaluate the cost-effectiveness, cost-utility, and harm-to-benefit ratios of alternative breast cancer screening scenarios for average-risk women in Canada using the OncoSim-Breast microsimulation model.

Setting: The entire female Canadian population is modeled, with outcomes reported for the period 2020–2039.

Methods: We compare the economic and clinical outcomes of multiple screening scenarios against the current recommended guideline in Canada, biennial screening for women aged 50–74, which serves as the baseline. Next, we evaluate economic trade-offs through extensive cost-effectiveness analyses. Other than a focus on economic efficiency, we also perform a harm-to-benefit analysis as an alternative decision-making tool that takes the ethical or social impact as main criterion. Sensitivity analyses are conducted by varying key input parameters to evaluate the robustness of our findings.

Results: The least intensive scenario, triennial screening for women aged 50-74, reduces the number of screens by 32%, whereas the most intensive scenario, annual screening for women aged 40-74, increases this by 166%. In terms of stage distribution, the proportion of detected Stage 0 cases is 7% in the least intensive scenario and 10% in the most intensive scenario, indicating a favorable stage shift when the screening intensity is increased. Notably, the most intensive screening scenario results in the lowest total treatment cost, with an 8% reduction compared to the baseline. The most cost efficient scenario is a combination of biennial screening for women aged 45–49 and triennial screening for those aged 50–74. For the twenty-year horizon of our study, this hybrid approach yields a total of 3,825 additional life-years and 5,433 additional quality-adjusted life-years, while reducing the total cost by CA$ 280,954,705 compared to the baseline of biennial screening for women aged 50-74.

Conclusions: Hybrid strategies that begin with annual or biennial screening before age 50 while maintaining longer intervals between screenings for women over age 50 exhibit superior cost-effectiveness compared to the current recommended guideline. In contrast, hybrid strategies with triennial screening for women under age 50 are shown to be inefficient. The design of optimal screening strategies depends on how policymakers prioritize trade-offs between potential screening harms and benefits and their willingness to pay for additional screening.

Keywords: Breast Cancer; Screening; Epidemiology; Economic Analysis; Microsimulation Model

Received:
Revised:
Accepted:
Published:

Citation: Milani, H.; Bijvank, M.; Piri, H. Trade-offs of Breast Cancer Screening Scenarios. *Curr. Oncol.* **2025**, *1*, 0. https://doi.org/

1. Introduction

Breast cancer poses a major public health concern as one of the most common cancers and the second leading cause of cancer-related deaths among women in Canada [1]. According to projections by the Canadian Cancer Society (CCS), 1 in 8 women would be diagnosed with breast cancer, and 1 in 36 would die from it in 2024 [1]. The trend in breast cancer age-standardized mortality rates in Canada highlights notable progress in prevention and treatment over the past three decades. This rate has declined by 46%, from 41.6 per 100,000 women in 1990 to 22.4 in 2022, largely due to the implementation of mammography-based screening programs since the 1990s and advancements in treatment [2]. Mammography-based screening aims to detect hidden and silent cancerous cells during their sojourn time, enabling earlier and more effective treatments that significantly improve the survival rate [3–5]. However, these benefits come with potential clinical harms, particularly high rates of overdiagnosis and false-positive results, as well as considerable monetary costs [6–8]. The false-positive rate for mammography screening is approximately 14% [6], and has significant population-level implications, leading to tens of thousands of individuals undergoing unnecessary follow-up tests each year and experiencing considerable anxiety [9].

The trade-offs between benefits, harms, and costs of screening is a nuanced issue and has been the subject of a longstanding debate [11–14]. Countries, and even programs within a country, may balance this trade-off differently based on their varying priorities. On one hand, some programs prioritize reducing cancer-related deaths, accepting a certain level of overdiagnosis as a necessary trade-off. On the other hand, programs that outweigh societal concerns about potential harms over perceived benefits tend to favor less intensive screening policies [15]. For instance, the United States Preventive Services Task Force (USPSTF) recommends biennial screening starting at age 40, while the Canadian Task Force on Preventive Health Care (CTFPHC) and the National Health Service of the United Kingdom advise triennial screening starting at age 50 [16–18]. Advocates of early screening argue that younger women are more likely to develop aggressive and fatal cancers, making early detection critical [19]. However, critics of early screening focus on the higher false-positive rates in younger women due to denser breast tissue and the lower incidence rates in these age groups, recommending a more cautious approach to initiate screening at younger ages [20].

To address these trade-offs, researchers typically rely on two main approaches, model-based studies, such as simulation tools, and empirical studies, such as randomized controlled trials. Both approaches aim to assess the efficacy of screening strategies, but the way efficacy is defined can vary depending on societal needs and preferences. For example, if efficacy is measured by mortality reduction, more intensive screening strategies tend to be favored. However, when evaluated based on quality-adjusted life years (QALYs), less intensive strategies may be preferred [32]. This highlights the importance of evaluating not just the benefits, but also the potential harms and costs of each strategy. Unlike empirical studies, model-based studies allow for a broader and more controlled evaluation of various strategies. However, a common limitation of these model-based studies is their context-specific nature, as models are calibrated using the best available evidence tailored to a country's demographic characteristics. This limitation is frequently noted in the literature and underscores the need for updated studies using the most recent and relevant data [32]. In Canada, a cancer microsimulation modeling tool called OncoSim-Breast, developed by the Canadian Partnership Against Cancer and Statistics Canada, is available to model health and economic outcomes based on provincial-level demographics of the Canadian population. This tool has been validated to reflect breast cancer incidence, mortality, and

screening efficacy in Canada using multiple data sources, including the Canadian Cancer Registry, Vital Statistics, and the UK Age trial [22].

Researchers have used OncoSim to evaluate breast cancer screening interventions. Yaffe and Mainprize [22] were one of the first researchers to use OncoSim-Breast to demonstrate that starting annual or biennial screening of women at age 40, rather than 50, reduces mortality rates. Recently, Basmadjian et al. [23] used OncoSim-Breast to estimate the resource requirements for expanding breast cancer screening programs to include average-risk women aged 40–49 across Canada. Their study helps to ensure that the Canadian healthcare system is prepared to accommodate the increased demand that may result from policy changes. One of their key findings is that the most intensive screening scenario prevents the greatest number of cancer-related deaths and leads to the highest number of early-stage cancer detection, but it also has the highest cost. They highlight the need for a detailed economic analysis to determine whether the increased screening expenses could be offset by the reduction in treatment costs. In this paper, we will conduct such a thorough economic analysis for an extensive set of screening scenarios.

In this current study, we evaluate the cost-effectiveness, cost-utility, and harm-to-benefit ratios of multiple breast cancer screening scenarios using the OncoSim-Breast microsimulation model. We examine scenarios that expand current guidelines by introducing the screening of women at the age of 40 and 45 with varying screening intervals. Additionally, we consider hybrid scenarios with different screening intervals for women who are below or above age 50. Finally, we assess the impact of key parameters to test the robustness of our findings and explore the uncertainty with respect to estimated benefits, harms, and costs. A key strength of our study is its pioneering use of OncoSim-Breast for economic evaluation, enabling a detailed assessment of cost-effectiveness and harm-to-benefit trade-offs which to the best of our knowledge has not been considered in earlier studies. Unlike previous studies [22,23,25], our analysis considers a broad range of screening policies, including hybrid and single-phase strategies for younger age groups that have not been extensively examined in the literature. Through this extensive set of scenarios, our analyses highlight the superior performance of hybrid strategies that initiate screening of women before age 50 while maintaining longer intervals for women aged 50 and older. In particular, we recommend to implement the scenario that offers annual screening for women aged 45–49 and triennial screening for those aged 50–74 as it is one of the most cost effective strategies. This would increase the number of screenings. Alternatively, we recommend the strategy to screen women aged 45-49 biennially and those aged 50-74 triennially to improve the current strategy without increasing the required screening capacity.

2. Methods

2.1. OncoSim-Breast Microsimulation Model

We used OncoSim-Breast to model the economic and health outcomes of various breast cancer screening interventions. OncoSim is a cancer microsimulation modeling tool that has been developed by the Canadian Partnership Against Cancer in collaboration with Statistics Canada. The development, application, and validation of OncoSim-Breast have been documented by Yong et al. [21]. OncoSim-Breast simulates the natural history, clinical detection, screening intervention, and treatment of breast cancer (see Figure A1 in Appendix). The model simulates individual-level trajectories, reflecting age and sex distributions and all-cause mortality rates of breast cancer for women in all provinces and territories across Canada. The key attributes of each simulated individual include demographics (sex, province/territory of residence) and breast cancer risk factors (BRCA1/2 gene mutation status, family history, hormone replacement therapy exposure). The model tracks individuals from birth until death or age 109, with results reported from calendar

years 2015 to 2051. We only use the outcomes of years 2020 to 2039 for our analysis. We provide a description of the natural history component of OncoSim-Breast in Section A.2 in the Appendix, as it is a core element of the model and essential for understanding the simulation's underlying mechanism.

To evaluate different screening scenarios and their associated efficacy, the model allows users to define screening protocols by modifying the following key input parameters: recruitment strategy (start/end age and years), participation and retention, screening frequency, screening modality, and follow-up protocol after abnormal screening results. Women with an abnormal mammogram receive additional follow-up testing, such as diagnostic imaging, biopsy, and fine-needle aspiration. In case the follow-up test confirms the first result to be true positive, the model assigns a treatment based on the age, subtype, and size of the tumor.

2.2. Screening Scenarios

We simulated 17 screening scenarios, categorized into hybrid and single-phase groups, all ending at age 75. These scenarios vary by starting age (40, 45, 50) and screening interval (annual, biennial, triennial). See Table 1 for a description of all scenarios. Each scenario is labeled using a bracket notation. Single-phase scenarios are represented by a single element within the bracket, combining a letter to indicate the screening frequency and two numbers for the starting and ending ages. Hybrid scenarios include two such elements. For example, [A40-49, B50-74] denotes a hybrid scenario where women aged 40 to 49 are screened annually and women aged 50 to 74 are screened biennially. Given that previous studies have established clinical benefits of more intensive screening strategies [22,23], our analysis does not consider scenarios that involve no screening. Screening beyond age 74 was excluded as the majority of screening guidelines published by different institutions typically do not extend beyond this age, e.g., US Preventive Services Task Force, UK's National Health Service, and European Commission Initiative on Breast Cancer [16–18,27].

All scenarios are implemented starting in the 2015 calendar year, with prior years reflecting the previous practices of Canadian screening programs. Current screening protocols do not account for higher-risk groups, such as women with dense breast tissue, a family history of breast cancer, or BRCA1/2 mutations, as these groups require specialized screening guidelines. The initial screening participation rate is set at 0.9, with a subsequent participation rate of 0.8, and no dropouts are allowed. These values are the default input parameters in OncoSim-Breast, and we did not modify them.

Table 1. Description of Screening Scenarios.

Group	Scenario	Description
Annual	[A40-74]	Annual screening for women aged 40-74
	[A45-74]	Annual screening for women aged 45-74
	[A50-74]	Annual screening for women aged 50-74
Biennial	[B40-74]	Biennial screening for women aged 40-74
	[B45-74]	Biennial screening for women aged 45-74
	[B50-74]	Biennial screening for women aged 50-74
Triennial	[T40-74]	Triennial screening for women aged 40-74
	[T45-74]	Triennial screening for women aged 45-74
	[T50-74]	Triennial screening for women aged 50-74
Hybrid 1	[A40-49, B50-74]	Annual screening for women aged 40–49; and biennial for 50–74
	[A45-49, B50-74]	Annual screening for women aged 45–49; and biennial for 50–74
	[T40-49, B50-74]	Triennial screening for women aged 40–49; and biennial for 50–74
	[T45-49, B50-74]	Triennial screening for women aged 45–49; and biennial for 50–74
Hybrid 2	[A40-49, T50-74]	Annual screening for women aged 40–49; and triennial for 50–74
	[A45-49, T50-74]	Annual screening for women aged 45–49; and triennial for 50–74
	[B40-49, T50-74]	Biennial screening for women aged 40–49; and triennial for 50–74
	[B45-49, T50-74]	Biennial screening for women aged 45–49; and triennial for 50–74

Notes: 1. All scenarios are effective only for average-risk women. 2. All scenarios are implemented starting in calendar year 2015. 3. In all scenarios, the recruitment rate and the rescreen rate are 0.9 and 0.8, respectively.

2.3. Costs and Resources

The simulation model of OncoSim-Breast includes healthcare costs associated with breast cancer from the perspective of a public healthcare payer, such as the Ministry of Health. These costs cover screening tests, follow-up diagnostic tests, breast cancer surgery, radiation therapy, chemotherapy, hormonal therapy, and oncology physician fees, as well as acute hospitalizations, emergency department visits, home care, long-term care, and complex continuing care. The model captures lifetime breast cancer treatment costs across three phases of care: the first 18 months after diagnosis, continuing care, and terminal care.

2.4. Economic and Clinical Outcomes

In OncoSim, all outcomes are reported annually on the last day of the year. We report the undiscounted total number of outcomes accumulated over the years 2020 to 2039. We categorize outcomes into economic and clinical outcomes. Economic outcomes include the total number of women screened, screening tests performed, abnormal recalls, abnormal recalls without cancer (or false-positives), biopsies performed, and benign biopsies. Benign biopsies result from abnormal recalls without cancer, as some abnormal recalls require confirmation through biopsy. Additionally, we report the total costs associated with screening, diagnostic procedures, and treatments. Economic outcomes are considered either as measure of harm or cost in the statistical analysis.

Clinical outcomes include the total number of invasive and ductal carcinoma in situ (DCIS) breast cancers by stage, regardless of whether they are detected through screening or not. We use this data to calculate the stage distribution and stage shifts across different screening scenarios. Additionally, we include the total number of breast cancer cases detected through screening across all stages. Total life years (LYs) and quality-adjusted life years (QALYs) based on age- and status-dependent utility values are also reported. Finally, we report the total number of breast cancer-related deaths and the mortality rate per 1,000 women. To assess the benefits of screening, we consider the number of averted deaths and the additional LYs and QALYs gained in screening scenarios compared to the baseline scenario.

2.5. Cost-Effectiveness Analysis

To illustrate the cost effectiveness of changing the screening policy, we define the Marginal Cost-Effectiveness Ratio (MCER) as the ratio of additional cost to additional life years gained compared to the baseline. Similarly, we define the Marginal Cost-Utility Ratio (MCUR) as the ratio of additional cost to additional quality-adjusted life years gained. That is, for a screening scenario X,

$$\text{MCER} = \frac{\text{total cost scenario } X - \text{total cost baseline scenario}}{\text{LYs scenario } X - \text{LYs baseline scenario}}, \quad (1)$$

and

$$\text{MCUR} = \frac{\text{total cost scenario } X - \text{total cost baseline scenario}}{\text{QALYs scenario } X - \text{QALYs baseline scenario}}, \quad (2)$$

where the baseline scenario corresponds to the current screening guidelines of CTFPHC, i.e., biennial screening from ages 50 to 74. This means that MCER (MCUR) represents the cost of gaining one additional unit of LYs (QALYs) compared to the baseline scenario. If a scenario provides lower benefits in term of LYs and QALYs than the baseline, the denominator for MCER or MCUR is negative. In such cases, the scenario is classified as strongly dominated. In contrast, when a scenario incurs lower costs while providing greater benefits compared to the baseline scenario (i.e., when MCER or MCUR takes a negative value), the alternative scenario is superior to the baseline scenario. In conducting the marginal cost-effectiveness and cost-utility ratio analysis, we follow the method outlined by Mittmann et al. [24].

Ranking the screening scenarios based on MCER or MCUR is particularly useful when decision-makers seek screening policies that perform better than the benchmark scenario. However, there is no consideration of a budget limitation. An alternatively approach is to visualize the clinical outcomes against the total discounted costs. Screening scenarios that are on the efficiency frontier of such a visualization can be identified with the so-called incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) for the LYs and QALY, respectively. A geometric interpretation of this efficiency frontier is presented in Section A.3 in the Appendix.

In cost-effectiveness analysis, MCER (or MCUR) is used to assess the cost-effectiveness of an intervention in relation to the current program as it changes in scale. As a result, it examines how the cost per outcome changes with program size (or number of screens). ICER (or ICUR) compares an intervention to the next most effective intervention by dividing the difference in their costs by the difference in their outcomes. To calculate ICER and ICUR, we sort the screening alternatives by their associated total cost in a descending order, and define the initial baseline as the scenario with the lowest total cost. We then determine the ratio similar to Eq. (1) or (2) for the screening scenario with the second lowest total cost. If this ratio is negative – due to a lower outcome than the baseline scenario – the alternative scenario is strongly dominated by the current baseline scenario. Such strongly dominated scenarios are ruled out. Otherwise, the next incrementally efficient scenario is identified as it has the lowest cost per additional life year or quality-adjusted life year gained. However, if the incremental cost ratio associated with moving to the more costly alternative decreases, then the lower-cost alternative that was used to calculate the incremental cost ratio is weakly dominated by the most recently identified incrementally efficient scenario. This weakly dominated scenario should also be ruled out, and the incremental cost ratios have to be recalculated. Whenever a scenario is neither strongly nor weakly dominated, it becomes the new baseline for the remainder of the calculations. This process of selecting the next most efficient scenario among those with higher total costs than the previously selected scenario is continued until all scenarios are analyzed. For the incremental cost-effectiveness

and cost-utility ratio analysis, we follow the analytical approach introduced by Drummond et al. [35].

2.6. Harm-to-Benefit Analysis

Other that a focus on economic efficiency, we perform a harm-to-benefit analysis in this section as an alternative decision-making tool that takes the ethical or social impact as main criterion. This analysis is similar to the incremental cost ratio analysis introduced above, with the key difference that we consider the number of screens and the number of abnormal recalls without cancer as measures of harm instead of monetary cost. As measures of benefit, we use the number of averted deaths in comparison to the current screening policy, [B50-74].

3. Results

3.1. Overall Results on Economic and Clinical Outcomes

The undiscounted total number of economic and clinical outcomes are reported in Tables 2 and 3, respectively. The baseline scenario is [B50-74], reflecting the current screening guideline recommended by the CTFPHC. Full details including relative changes compared to the baseline are presented in Tables A1 and A2 in the Appendix. Four scenarios, [T50-74], [T45-74], [B45-49, T50-74], and [T40-74T], have fewer total screens compared to the baseline. The least intensive scenario, [T50-74], results in a 32.35% reduction in the number of screens, whereas the most intensive scenario, [A40-74], result in a 166.12% increase in the number of screens.

We observe from the economic outcomes in Tables 2 and A1 that the total number of abnormal recalls without cancer, biopsies, and benign biopsies increases almost linearly with the number of screens. The total costs, including the costs of screening, diagnostic procedures, and treatments, also rise with the number of screens but not with a strictly linear relationship (Table 2). In contrast, total treatment costs decrease as the number of screens increases, due to earlier cancer detection, which leads to more effective and cost-efficient treatments (Table 2). One key observation from Table 2 is that the most intensive scenario, [A40-74], results in the lowest total treatment cost, with an 8.81% reduction compared to the baseline. This suggests that lower treatment costs can partially offset the overall cost increase in more intensive screening scenarios.

Figure A3 illustrates the relationship between the undiscounted number of screening tests performed and the total screening cost, treatment cost, and overall cost, grouped by single-phase and hybrid scenarios. As expected, screening costs increase linearly with the number of screening tests in both single-phase and hybrid scenarios. A key insight from this figure is the advantage of hybrid scenarios, which achieve lower treatment costs while maintaining similar screening costs to single-phase strategies. Notably, a local minimum in the total cost graph is observed at the 10th scenario, corresponding to [A45–49, T50–74], indicating a potentially efficient screening strategy. This scenario, along with other promising candidates, will be further evaluated in the cost-effectiveness analysis presented in Section 3.3. Another interesting observation is that the decrease in treatment costs isn't as steep as the increase in screening costs when more screenings are performed. This indicates that screening is only beneficial up to certain point, and overscreening should be avoided as the added value to detect breast cancer becomes minimal.

Next, we observe from the clinical outcomes in Tables 3 and A2 that the least intensive scenario, [T50-74], has the lowest total number of invasive and DCIS cases, with reductions of 1.62% and 2.60% compared to the baseline, respectively, and a 19.96% decrease in screen-detected cancers. Conversely, the most intensive scenario, [A40-74], has the highest total number of invasive and DCIS cases, with increases of 2.47% and 4.85%, respectively,

Table 2. Undiscounted accumulated total number of economic outcomes and costs among all women in Canada from 2020 to 2039.

Scenario	Screening Tests Performed	Abnormal Recalls without Cancer	Total Treatment Cost ($)	Total Cost ($)
[A40-74]	159,337,942	11,672,111	39,863,215,284	52,337,137,379
[A45-74]	137,228,230	10,098,077	40,543,546,716	51,313,896,852
[A50-74]	116,344,854	8,560,442	41,337,751,365	50,493,640,296
[B40-74]	81,828,955	6,283,073	42,790,552,473	49,299,353,384
[B45-74]	70,671,984	5,472,048	43,229,844,050	48,877,279,550
[B50-74]	59,960,875	4,639,835	43,713,652,310	48,529,124,587
[T40-74]	55,622,911	4,463,364	43,972,566,105	48,462,656,093
[T45-74]	48,024,954	3,899,522	44,335,415,712	48,237,787,063
[T50-74]	40,563,922	3,293,993	44,715,508,410	48,035,863,989
[A40-49, B50-74]	133,001,331	9,842,432	40,213,548,171	50,657,089,915
[A45-49, B50-74]	94,436,484	7,125,985	41,681,419,273	49,154,949,593
[T40-49, B50-74]	63,491,656	5,009,353	44,021,652,475	49,119,636,594
[T45-49, B50-74]	62,773,907	4,923,080	43,980,439,881	49,020,925,154
[A40-49, T50-74]	124,290,029	9,238,511	40,249,209,729	50,019,978,034
[A45-49, T50-74]	80,246,635	6,142,750	42,071,206,861	48,449,957,940
[B40-49, T50-74]	74,392,908	5,768,790	42,747,778,904	48,682,114,724
[B45-49, T50-74]	56,421,239	4,482,713	43,591,508,032	48,139,488,818

along with a 46.33% rise in screen-detected cancers. The increase in invasive and DCIS cases in more intensive screening scenarios is due to the detection of additional cases through screening that would otherwise remain undetected in the absence of screening. In Section 3.2, we will further examine the impact of this increase on stage distribution, demonstrating that more intensive screening scenarios tend to shift the distribution toward earlier stages, whereas less intensive scenarios result in a greater proportion of cases detected at later stages.

In addition to a shift in the distribution of cancer stage at diagnosis, the screening intensity also impacts the number of cancer-related deaths, as well as the life years (LYs) and quality-adjusted life years (QALYs) of patients. Table 3 shows that the most intensive scenario results in the lowest number of cancer-related deaths, while the least intensive scenario results in the highest number of deaths. Additionally, it shows that the total LYs gained increases with the number of screens. Interestingly, some scenarios with only a slightly higher number of screens than the baseline result in lower QALYs, suggesting that excessive screening and abnormal recalls without cancer slightly reduce QALYs due to the associated disutility. However, in more intensive screening scenarios, the increase in LYs appears to offset this disutility.

3.2. Breast Cancer Cases by Stage

The distribution (or proportion) of cancer cases by stage for the different screening scenarios is reported in Table 4. This table is derived from the total number of cancer incidences by stage, provided in Table A3 in the Appendix. We also report the percentage change relative to the baseline in parentheses in Tables 4 and A3. The baseline scenario is again [B50-74].

In the least intensive scenario, [T50-74], which has 32.35% fewer screens, the proportion of Stage 0 cases decreases by 11%, while the proportion of Stage III and Stage IV cases increases by 15% and 12%, respectively. Conversely, in the most intensive scenario, [A40-74], which has 165.74% more screens, the proportion of Stage 0 cases increases by 24%, while the proportion of Stage III and Stage IV cases decreases by 31% and 27%, respectively.

Table 3. Undiscounted accumulated total number of health outcomes among all women in Canada from 2020 to 2039.

Scenario	Invasive Cancer Cases	DCIS Cases	Cancer-caused Deaths	Life Years (LYs)	Quality-Adjusted Life Years (QALYs)
[A40-74]	667,531	749,052	103,853	407,925,338	348,995,268
[A45-74]	666,912	746,371	106,225	407,906,318	348,995,145
[A50-74]	663,740	740,313	109,790	407,879,945	348,988,488
[B40-74]	654,081	719,715	116,606	407,837,532	348,980,091
[B45-74]	653,246	717,453	118,286	407,824,065	348,976,827
[B50-74]	651,440	714,379	120,693	407,806,037	348,970,001
[T40-74]	644,206	700,662	123,410	407,794,036	348,965,605
[T45-74]	643,217	698,734	124,726	407,783,793	348,962,411
[T50-74]	640,916	695,827	126,748	407,768,416	348,955,376
[A40-49, B50-74]	649,224	723,228	106,241	407,917,434	349,008,545
[A45-49, B50-74]	645,872	713,461	112,358	407,878,718	349,004,275
[T40-49, B50-74]	653,564	714,161	122,336	407,797,027	348,960,894
[T45-49, B50-74]	655,911	718,275	121,469	407,797,985	348,961,481
[A40-49, T50-74]	638,603	709,000	107,202	407,913,174	349,012,333
[A45-49, T50-74]	632,963	694,898	115,190	407,864,329	349,004,097
[B40-49, T50-74]	644,356	706,305	117,433	407,834,482	348,984,262
[B45-49, T50-74]	641,777	699,647	121,272	407,811,042	348,977,927

These results confirm that increased screening facilitates earlier cancer detection before cancer cells progress to more advanced stages, reducing the number of cases diagnosed at later stages.

We illustrate the differences in stage proportion (compared to the baseline) across all scenarios in Figure 1, which is based on the data in Table 4. As shown in Figure 1, hybrid scenarios (marked in blue and green), along with the most intensive scenarios (annual scenarios marked in red), exhibit notable positive differences in early-stage proportions and negative differences in later-stage proportions. This pattern confirms the superior performance of hybrid strategies in increasing early-stage diagnoses while reducing diagnoses at later stages. In contrast, the least intensive scenarios (triennial scenarios marked in gray) show the opposite trend.

3.3. Cost-Effectiveness Analysis

The previous sections reported the undiscounted economic and health outcomes as the sum of absolute numbers. In contrast, discounting reduces the weight of outcomes that are further in the future. It reflects a preference for present over future values, and allows to compare costs and benefits that occur at different points in time in a consistent manner. Especially in cost-effectiveness analysis (CEA), discounting is used to adjust future costs and health outcomes (like LYs and QALYs) to present values. In the remainder of our analysis, we apply a 3% discount rate, as reported in the majority of recent studies (e.g. [28,29]). It is conventional to use the same discount rate for both health and economic outcomes [31]. Additionally, in our analysis, we use 2020 as the reference year and 2039 as the comparator year, summing the discounted values over this period.

Discounted total costs, LYs, QALYs, and the corresponding MCER and MCUR values are presented in Table 5. In general, scenarios with a higher number of screens result in higher LYs and QALYs, with two exceptions: [T40-49,B50-74] and [T45-49, B50-74]. These two scenarios are the only less intensive scenarios that consider triennial screening for women under age 50 but yield lower LYs and QALYs, making them strongly dominated.

Table 4. Proportion (and percentage change) of cancer cases by stage among all women in Canada, accumulated from 2020 to 2039.

Scenario	Proportion of Stage 0 Cases (percentage change)[1]	Proportion of Stage I Cases (percentage change)	Proportion of Stage II Cases (percentage change)	Proportion of Stage III Cases (percentage change)	Proportion of Stage IV Cases (percentage change)
[A40-74]	0.10897 (24%)	0.49535 (23%)	0.28554 (-19%)	0.07778 (-31%)	0.03236 (-27%)
[A45-74]	0.10656 (21%)	0.48471 (21%)	0.29261 (-17%)	0.08214 (-28%)	0.03399 (-23%)
[A50-74]	0.10350 (18%)	0.46923 (17%)	0.30271 (-14%)	0.08828 (-22%)	0.03629 (-18%)
[B40-74]	0.09112 (4%)	0.41784 (4%)	0.34292 (-3%)	0.10659 (-6%)	0.04152 (-6%)
[B45-74]	0.08942 (2%)	0.41114 (2%)	0.34702 (-2%)	0.10956 (-3%)	0.04286 (-3%)
[B50-74]	0.08801 (0%)	0.40154 (0%)	0.35277 (0%)	0.11339 (0%)	0.04429 (0%)
[T40-74]	0.07881 (-10%)	0.37199 (-7%)	0.37485 (6%)	0.12685 (12%)	0.04750 (7%)
[T45-74]	0.07832 (-11%)	0.36885 (-8%)	0.37655 (7%)	0.12795 (13%)	0.04834 (9%)
[T50-74]	0.07798 (-11%)	0.36238 (-10%)	0.37997 (8%)	0.13016 (15%)	0.04951 (12%)
[A40-49, B50-74]	0.10263 (17%)	0.46574 (16%)	0.30734 (-13%)	0.08900 (-22%)	0.03528 (-20%)
[A45-49, B50-74]	0.09502 (8%)	0.43472 (8%)	0.32956 (-7%)	0.10110 (-11%)	0.03960 (-11%)
[T40-49, B50-74]	0.08385 (-5%)	0.39039 (-3%)	0.36149 (2%)	0.11862 (5%)	0.04565 (3%)
[T45-49, B50-74]	0.08635 (-2%)	0.40083 (0%)	0.35374 (0%)	0.11445 (1%)	0.04463 (1%)
[A40-49, T50-74]	0.09958 (13%)	0.45179 (13%)	0.31685 (-10%)	0.09468 (-17%)	0.03709 (-16%)
[A45-49, T50-74]	0.08950 (2%)	0.40939 (2%)	0.34667 (-2%)	0.11147 (-2%)	0.04297 (-3%)
[B40-49, T50-74]	0.08773 (0%)	0.40466 (1%)	0.35232 (0%)	0.11226 (-1%)	0.04303 (-3%)
[B45-49, T50-74]	0.08268 (-6%)	0.38540 (-4%)	0.36511 (4%)	0.12045 (6%)	0.04635 (5%)

1: We calculate the percentage change relative to the baseline scenario by determining the difference between the scenario outcome and the baseline outcome, dividing that difference by the baseline outcome, and then multiplying the result by 100. Baseline: [B50-74].

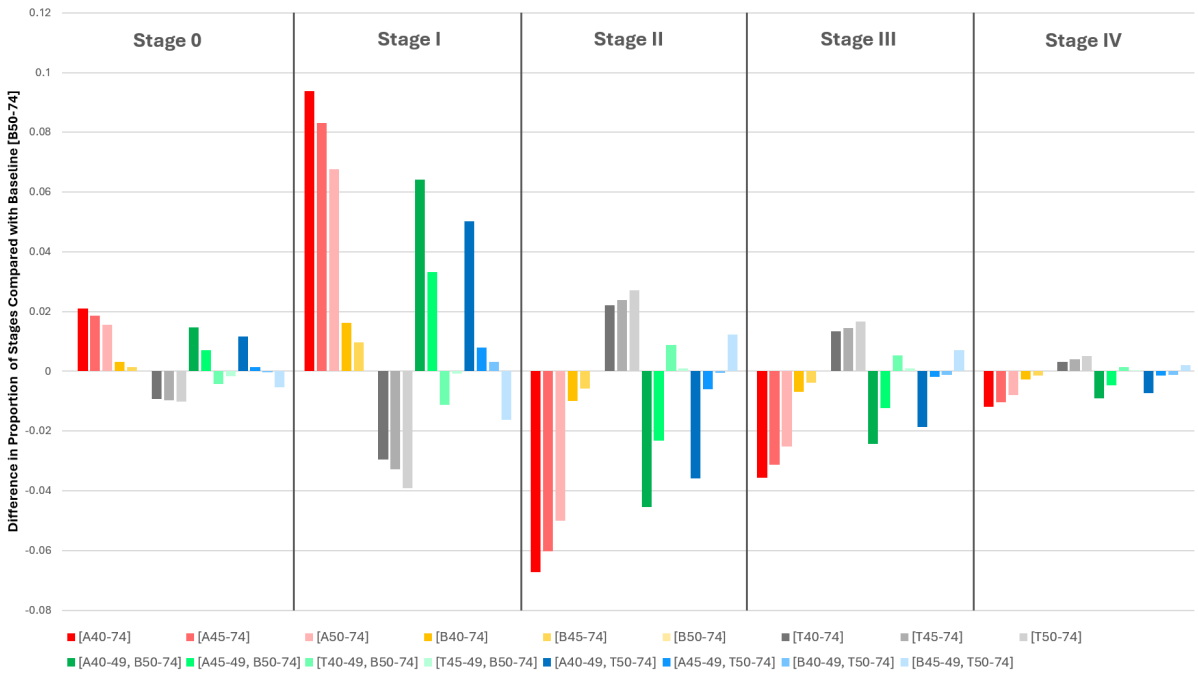


Figure 1. Difference in the proportion of cancer stages under various screening scenarios compared to the baseline scenario [B50–74], accumulated across all women in Canada from 2020 to 2039. Each color represents a group of scenarios (see Table 1 for group definitions): red for Annual, yellow for Biennial, gray for Triennial, green for Hybrid 1, and blue for Hybrid 2.

This suggests that triennial screening for younger women is not efficient. Among the less intensive scenarios, [B45-49, T50-74] is a notable exception, as it achieves higher LYs and QALYs while also reducing total costs. As a result, this scenario results in negative values

Table 5. Marginal cost-effectiveness and cost-utility ratios of various screening scenarios for all women in Canada from 2020 to 2039 compared to baseline: [B50-74]. Discount rate=3%.

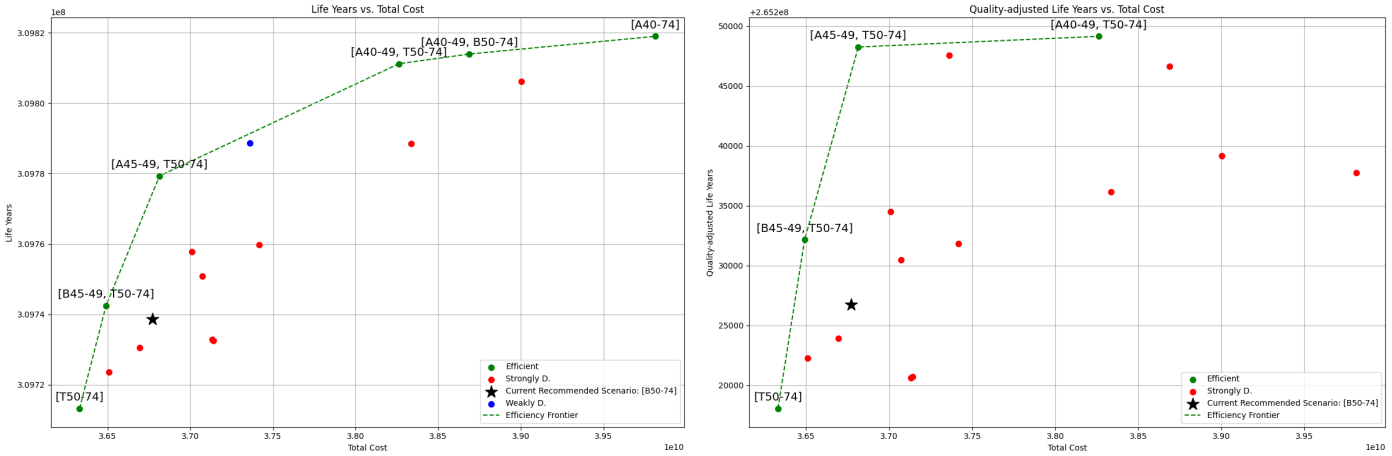
Scenario	Total Cost ($)	Total Life Years (LYs)	Total Quality-Adjusted Life Years (QALYs)	Marginal Cost-Effectiveness Ratio (MCER)	Marginal Cost-Utility Ratio (MCUR)
[A40-74]	39,813,670,477	309,818,968	265,237,737	37,884	276,058
[A45-74]	39,003,041,788	309,806,166	265,239,150	33,060	179,483
[A50-74]	38,334,665,285	309,788,528	265,236,166	31,349	165,421
[B40-74]	37,415,916,687	309,759,779	265,231,819	30,521	126,288
[B45-74]	37,071,951,976	309,750,795	265,230,490	24,771	79,630
[B50-74]	36,771,515,974	309,738,666	265,226,717	-	-
[T40-74]	36,692,551,383	309,730,579	265,223,899	Strongly D.[1]	Strongly D.
[T45-74]	36,508,123,144	309,723,692	265,222,274	Strongly D.	Strongly D.
[T50-74]	36,330,207,746	309,713,265	265,218,058	Strongly D.	Strongly D.
[A40-49, B50-74]	38,688,134,074	309,813,937	265,246,622	25,463	96,286
[A45-49, B50-74]	37,362,372,213	309,788,571	265,247,539	11,840	28,376
[T40-49, B50-74]	37,139,669,869	309,732,508	265,220,726	Strongly D.	Strongly D.
[T45-49, B50-74]	37,131,921,790	309,732,807	265,220,636	Strongly D.	Strongly D.
[A40-49, T50-74]	38,262,576,975	309,811,183	265,249,144	20,561	66,483
[A45-49, T50-74]	36,813,963,301	309,779,310	265,248,249	1,044	1,971
[B40-49, T50-74]	37,009,354,346	309,757,803	265,234,525	12,428	30,460
[B45-49, T50-74]	36,490,561,268	309,742,491	265,232,150	-73,446	-51,705

1: Strongly D. = Strongly Dominated.

for MCER and MCUR, meaning that this scenario is both cost saving and more effective than the baseline scenario. The ranking of the scenarios based on either MCER or MCUR remains consistent. After the most efficient scenario with negative MCER and MCUR, [A45-49, T50-74] has the lowest cost per additional LYs and QALYs gained, at $1,044 per LY and $1,971 per QALY, respectively. As the most intensive scenario, [A40-74] has the highest values, at $37,884 per LY and $276,058 per QALY, respectively.

A visualization of the clinical outcomes against the total discounted cost is illustrated in Figure 2 (a) and (b) for the LYs and QALYs, respectively. We included the efficiency frontiers in both figures to highlight which breast cancer screening scenarios are the most cost efficient among the alternatives. As discussed in Section 2.5, these scenarios are identified with the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) for the LYs and QALY, respectively.

The detailed results of the incremental cost ratio analysis are presented in Table A4 in the Appendix, whereas these results are summarized in Table 6. The scenario with the lowest total cost is [T50-74]. In the ICER analysis, the first incrementally efficient scenario after [T50-74] is [B45-49B, T50-74] with an ICER of $5,487 per LY. The subsequent efficient scenarios are [A45-49, T50-74], [A40-49, T50-74], [A40-49, B50-74], and [A40-74], with ICER values of $8,784 per LY, $45,449 per LY, $154,555 per LY, and $223,726 per LY, respectively. Scenario [A45-49, B50-74] is weakly dominated by [A40-49, T50-74]. For the ICUR analysis, the first incrementally efficient scenario after [T50-74] is again [B45-49B, T50-74], with an ICUR of $11,378 per QALY. Only two additional scenarios remain incrementally efficient, [A45-49, T50-74] and [A40-49, T50-74], with ICUR values of $20,089 per QALY and $1,617,874 per QALY, respectively. A key observation is that two scenarios, [A40-49, B50-74] and [A40-74], are no longer cost efficient under ICUR, as they now become strongly dominated by scenario [A40-49A, T50-74].



(**a**) (**b**)

Figure 2. (**a**) Visual illustration of efficiency frontier for incremental cost-effectiveness ratios. (**b**) Visual illustration of efficiency frontier for incremental cost-utility ratios.

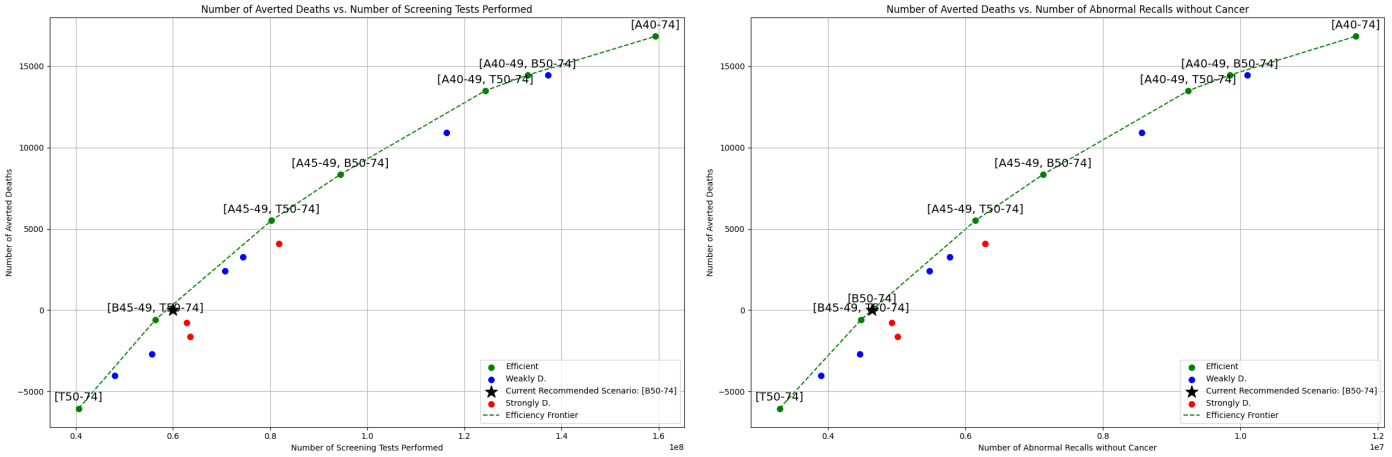
Table 6. Consolidated incremental cost-effectiveness, cost-utility, and and harm-to-benefit ratios of various screening scenarios for all women in Canada from 2020 to 2039. Number of Averted Deaths is calculated compared to baseline: [B50-74]. Discount rate=3%.

Scenario	Incremental Cost-Effectiveness Ratio ($/LY)	Incremental Cost-Utility Ratio ($/QALY)	Incremental Number of Screening Tests to Number of Averted Deaths Ratio	Incremental Number of Abnormal Recalls without Cancer to Number of Averted Deaths Ratio
[A40-74]	223,726	Strongly D.[1]	11,029	766
[A45-74]	Strongly D.	Strongly D.	Weakly D.[2]	Weakly D.
[A50-74]	Strongly D.	Strongly D.	Weakly D.	Weakly D.
[B40-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[B45-74]	Strongly D.	Strongly D.	Weakly D.	Weakly D.
[B50-74]	Strongly D.	Strongly D.	Weakly D.	271
[T40-74]	Strongly D.	Strongly D.	Weakly D.	Weakly D.
[T45-74]	Strongly D.	Strongly D.	Weakly D.	Weakly D.
[T50-74]	–	–	-	-
[A40-49,B50-74]	154,555	Strongly D.	9,064	628
[A45-49,B50-74]	Weakly D.	Strongly D.	5,010	347
[T40-49,B50-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[T45-49,B50-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[A40-49,T50-74]	45,449	1,617,874	5,790	410
[A45-49,T50-74]	8,784	20,089	3,918	273
[B40-49,T50-74]	Strongly D.	Strongly D.	Weakly D.	Weakly D.
[B45-49,T50-74]	5,487	11,378	2,896	217

1: Strongly D. = Strongly Dominated. 2: Weakly D. = Weakly Dominated.

3.4. Harm-to-Benefit Analysis

In the harm-to-benefit analysis, we compare the incremental harm (number of screens and number of abnormal recalls without cancer) to the incremental benefit (averted deaths) similar to the incremental cost ratio analysis. Figures 3 (a) and 3 (b) illustrate the number of averted deaths versus the number of screens and number of abnormal recalls without cancer, respectively, for each scenario. Similar to Figure 2, we include the efficiency frontiers



(**a**) (**b**)

Figure 3. (**a**) Efficiency frontier for number of averted deaths versus number of screens performed. (**b**) Efficiency frontier for number of averted deaths versus number of false positives.

in both figures. The scenarios that lie on the efficiency frontier represent the incrementally most efficient options. These scenarios, as well as the strongly and weakly dominated scenarios, are identified with the same methodology as explained in Section 2.5. See also CISNET's study [24] and Knudsen et al. [26]. Notably, all efficiency frontiers in Figures 2 and 3 exhibit perfect convexity, reflecting diminishing returns in benefits as costs or harms increase, an observation consistent with findings from previous studies (e.g., see [33]). Table 6 provides a summary of the harm-to-benefit analysis. It shows that all scenarios identified as efficient in the ICER analysis also appear to be efficient in the harm-to-benefit analysis. For the averted number of deaths versus the number of performed screens in Figure 3 (a), one additional scenario, [A45-49A, B50-74], appears on the efficiency frontier (compared to the ICER analysis), indicating its effectiveness in reducing cancer-related mortality. In Figure 3 (b), when using the number of abnormal recalls without cancer as the harm measure, two additional scenarios, [B50-74] and [A45-49A, B50-74], emerge as efficient (compared to the ICER analysis). This suggests that these scenarios perform efficiently in reducing cancer-related mortality when we ignore monetary costs and consider abnormal recalls without cancer as the only harm measure. The details of the harm-to-benefit analysis are included in Table A5 in the Appendix.

3.5. Sensitivity Analysis

To assess the robustness of our findings, we vary key input parameters and examine their impact on marginal costs. Specifically, we modify age-based and status-based utility values when awaiting follow-up testing after a positive mammogram, participation rates, the discount rate, and per-case treatment costs by stage. See Table 7 for parameter ranges used in each experiment of our sensitivity analysis. In the case of the discount rate, we account for changes in recommended values over time. While a 5% discount rate was commonly used in 2012, more recent guidelines have gradually reduced this to 3%, and even to 1.5% in 2017 [25,30]. Accordingly, we consider discount rates of 1.5% and 4.5% in our sensitivity analysis experiments. For the per-case treatment costs, we draw on external evidence to update the parameter values of the simulation model. Wilkinson et al. [27] conducted a comprehensive analysis to estimate per-case breast cancer treatment costs by stage and molecular subtype. They found that Stage IV treatment costs reached $516,415 (CAD) per case, 10.9 times the cost of Stage I cancers and 35.6 times that of DCIS. We incorporate their findings as input parameters for per-case treatment costs in our sensitivity

analysis to assess whether these new values impact the cost effectiveness of screening scenarios. As lifetime per-case treatment cost for Stage 0, Stage I, Stage II, Stage III, and Stage IV, we consider $14,505, $39,263, $76,446, $97,668, and $370,398 (CAD), respectively. For each experiment, we compute the marginal cost-utility ratios of the scenarios to evaluate how variations in these input parameters influence the outcomes.

The results of the sensitivity analysis are presented in Table 7. We report only the marginal cost-utility ratios (MCURs) for each set of sensitivity analysis experiments. In most cases, the MCUR values and the ranking of scenarios do not change drastically. The key observations are as follows: (1) When age-based and status-based utility values are increased by 7%, the MCUR decreases across all scenarios. Since higher utility values lead to greater total QALYs, the cost per additional QALY decreases while total costs remain unchanged. (2) When the rescreen rate is reduced from 0.8 to 0.4, the total costs remain relatively stable in less intensive scenarios, as screening and diagnostic costs account for a relatively small proportion of the overall costs in these scenarios. However, LYs and QALYs decline at a higher rate, leading to an overall increase in MCURs. There are two exceptions: in the scenarios that involve triennial screening for women under age 50, [T40-49, B50-74] and [T40-74], the reduced frequency of screening mitigates the disutility that is associated with initial screening, leading to a net benefit. As a result, these scenarios exhibit negative MCURs instead of being strongly dominated. (3) When the discount rate is adjusted from 3% to 1.5% and 4.5%, the MCURs slightly decrease and increase, respectively. This suggests that the denominator of the MCUR (i.e., QALYs) is more sensitive to changes in the discount rate than the total costs. This sensitivity may explain why some studies recommend using different discount rates for health and economic outcomes [34]. Discounting reduces the present value of future costs and health outcomes, meaning that events occurring further in the future are weighted less. As the discount rate increases, this effect becomes bigger, making long-term costs and benefits contribute minimally to the overall evaluation. (4) When the lifetime per-case treatment cost is modified based on Wilkinson et al. [27], the total costs increase for all scenarios, which is expected. However, the rate of increase varies across scenarios due to the differences in stage distribution and total treatment costs. In most cases, where QALYs are higher than the baseline scenario, the MCUR decreases, which indicates that incorporating more realistic treatment costs strengthens the relative benefits of more intensive screening strategies.

4. Discussion

This study evaluates the economic and health implications of alternative breast cancer screening strategies using the OncoSim-Breast microsimulation model. Unlike previous studies, our analysis considers a broad range of screening strategies, including single-phase and hybrid strategies for younger age groups that have not been extensively examined before. By examining multiple dimensions of cost-effectiveness, cost-utility, and harm-to-benefit ratios across our extensive set of 17 screening scenarios, this study provides a broad perspective on the trade-offs involved in revising current screening guidelines in Canada. Another key strength of our study is its pioneering use of OncoSim-Breast for economic evaluation, enabling a detailed assessment of cost-effectiveness and harm-to-benefit trade-offs, which to the best of our knowledge has not been considered in earlier studies. Additionally, by using the current guideline (biennial screening from ages 50 to 74) as the baseline rather than a no-screening alternative, our results provide practical insights for refining existing policies rather than evaluating basic benefits and harms.

Among the screening strategies analyzed, hybrid scenarios that include screening before age 50 while maintaining longer intervals between screenings for women over age 50, particularly [A45-49, T50-74] and [B45-49, T50-74], exhibit superior cost-effectiveness

Table 7. Results of sensitivity analysis experiments. Marginal cost-utility ratio (MCUR) of various scenarios in sensitivity analysis experiments. Values are for all women in Canada from 2020 to 2039 compared to baseline: [B50-74]. Baseline discount rate=3%.

Scenario	Marginal Cost-Utility Ratio ($/QALY)					
	Base Case	Utility+7%	Rescreen Rate=0.4	Discount Rate=1.5%	Discount Rate=4.5%	Wilkinson per-case Costs
[A40-74]	276,058	257,998	87,419	197,152	437,228	237,989
[A45-74]	179,483	167,741	73,471	138,229	247,384	145,875
[A50-74]	165,421	154,599	71,482	130,310	220,741	121,921
[B40-74]	126,288	118,026	48,909	96,643	172,970	129,030
[B45-74]	79,630	74,421	40,890	63,255	102,336	84,161
[B50-74]	-	-	-	-	-	-
[T40-74]	Strongly D.	Strongly D.	-197,428	Strongly D.	Strongly D.	Strongly D.
[T45-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[T50-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[A40-49, B50-74]	96,286	89,987	87,409	71,949	134,212	73,223
[A45-49, B50-74]	28,376	26,520	30,894	22,655	35,925	11,361
[T40-49, B50-74]	Strongly D.	Strongly D.	-162,734	Strongly D.	Strongly D.	Strongly D.
[T45-49, B50-74]	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.	Strongly D.
[A40-49, T50-74]	66,483	62,134	89,311	48,113	94,194	45,671
[A45-49, T50-74]	1,971	1,842	19,739	-515	5,357	-11,817
[B40-49, T50-74]	30,460	28,468	39,832	19,042	46,774	33,972
[B45-49, T50-74]	-51,705	-48,323	-32,566	-50,449	-52,912	-23,551

compared to the current screening strategy. These findings suggest that screening initiation before age 50, particularly at 45, while maintaining a biennial or triennial interval after age 50, provides a favorable balance between benefits and costs. Conversely, scenarios with triennial screening for women under age 50 perform poorly in both marginal and incremental analyses, reinforcing that such strategies are not beneficial. In terms of harm-to-benefit ratios, the scenarios [A45-49, B50-74], [B50-74], and [A45-49, B50-74] perform well, suggesting that these strategies achieve a favorable trade-off between the reduction in mortality and the associated harms of screening. Our findings also demonstrate that more intensive screening scenarios shift the stage distribution toward earlier stages, with a notable increase in Stage 0 and Stage I cancers and a corresponding decline in Stage II, III, and IV cases. This stage shift highlights the potential benefit of earlier detection in reducing the burden of advanced-stage disease, a factor that has not been considered in previous works [22,23,25]. However, we don't advocate more intensive screening strategies by itself, as we also illustrate that at some point the benefit of performing more breast cancer screenings (in terms of treatment costs) is diminishing in relation to the additional screening costs.

To identify a final recommendation among the most promising strategies, we focus on the three scenarios that are non-dominated across all analyses presented in Table 6, which are [B45–49, T50–74], [A45–49, T50–74], and [A40–49, T50–74]. To support the selection of a preferred scenario, we apply a heuristic inspired by the "elbow method" commonly used in machine learning for determining the optimal number of clusters. In that context, the elbow point reflects the balance between model complexity and predictive performance. Analogously, in this setting, it can be interpreted as the point at which incremental benefits from additional screening begin to diminish relative to the total costs and harms. As illustrated in Figures 2 and 3, [A45–49, T50–74] represents this turning point, offering a favorable balance before marginal gains become smaller. However, this scenario requires

33.83% more screening tests compared to the current recommended guideline [B50-74]. Whether the current publicly funded healthcare system in Canada can accommodate this increase in screening demand depends on both existing capacity and its current level of utilization, factors that lie outside the scope of this study. For jurisdictions with limited screening capacity or tighter budget constraints, [B45–49, T50–74] emerges as the next best option given its superior performance in cost-effectiveness and comparable outcomes in harm-to-benefit metrics compared to the current guideline, while requiring 5.9% fewer screening tests. Finally, although [A40–49, T50–74] delivers higher benefits, these come at a relatively higher cost with significantly more screenings to perform.

Furthermore, we explore the effect of varying key input parameter values of the OncoSim simulation model, including participation rates and treatment costs, to assess the robustness of our results. Our sensitivity analyses indicate that our primary qualitative findings remain robust under variations in key input parameters. This consistency strengthens the reliability of our insights and recommendations, and it underscores the value of conducting economic evaluations when considering adjustments to breast cancer screening strategies.

However, this study has some limitations. We did not evaluate screening strategies tailored toward higher-risk groups, nor did we incorporate OncoSim's risk-based screening modules. Additionally, we did not account for variations in breast tissue density when modeling screening sensitivity and specificity, nor did we differentiate between the sensitivity and specificity of different imaging modalities (mammography, ultrasound, MRI). Furthermore, our sensitivity analysis did not consider lower utility values or longer time horizons, which could impact cost-effectiveness estimates. Lastly, while we used Wilkinson et al.'s [27] lifetime per-case treatment costs in our sensitivity analysis, we aggregated substage and subtype-specific costs, as well as all recurrence types, which may have led to an underestimation of the benefit of incorporating more granular treatment cost estimates.

5. Conclusion

The findings of this study offer valuable insights for policymakers within the Canadian publicly funded healthcare system. Since even small modifications in screening policy design can have significant economic and health implications, incorporating a comprehensive range of analyses can help policymakers navigate the trade-offs between screening costs, harms, and benefits. The design of optimal screening strategies depends on how policymakers weigh different aspects of these trade-offs and their willingness to pay for additional screening. By presenting cost-effectiveness, cost-utility, and harm-to-benefit ratios across multiple screening strategies, this study contributes to a more informed approach to breast cancer screening policy decisions. Taking all dimensions of our analysis into account, we recommend the hybrid scenario that offers annual screening for women aged 45–49 and triennial screening for those aged 50–74, due to its superior performance in balancing the trade-offs between costs, harms, and benefits. If there is insufficient capacity to support the additional screenings with this strategy, we recommend to lower the frequency in the younger age group to biannually, which already results in a lower number screenings to perform and an increase in benefits compared to the current screening strategy.

Appendix A.

Appendix A.1. Schematic diagram of the OncoSim-Breast model

Figure A1 is adapted from Yong et al. [21].

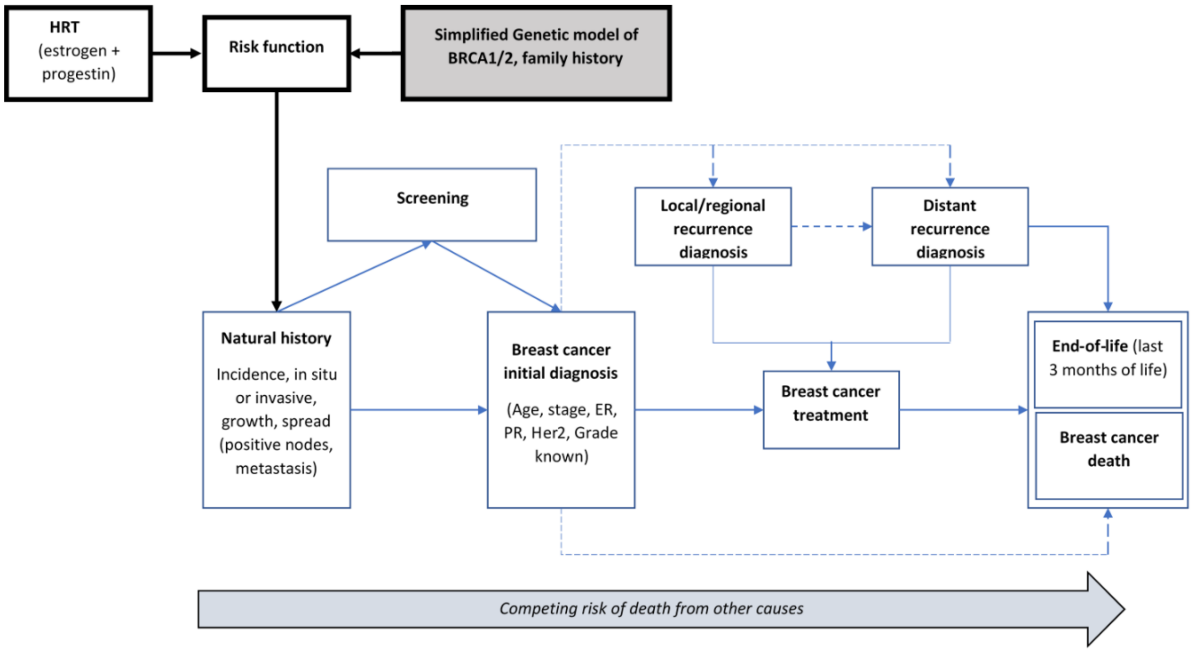


Figure A1. Schematic diagram of the OncoSim-Breast model

Appendix A.2. Natural history component of OncoSim-Breast

The natural history component of OncoSim-Breast was inspired by the University of Wisconsin breast cancer microsimulation model, which simulates the onset, growth, and spread of invasive and ductal carcinoma in situ (DCIS) tumors. tumors are initiated at 2 mm diameter, a minimum size detectable by mammography, as a function of age, calendar years, and breast cancer risk factors. Tumor growth is modeled as a function of time since onset, BRCA1/2 gene mutation status, tumor type (DCIS or invasive), and tumor aggressiveness. Tumor diameter is determined by a Gompertz distribution as a function of years since tumor onset, scaled according to the maximum diameter allowed for a tumor type. Invasive tumors have the potential to spread to lymph nodes and other parts of the body. The likelihood of lymph node involvement is a function of tumor size, growth rate, and the time since tumor onset. Cancer detection may occur through self-detection, clinical examination, or screening. However, some cancers may remain undetected until the individual dies of non-cancer cause of mortality. The likelihood of clinical detection is a function of tumor size and the number of tumors. Cancer stage at detection is determined according to the American Joint Committee on Cancer (AJCC) staging system, which assesses tumor size (T), nodal involvement (N), and distant metastasis (M). Tumor size and nodal status at detection are estimated based on age, tumor size, and the number of positive lymph nodes. In OncoSim, screening helps detect tumors in their sojourn time earlier than they would normally be diagnosed without screening. The time from when cancer is detected by screening to when a person might die from it includes both the lead time of cancer progression and any survival improvement due to earlier detection. These values are not directly entered into the model; they are instead calculated based on the model's results. The model incorporates various screening modalities (e.g., digital mammography, ultrasound, MRI), allowing for adjustments in sensitivity and specificity based on age group, tumor size, and screening sequence.

Appendix A.3. Geometric Interpretation of Efficiency Frontier

To define the efficiency frontier, we begin with the scenario that has the lowest harm (point A in Figure A2). We then identify the next point that forms the steepest connecting

line with the first scenario (point B in Figure A2). This point represents the scenario that provides the greatest additional benefit for a similar additional harm. After determining the first point on the efficiency frontier, we continue iteratively by selecting the next scenario with the steepest connecting line. The scenarios that lie on the efficiency frontier represent the incrementally most efficient options (points A, B, C, and D in Figure A2), while those positioned near and far below the frontier are classified as weakly and strongly dominated options, respectively (orange color points in Figure A2).

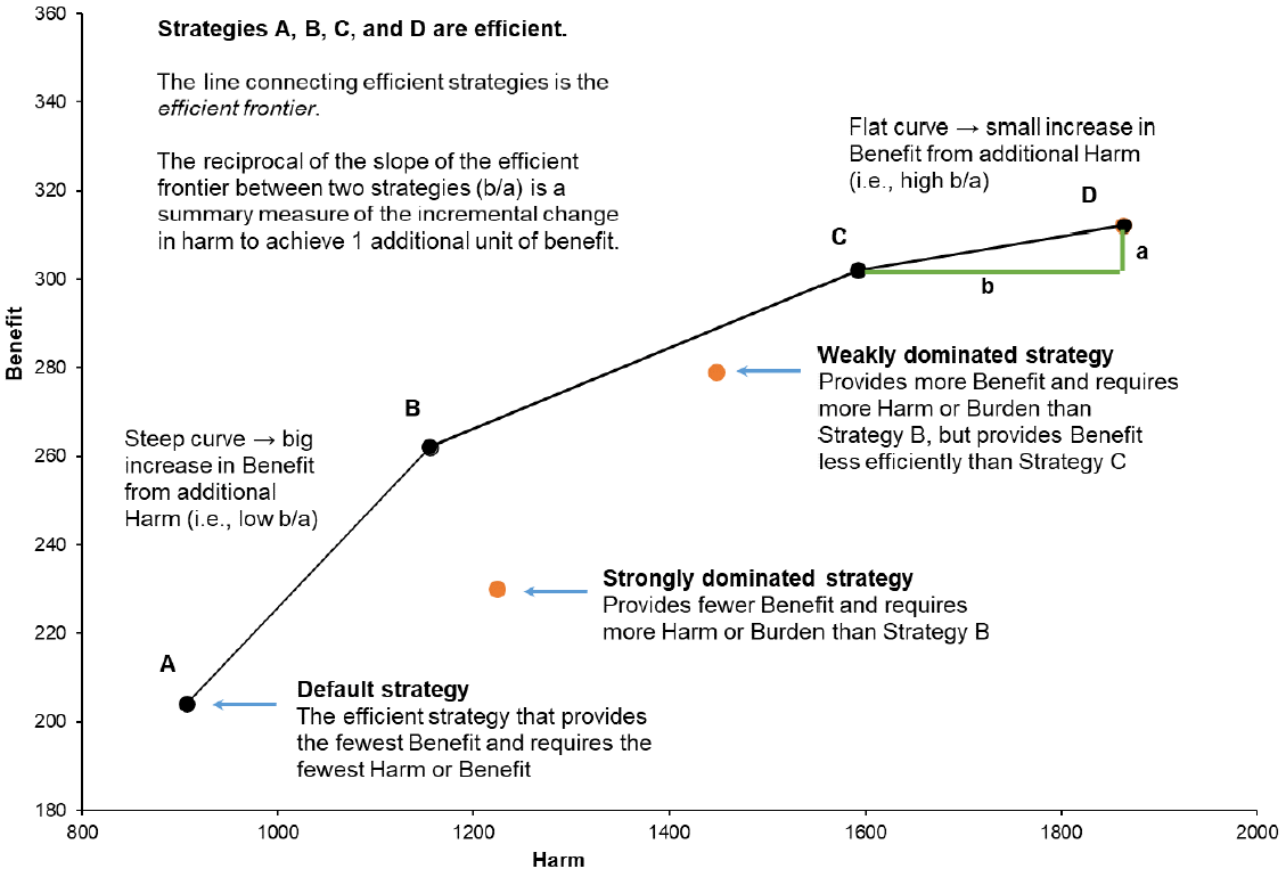


Figure A2. Geometric interpretation of efficiency frontier, efficient screening scenarios, and incremental ratios. Adapted From: Knudsen et al. [26].

Appendix A.4. Detailed Numerical Results

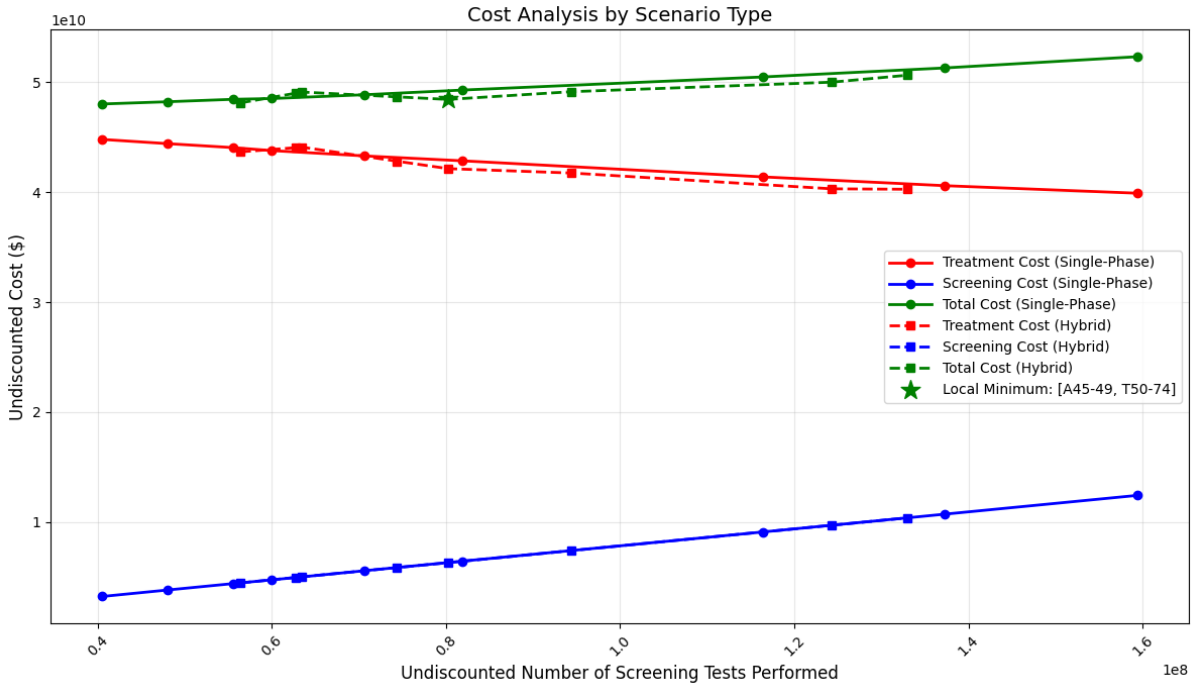


Figure A3. Cost analysis based on screening intensity by scenario type (single-phase or hybrid)

Table A1. Detailed undiscounted accumulated total number of economic outcomes and costs among all women in Canada from 2020 to 2039.

Scenario	Women Screened (percentage change)[1]	Screening Tests Performed (percentage change)	Abnormal Recalls without Cancer (percentage change)	Biopsy Tests Performed (percentage change)	Benign Biopsy Results (percentage change)	Total Treatment Cost ($) (percentage change)	Total Cost ($) (percentage change)
[A40-74]	158,398,440 (166.12%)	159,337,942 (165.74%)	11,672,111 (151.56%)	1,550,977 (103.28%)	1,038,818 (151.56%)	39,863,215,284 (-8.81%)	52,337,137,379 (7.85%)
[A45-74]	136,324,126 (129.04%)	137,228,230 (128.86%)	10,098,077 (117.64%)	1,389,008 (82.06%)	898,729 (117.64%)	40,543,546,716 (-7.25%)	51,313,896,852 (5.74%)
[A50-74]	115,473,355 (94.00%)	116,344,854 (94.03%)	8,560,442 (84.50%)	1,218,713 (59.74%)	761,879 (84.50%)	41,337,751,365 (-5.44%)	50,493,640,296 (4.05%)
[B40-74]	81,353,379 (36.68%)	81,828,955 (36.47%)	6,283,073 (35.42%)	945,829 (23.97%)	559,193 (35.42%)	42,790,552,473 (-2.11%)	49,299,353,384 (1.59%)
[B45-74]	70,214,946 (17.97%)	70,671,984 (17.86%)	5,472,048 (17.94%)	857,618 (12.41%)	487,012 (17.94%)	43,229,844,050 (-1.11%)	48,877,279,550 (0.72%)
[B50-74]	59,520,868 (0.00%)	59,960,875 (0.00%)	4,639,835 (0.00%)	762,959 (0.00%)	412,945 (0.00%)	43,713,652,310 (0.00%)	48,529,124,587 (0.00%)
[T40-74]	55,304,052 (-7.08%)	55,622,911 (-7.23%)	4,463,364 (-3.80%)	704,637 (-7.64%)	397,239 (-3.80%)	43,972,566,105 (0.59%)	48,462,656,093 (-0.14%)
[T45-74]	47,718,838 (-19.83%)	48,024,954 (-19.91%)	3,899,522 (-15.96%)	643,207 (-15.70%)	347,057 (-15.96%)	44,335,415,712 (1.42%)	48,237,787,063 (-0.60%)
[T50-74]	40,269,854 (-32.34%)	40,563,922 (-32.35%)	3,293,993 (-29.01%)	573,323 (-24.86%)	293,165 (-29.01%)	44,715,508,410 (2.29%)	48,035,863,989 (-1.02%)
[A40-49, B50-74]	132,315,590 (122.30%)	133,001,331 (121.81%)	9,842,432 (112.13%)	1,327,880 (74.04%)	875,976 (112.13%)	40,213,548,171 (-8.01%)	50,657,089,915 (4.38%)
[A45-49, B50-74]	93,899,478 (57.76%)	94,436,484 (57.50%)	7,125,985 (53.58%)	1,033,071 (35.40%)	634,213 (53.58%)	41,681,419,273 (-4.65%)	49,154,949,593 (1.29%)
[T40-49, B50-74]	63,097,487 (6.01%)	63,491,656 (5.89%)	5,009,353 (7.96%)	787,206 (3.18%)	445,832 (7.96%)	44,021,652,475 (0.70%)	49,119,636,594 (1.22%)
[T45-49, B50-74]	62,343,804 (4.74%)	62,773,907 (4.69%)	4,923,080 (6.10%)	792,405 (3.86%)	438,154 (6.10%)	43,980,439,881 (0.61%)	49,020,925,154 (1.01%)
[A40-49, T50-74]	123,685,709 (107.80%)	124,290,029 (107.29%)	9,238,511 (99.11%)	1,240,371 (62.57%)	822,227 (99.11%)	40,249,209,729 (-7.93%)	50,019,978,034 (3.07%)
[A45-49, T50-74]	79,831,222 (34.12%)	80,246,635 (33.83%)	6,142,750 (32.39%)	892,015 (16.92%)	546,705 (32.39%)	42,071,206,861 (-3.76%)	48,449,957,940 (-0.16%)
[B40-49, T50-74]	73,990,309 (24.31%)	74,392,908 (24.07%)	5,768,790 (24.33%)	868,360 (13.81%)	513,422 (24.33%)	42,747,778,904 (-2.21%)	48,682,114,724 (0.32%)
[B45-49, T50-74]	56,084,695 (-5.77%)	56,421,239 (-5.90%)	4,482,713 (-3.39%)	715,058 (-6.28%)	398,961 (-3.39%)	43,591,508,032 (-0.28%)	48,139,488,818 (-0.80%)

1: We calculate the percent change relative to the baseline scenario by determining the difference between the scenario outcome and the baseline outcome, dividing that difference by the baseline outcome, and then multiplying the result by 100. Baseline: [B50-74].

Table A2. Detailed Undiscounted accumulated total number of health outcomes among all women in Canada from 2020 to 2039.

Scenario	Invasive Cancer Cases (percentage change)[1]	DCIS Cases (percentage change)	Screen Detected Cases (percentage change)	Cancer-caused Deaths (percentage change)	Life Years (LYs) (percentage change)	Quality-Adjusted Life Years (QALYs) (percentage change)	Mortality Rate (per 1000 women) (percentage change)
[A40-74]	667,531 (2.47%)	749,052 (4.85%)	512,159 (46.33%)	103,853 (-13.95%)	407,925,338 (0.03%)	348,995,268 (0.01%)	0.25574 (-13.69%)
[A45-74]	666,912 (2.38%)	746,371 (4.48%)	490,279 (40.07%)	106,225 (-11.99%)	407,906,318 (0.02%)	348,995,145 (0.01%)	0.26147 (-11.76%)
[A50-74]	663,740 (1.89%)	740,313 (3.63%)	456,833 (30.52%)	109,790 (-9.03%)	407,879,945 (0.02%)	348,988,488 (0.01%)	0.27003 (-8.87%)
[B40-74]	654,081 (0.41%)	719,715 (0.75%)	386,636 (10.46%)	116,606 (-3.39%)	407,837,532 (0.01%)	348,980,091 (0.00%)	0.28647 (-3.32%)
[B45-74]	653,246 (0.28%)	717,453 (0.43%)	370,606 (5.88%)	118,286 (-1.99%)	407,824,064 (0.00%)	348,976,827 (0.00%)	0.29052 (-1.95%)
[B50-74]	651,440 (0.00%)	714,379 (0.00%)	350,013 (0.00%)	120,693 (0.00%)	407,806,037 (0.00%)	348,970,001 (0.00%)	0.29630 (0.00%)
[T40-74]	644,206 (-1.11%)	700,662 (-1.92%)	307,398 (-12.18%)	123,410 (2.25%)	407,794,036 (0.00%)	348,965,605 (0.00%)	0.30282 (2.20%)
[T45-74]	643,217 (-1.26%)	698,734 (-2.19%)	296,150 (-15.39%)	124,726 (3.34%)	407,783,794 (-0.01%)	348,962,411 (0.00%)	0.30600 (3.27%)
[T50-74]	640,916 (-1.62%)	695,827 (-2.60%)	280,158 (-19.96%)	126,748 (5.02%)	407,768,416 (-0.01%)	348,955,376 (0.00%)	0.31086 (4.91%)
[A40-49, B50-74]	649,224 (-0.34%)	723,228 (1.24%)	451,904 (29.11%)	106,241 (-11.97%)	407,917,434 (0.03%)	349,008,545 (0.01%)	0.26130 (-11.81%)
[A45-49, B50-74]	645,872 (-0.85%)	713,461 (-0.13%)	398,859 (13.96%)	112,358 (-6.91%)	407,878,718 (0.02%)	349,004,275 (0.01%)	0.27591 (-6.88%)
[T40-49, B50-74]	653,564 (0.33%)	714,161 (-0.03%)	341,374 (-2.47%)	122,336 (1.36%)	407,797,027 (0.00%)	348,960,894 (0.00%)	0.30033 (1.36%)
[T45-49, B50-74]	655,911 (0.69%)	718,275 (0.55%)	354,251 (1.21%)	121,469 (0.64%)	407,797,985 (0.00%)	348,961,481 (0.00%)	0.29832 (0.68%)
[A40-49, T50-74]	638,603 (-1.97%)	709,000 (-0.75%)	418,143 (19.46%)	107,202 (-11.18%)	407,913,174 (0.03%)	349,012,333 (0.01%)	0.26355 (-11.05%)
[A45-49, T50-74]	632,963 (-2.84%)	694,898 (-2.73%)	345,310 (-1.34%)	115,190 (-4.56%)	407,864,328 (0.01%)	349,004,096 (0.01%)	0.28262 (-4.62%)
[B40-49, T50-74]	644,356 (-1.09%)	706,305 (-1.13%)	354,937 (1.41%)	117,433 (-2.70%)	407,834,482 (0.01%)	348,984,262 (0.00%)	0.28839 (-2.67%)
[B45-49, T50-74]	641,777 (-1.48%)	699,647 (-2.06%)	316,096 (-9.69%)	121,272 (0.48%)	407,811,042 (0.00%)	348,977,927 (0.00%)	0.29754 (0.42%)

1: We calculate the percent change relative to the baseline scenario by determining the difference between the scenario outcome and the baseline outcome, dividing that difference by the baseline outcome, and then multiplying the result by 100. Baseline: [B50-74].

Table A3. Total number and percent change of cancer cases by stage among all women in Canada, accumulated from 2020 to 2039.

Scenario	Number of Stage 0 Cases (percentage change)[1]	Number of Stage I Cases (percentage change)	Number of Stage II Cases (percentage change)	Number of Stage III Cases (percentage change)	Number of Stage IV Cases (percentage change)
[A40-74]	81,521 (30%)	371,734 (29%)	213,575 (-15%)	58,055 (-28%)	24,165 (-24%)
[A45-74]	79,458 (26%)	362,483 (26%)	218,074 (-13%)	61,062 (-24%)	25,290 (-20%)
[A50-74]	76,572 (22%)	348,061 (21%)	223,765 (-11%)	65,111 (-19%)	26,801 (-15%)
[B40-74]	65,634 (4%)	301,240 (5%)	246,520 (-2%)	76,492 (-5%)	29,827 (-6%)
[B45-74]	64,207 (2%)	295,511 (3%)	248,647 (-1%)	78,390 (-3%)	30,696 (-3%)
[B50-74]	62,939 (0%)	287,359 (0%)	251,700 (0%)	80,772 (0%)	31,606 (0%)
[T40-74]	56,456 (-10%)	265,853 (-7%)	259,190 (3%)	86,143 (7%)	33,017 (4%)
[T45-74]	55,516 (-12%)	262,009 (-9%)	260,364 (3%)	87,274 (8%)	33,569 (6%)
[T50-74]	54,911 (-13%)	255,738 (-11%)	262,106 (4%)	88,798 (10%)	34,272 (8%)
[A40-49, B50-74]	74,004 (18%)	336,519 (17%)	222,627 (-12%)	64,525 (-20%)	25,552 (-19%)
[A45-49, B50-74]	67,588 (7%)	310,003 (8%)	235,372 (-6%)	72,173 (-11%)	28,322 (-10%)
[T40-49, B50-74]	60,597 (-4%)	281,705 (-2%)	256,185 (2%)	83,298 (3%)	32,374 (2%)
[T45-49, B50-74]	62,363 (-1%)	289,421 (1%)	253,097 (1%)	81,504 (1%)	31,886 (1%)
[A40-49, T50-74]	70,396 (12%)	319,916 (11%)	225,006 (-11%)	67,316 (-17%)	26,362 (-17%)
[A45-49, T50-74]	61,935 (-2%)	284,085 (-1%)	241,268 (-4%)	77,601 (-4%)	30,007 (-5%)
[B40-49, T50-74]	61,948 (-2%)	285,964 (0%)	248,792 (-1%)	79,189 (-2%)	30,408 (-4%)
[B45-49, T50-74]	65,634 (4%)	301,240 (5%)	246,520 (-2%)	76,492 (-5%)	29,827 (-6%)

1: We calculate the percent change relative to the baseline scenario by determining the difference between the scenario outcome and the baseline outcome, dividing that difference by the baseline outcome, and then multiplying the result by 100. Baseline: [B50-74]. To be consistent with Table 4, percent change values are rounded to integers.

Table A4. Detailed Incremental cost-effectiveness and cost-utility ratios of various screening scenarios for all women in Canada from 2020 to 2039 compared to baseline: [T50-74]. Discount rate=3%.

Scenario	Total Cost ($)	Life Years (LYs)	Quality-Adjusted Life Years (QALYs)	Incremental Cost-Effectiveness Ratio (ICER) ($/LY)	Incremental Cost-Utility Ratio (ICUR) ($/QALY)
[T50-74]	36,330,207,746	309,713,265	265,218,058	–	-
[B45-49, T50-74]	36,490,561,268	309,742,491	265,232,150	5,487	11,378
[T45-74]	36,508,123,144	309,723,692	265,222,274	Strongly D.[1]	Strongly D.
[T40-74]	36,692,551,383	309,730,579	265,223,899	Strongly D.	Strongly D.
[B50-74]	36,771,515,974	309,738,666	265,226,717	Strongly D.	Strongly D.
[A45-49, T50-74]	36,813,963,301	309,779,310	265,248,249	8,784	20,089
[B40-49, T50-74]	37,009,354,346	309,757,803	265,234,525	Strongly D.	Strongly D.
[B45-74]	37,071,951,976	309,750,795	265,230,490	Strongly D.	Strongly D.
[T45-49, B50-74]	37,131,921,790	309,732,807	265,220,636	Strongly D.	Strongly D.
[T40-49, B50-74]	37,139,669,869	309,732,508	265,220,726	Strongly D.	Strongly D.
[A45-49, B50-74]	37,362,372,213	309,788,571	265,247,539	Weakly D.[2]	Strongly D.
[B40-74]	37,415,916,687	309,759,779	265,231,819	Strongly D.	Strongly D.
[A40-49, T50-74]	38,262,576,975	309,811,183	265,249,144	45,449	1,617,874
[A50-74]	38,334,665,285	309,788,528	265,236,166	Strongly D.	Strongly D.
[A40-49, B50-74]	38,688,134,074	309,813,937	265,246,622	154,555	Strongly D.
[A45-74]	39,003,041,788	309,806,166	265,239,150	Strongly D.	Strongly D.
[A40-74]	39,813,670,477	309,818,968	265,237,737	223,726	Strongly D.

1: Strongly D. = Strongly Dominated. 2: Weakly D. = Weakly Dominated.

Table A5. Detailed incremental harm-to-benefit ratios of various screening scenarios for all women in Canada from 2020 to 2039. Number of Averted Deaths is calculated compared to baseline: [B50-74]. Discount rate=3%.

Scenario	Number of Screening Tests Performed	Number of Abnormal Recalls without Cancer	Number of Averted Deaths	Incremental Number of Screening Tests-to-Number of Averted Deaths Ratio	Incremental Number of Abnormal Recalls without Cancer-to-Number of Averted Deaths Ratio
[T50-74]	40,563,922	3,293,993	-6,055	-	-
[T45-74]	48,024,954	3,899,522	-4,033	Weakly D.[1]	Weakly D.
[T40-74]	55,622,911	4,463,364	-2,716	Weakly D.	Weakly D.
[B45-49, T50-74]	56,421,239	4,482,713	-579	2,896	217
[B50-74]	59,960,875	4,639,835	0	Weakly D.	271
[T45-49, B50-74]	62,773,907	4,923,080	-775	Strongly D.[2]	Strongly D.
[T40-49, B50-74]	63,491,656	5,009,353	-1,642	Strongly D.	Strongly D.
[B45-74]	70,671,984	5,472,048	2,407	Weakly D.	Weakly D.
[B40-49, T50-74]	74,392,908	5,768,790	3,260	Weakly D.	Weakly D.
[A45-49, T50-74]	80,246,635	6,142,750	5,503	3,918	273
[B40-74]	81,828,955	6,283,073	4,087	Strongly D.	Strongly D.
[A45-49, B50-74]	94,436,484	7,125,985	8,335	5,010	347
[A50-74]	116,344,853	8,560,442	10,904	Weakly D.	Weakly D.
[A40-49, T50-74]	124,290,029	9,238,511	13,491	5,790	410
[A40-49, B50-74]	133,001,331	9,842,432	14,452	9,064	628
[A45-74]	137,228,229	10,098,077	14,468	Weakly D.	Weakly D.
[A40-74]	159,337,941	11,672,111	16,840	11,029	766

1: Weakly D. = Weakly Dominated. 2: Strongly D. = Strongly Dominated.

References

1. Canadian Cancer Statistics Advisory Committee, Canadian Cancer Society, Statistics Canada **(2024)** Canadian Cancer Statistics 2024. Available at: https://cancer.ca/en/research/cancer-statistics.
2. Canadian Cancer Statistics Advisory Committee, Canadian Cancer Society, Statistics Canada **(2021)** Canadian Cancer Statistics 2021. Available at: https://cancer.ca/Canadian-Cancer-Statistics-2021-EN.
3. Eby P.R., Ghate S., Hooley R. The benefits of early detection: Evidence from modern international mammography service screening programs. *Journal of Breast Imagingn* **2022**, *4(4)*, 346–356.
4. Helvie M., Hendrick R., Banerjee M. The benefits of early detection: Reduction in late-stage breast cancer incidence in the mammography era: implications for overdiagnosis of invasive cancer. *Cancer* **2014**, *120(14)*, 2649–2656.
5. Pocobelli G., Weiss N. Breast cancer mortality in relation to receipt of screening mammography: a case–control study in saskatchewan, canada. *Cancer Cause Control* **2015**, *26*, 231–237.
6. Løberg M., Lousdal M., Bretthauer M. Benefits and harms of mammography screening. *Breast Cancer Res* **2015**, *63(17)*.
7. Tosteson A., Fryback D., Hammond C. Consequences of false-positive screening mammograms. *AMA Intern Med* **2014**, *174(6)*, 954–961.
8. Alberdi R., Llanes A., Ortega R. Effect of radiologist experience on the risk of false-positive results in breast cancer screening programs. *Eur Radiol* **2011**, *21*, 2083–2090.
9. Brewer N.T. Systematic review: The long term effects of false-positive mammograms. *Ann. Internal Medicine* **2007**, *146(7)*, 502–510.
10. CPAC, Pan-canadian framework for action to address abnormal call rates in breast cancer screening. Canadian Partnership Against Cancer, Toronto. (2023) Available at: https://www.partnershipagainstcancer.ca/topics/abnormal-call-rates-breast-cancer-screening/current-state/ (Accessed: September 13th, 2024).
11. Esserman, L.J., the WISDOM Study and Athena Investigators. The WISDOM Study: breaking the deadlock in the breast cancer screening debate. *npj Breast Cancer* **2017**, *3, 34*.
12. Laura B. Shepardson, Laura Dean, Current controversies in breast cancer screening. *Seminars in Oncology* **2020**, *47(4)*, 177-181.
13. New York Times, In reversal, expert panel recommends breast cancer screening at 40 **(2024)**. Available at: https://www.nytimes.com/2024/04/30/health/breast-cancer-mammography-ultrasound.html?searchResultPosition=4 (Accessed: September 13th, 2024).

14. CBC, Advocates hope Alberta will follow new guidelines, lower breast cancer screening age to 40. **(2024)** CBC Available at: https://www.cbc.ca/lite/story/1.7206704 (Accessed: September 13th, 2024).
15. Ebell, M.H., Thai, T.N., Royalty, K.J., Cancer screening recommendations: an international comparison of high income countries. *Public Health Rev* **2018**, *39(7)*.
16. USPSTF, Screening for breast cancer: Us preventive services task force recommendation statement **2024**. *JAMA* **2024**, *332(22)*, 1918-1930.
17. CTFPHC, The draft recommendations for breast cancer screening **(May 30, 2024)**. Canadian Task Force on Preventive Health Care Available at: https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update-2024/ (Accessed: September 13th, 2024).
18. NHS, Breast screening: helping women decide **(2024)**. Available at: https://www.gov.uk/government/publications/breast-screening-helping-women-decide (Accessed: March 4th, 2025).
27. European Commission Initiative on Breast Cancer, European guidelines on breast cancer screening and diagnosis **(2017)**. Available at: https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc/european-breast-cancer-guidelines (Accessed: March 4th, 2025).
19. Jayasinghe U.W., Taylor R., Boyages J., Is age at diagnosis an independent prognostic factor for survival following breast cancer? *ANZ J. Surgery* **2005**, *75(9)*, 762–767.
20. Kerlikowske K., Carney P.A., Geller B., Mandelson M., Taplin S., Malvin K., Ernster V., Performance of screening mammography among women with and without a first-degree relative with breast cancer. *Ann. Internal Medicine* **2000**, *133(11)*, 855–863.
21. Yong JHE, Nadeau C, Flanagan WM, et al. The OncoSim-Breast cancer microsimulation model. *Curr Oncol* **2022**, *29*, 1619–1633.
22. Yaffe MJ and Mainprize JG. Effect of breast screening regimen on breast cancer outcomes: a modeling study. *Curr Oncol* **2023**, *30*, 9475–9483.
23. Basmadjian, R. B., Ruan, Y., Hutchinson, J. M., Warkentin, M. T., Alagoz, O., Coldman, A., Brenner, D. R., Examining breast cancer screening recommendations in Canada: The projected resource impact of screening among women aged 40-49. *Journal of medical screening* **2025**, *32(1)*, 35–43.
24. CISNET Breast Cancer Working Group, Breast cancer screening with mammography: an updated decision analysis for the U.S. Preventive Services Task Force.
25. Mittmann N, Stout NK, Tosteson ANA, et al., Cost-effectiveness of mammography from a publicly funded health care system perspective. *CMAJ Open* **2018**, *6*, E77–E86.
26. Knudsen AB, Rutter CM, Peterse EFP, et al., Colorectal Cancer Screening: An Updated Modeling Study for the US Preventive Services Task Force. *JAMA* **2021**, *325(19)*, 1998-2011.
27. Wilkinson AN, Seely JM, Rushton M, et al., Capturing the true cost of breast cancer treatment: molecular subtype and stage-specific per-case activity-based costing. *Curr Oncol* **2023**, *30*, 7860–7873.
28. Kareff SA, Han S, Haaland B, et al. International Cost-Effectiveness Analysis of Durvalumab in Stage III Non–Small Cell Lung Cancer. *AMA Netw Open* **2024**, *7(5)*, doi:10.1001/jamanetworkopen.2024.13938.
29. Shi, J., Guan, Y., Liang, D. et al. Cost-effectiveness evaluation of risk-based breast cancer screening in Urban Hebei Province. *Sci Rep* **2024**, *13, 3370*, https://doi.org/10.1038/s41598-023-29985-z.
30. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa:Canadian. *Agency for Drugs and Technologies in Health* **2017**, Available: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies -canada-4th-edition.
31. Katz DA, Welch HG. Discounting in cost-effectiveness analysis of healthcare programmes. *Pharmacoeconomics* **1993**, *3*, 276-85.
32. Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. *JAMA Oncol.* **2018**, *4(11)*, 1504–1510.
33. Ayvaci MU, Alagoz O, Burnside ES (2012) The effect of budgetary restrictions on breast cancer diagnostic decisions. *Manufacturing Service Operations Management* **2012**, *14(4)*, 600–617.
34. AJohn, J., Koerber, F. Schad, M. Differential discounting in the economic evaluation of healthcare programs. *Cost Eff Resour Alloc* **2019**, *17, 29*, https://doi.org/10.1186/s12962-019-0196-1.
35. Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L., Torrance, G.W. Methods for the Economic Evaluation of Health Care Programmes (4th ed.), Chapter 4. *Oxford University Press* **2015**.