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Article

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

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Abstract:
Objective: To evaluate the cost-effectiveness, cost-utility, and harm-to-benefit ratios of breast cancer screening scenarios for average-risk women using the OncoSim-Breast microsimulation model.
Setting: The entire female Canadian population is modeled, with outcomes reported for the period 2020–2039.
Methods: We first compare the undiscounted economic and clinical outcomes of alternative screening scenarios against the current recommended guideline in Canada, biennial screening for women aged 50–74, which serves as the baseline. We then assess their marginal and incremental cost-effectiveness and cost-utility ratios. Additionally, we examine harm-to-benefit ratios, after which we conduct sensitivity analyses 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 it by 166%. In terms of stage distribution, the proportion of Stage 0 cases is 7% in the least intensive scenario and 10% in the most intensive scenario, indicating a favorable stage shift with increased screening intensity. Notably, the most intensive scenario results in the lowest total treatment cost, with an 8% reduction compared to the baseline. The most efficient scenario is the 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 $CAD 280,954,705 compared to the baseline of biennial screening for women aged 50-74.
Conclusions: Hybrid strategies that begin annual or biennial screening before age 50 while maintaining longer intervals for women over 50 exhibit superior cost-effectiveness compared to the current recommended guideline. In contrast, triennial screening for women under 50 proves inefficient. The design of optimal screening strategies depends on how policymakers prioritize trade-offs between screening harms and benefits and their willingness to pay.

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

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1. Introduction

Breast cancer poses a major public health concern as the most common cancer and the second leading cause of cancer-related deaths among women in Canada [1]. According to the Canadian Cancer Society (CCS) projections, 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 survival rate [3–5]. However, these benefits come with clinical harms, particularly high rates of overdiagnosis and false-positive, as well as considerable monetary costs [6–8]. The false-positive rate of mammography screening, approximately 14% [6], 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 the 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 in which societal concerns about harms outweigh perceived benefits tend to oppose more intensive 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 initiating 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 of these 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 we measure efficacy 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 used to model health and economic outcomes based on the province-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 cancer screening interventions. Yaffe and Mainprize [22] were the first to use OncoSim-Breast to demonstrate that starting annual or biennial screening 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 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, which has the highest cost, prevents the greatest number of cancer-related deaths and also leads to the highest number of early-stage cases. They highlighted the need for an economic analysis to determine whether the reduction in treatment costs could offset the increased screening expenses. As part of our study in this paper, we will touch on this aspect by conducting a thorough economic analysis of an extensive set of screening scenarios.

In this current study, we evaluate the cost-effectiveness, cost-utility, and harm-to-benefit ratios of breast cancer screening scenarios using the OncoSim-Breast microsimulation model. We examine scenarios that expand current guidelines by introducing screening at ages 40 and 45 with varying intervals. Additionally, we consider hybrid scenarios with different screening intervals for ages below and above 50. Finally, we assess the impact of key parameters to test the robustness of our findings and explore the uncertainty surrounding 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 before, adding to the existing body of literature that had not considered this aspect. Through this extensive range of scenarios, our analyses highlight the superior performance of hybrid strategies that initiate screening before age 50 while maintaining longer intervals for women aged 50 and older, particularly the scenario that offers annual screening for women aged 45–49 and triennial screening for those aged 50–74.

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 developed by the Canadian Partnership Against Cancer in collaboration with Statistics Canada. The development, application, and validation of the 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 within each province and territory in 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 outcomes of years 2020 to 2039 for the 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 strategies 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-ups, such as diagnostic imaging, biopsy, and fine-needle aspiration. In case the additional follow-up confirms

the first result to be true positive, the model assign the treatment based on age, subtype, and size of the tumour. The survival from time of screen-detection to breast cancer death includes lead time and net survival benefit (see Figure A2 in Appendix).

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 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. 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 those 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[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[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 2015 calendar year. 3. In all scenarios, the recruitment rate and the rescreen rate are 0.9 and 0.8, respectively.

[1] Hybrid 1: the second phase of all scenarios consists of biennial screening for women aged 50–74.

[2] Hybrid 2: the second phase of all scenarios consists of triennial screening for women aged 50–74.

2.3. Costs and Resources

The model included healthcare costs associated with breast cancer from the perspective of a public healthcare payer, such as the Ministry of Health. These costs covered 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 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 treatment. Economic outcomes are considered either as measure of harm or cost in the statistical analysis. We also report the rate of clinical and economic outcomes per 100,000 screening tests in the supplementary.

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. Statistical Analysis

For brevity, we describe our statistical and sensitivity analysis methodology alongside the numerical results in Section 3.2 and Section 3.3.

3. Results

3.1. Economic and Clinical Outcomes

The undiscounted total number and percent change of economic and clinical outcomes are reported in Table 2 and Table 3, respectively, with full details available in Table A1 and Table A2 in the Appendix. The baseline scenario is [B50-74], reflecting the current guideline recommended by the CTFPHC. 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 Table 2 and Table A1 that the total number of abnormal recalls without cancer, biopsies, and benign biopsies increases almost linearly with the number of screens. The total cost, including the costs of screening, diagnostic procedures, and treatment, also rises with the number of screens but not in a strictly linear fashion (Table 2). In contrast, 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, in more intensive screening scenarios, lower treatment costs can partially offset the overall cost increase.

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

Scenario	Screening Test Performed	Abnormal Recalls without Cancer	Total Treatment Cost	Total Cost
[A40-74]	159,337,941	11,672,110	39,863,215,284	50,657,089,915
[A45-74]	133,001,331	9,842,432	40,213,548,171	49,154,949,593
[A50-74]	116,344,853	8,560,442	41,337,751,364	50,493,640,296
[B40-74]	81,828,955	6,283,072	42,790,552,473	49,299,353,384
[B45-74]	70,671,984	5,472,047	43,229,844,050	48,877,279,549
[B50-74]	59,960,875	4,639,834	43,713,652,309	48,529,124,587
[T40-74]	55,622,910	4,463,363	43,972,566,105	48,462,656,093
[T45-74]	48,024,953	3,899,521	44,335,415,712	48,237,787,062
[T50-74]	40,563,921	3,293,992	44,715,508,410	48,035,863,988
[A40-49, B50-74]	94,436,483	7,125,984	41,681,419,272	50,657,089,915
[A45-49, B50-74]	94,436,483	7,125,984	41,681,419,272	49,154,949,593
[T40-49, B50-74]	63,491,656	5,009,353	44,021,652,475	49,119,636,593
[T45-49, B50-74]	62,773,906	4,923,080	43,980,439,880	48,139,488,817
[A40-49, T50-74]	124,290,029	9,238,510	40,249,209,728	50,019,978,034
[A45-49, T50-74]	80,246,634	6,142,750	42,071,206,861	48,449,957,939
[B40-49, T50-74]	74,392,907	5,768,789	42,747,778,904	48,682,114,723
[B45-49, T50-74]	56,421,239	4,482,712	43,591,508,032	48,139,488,817

Next, we observe from the clinical outcomes in Table 3 and Table 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 19.26% 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, 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 3.2.1, 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. Moreover, 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. We will further examine the number of cancer-related deaths in Section 3.2.4.

We now turn into analyzing the life years (LYs) and quality-adjusted life years (QALYs). Table 3 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. In more intensive scenarios, however, the increase in LYs appears to offset this disutility. We will further examine LYs and QALYs in Section 3.2.2 and Section 3.2.3.

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

Scenario	Invasive Cancer Incidences	DCIS Incidences	Cancer-caused Deaths	Life Years (LYs)	Quality-adjusted Life Years (QALYs)
[A40-74]	667,531	749,052	103,853	407,925,338	348,995,267
[A45-74]	666,911	746,370	106,225	407,906,317	348,995,145
[A50-74]	663,740	740,313	109,789	407,879,945	348,988,488
[B40-74]	654,080	719,714	116,606	407,837,532	348,980,090
[B45-74]	653,246	717,453	118,286	407,824,064	348,976,827
[B50-74]	651,439	714,378	122,335	407,806,037	348,970,000
[T40-74]	644,205	700,661	123,409	407,794,036	348,965,604
[T45-74]	643,217	698,734	124,726	407,783,793	348,962,411
[T50-74]	640,915	695,826	126,748	407,768,415	348,955,376
[A40-49, B50-74]	645,872	713,460	106,241	407,878,718	349,004,275
[A45-49, B50-74]	649,223	723,228	112,358	407,917,434	349,008,545
[T40-49, B50-74]	653,563	714,160	122,335	407,797,027	348,960,893
[T45-49, B50-74]	655,911	718,274	121,468	407,797,984	348,961,481
[A40-49, T50-74]	638,602	708,999	107,202	407,913,174	349,012,333
[A45-49, T50-74]	632,962	694,897	115,190	407,864,328	349,004,096
[B40-49, T50-74]	644,356	706,304	117,432	407,834,482	348,984,262
[B45-49, T50-74]	641,777	699,646	121,272	407,811,042	348,977,927

3.2. Statistical Analysis

3.2.1. Total number and proportion of DCIS and invasive breast cancer cases by stage

The distribution/proportion of cancer stages 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 both Table 4 and Table 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 increase by 15% and 12%, respectively. Conversely, in the most intensive scenario, [A40-74], which has 166.12% 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. 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 baseline) across all scenarios in Figure 1, based on the data in Table 4. As shown in Figure 1, hybrid scenarios (marked blue and green), along with the most intensive scenarios (annual scenarios marked 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.

Table 4. Proportion (and percentage change) of Cancer Incidences by Stages among all women in Canada accumulated from 2020 to 2039.

Scenario	Proportion of Stage 0 (percentage change %)[1]	Proportion of Stage I (percentage change %)	Proportion of Stage II (percentage change %)	Proportion of Stage III (percentage change %)	Proportion of Stage IV (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] For simplicity in illustration, we rounded percent change values to integers.

Note: 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].

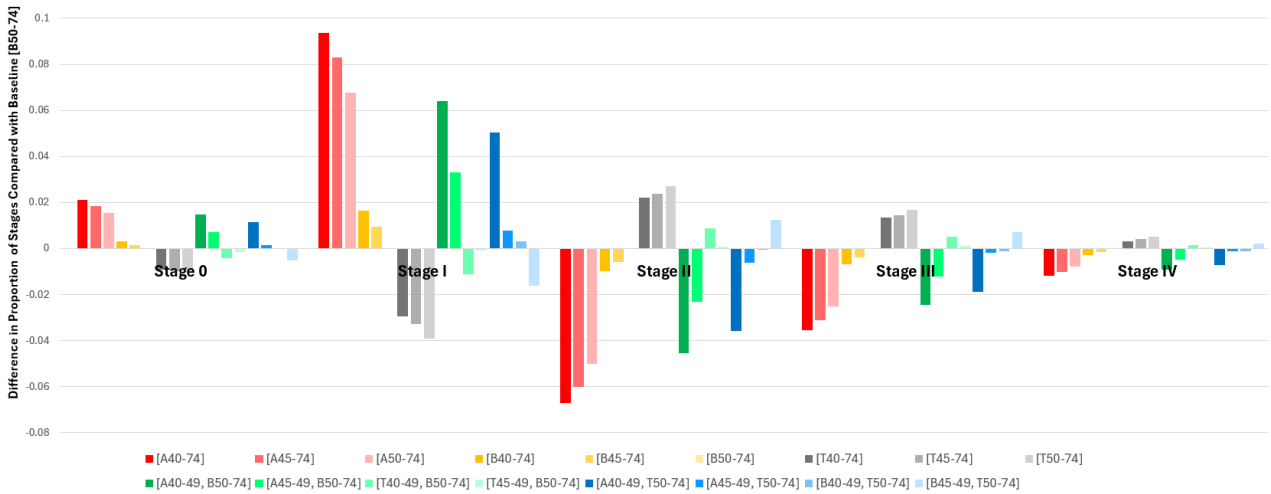


Figure 1. Difference in the proportion of cancer stages under various screening scenarios compared to the baseline scenario [B50–74], accumulated across all women in Canada from 2020 to 2039. Each color represents a group of scenarios (see Table 1 for groups' definition): red for Annual, yellow for Biennial,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

3.2.2. Marginal Cost Effectiveness and Utility Ratios (MCER and MCUR)

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 health-adjusted life years gained. In other words, MCER (MCUR) represents the cost of gaining one additional unit of LYs (QALYs) compared to the baseline. This analysis is particularly useful when

decision-makers seek the most favorable alternative without considering budget constraints. We apply a 3% discount rate, as reported in the majority of recent studies (e.g. [28,29]). In 2012, a 5% discount rate was commonly used, however, recommended rates have since declined to 3%, and then to 1.5% in 2017 [25,30]. It is conventional to use the same discount rate for both health and economic outcomes [31]. In our analysis, we use 2020 as the reference year and 2039 as the comparator year, summing the discounted values over this period. If a scenario provides lower benefits than the baseline, it is classified as an inferior scenario. MCER and MCUR can take negative values when a scenario incurs lower costs while providing greater benefits. In such cases, the baseline scenario is, in fact, inferior to the scenario with a negative MCER or MCUR. We again consider the current screening guidelines of CTFPHC, biennial screening from ages 50 to 74, as the baseline. Given that previous studies have established the clinical benefits of more intensive screening strategies [22,23], our analysis does not consider scenarios that involve less frequent or no screening. Instead, we use the existing guideline as the baseline and evaluate alternative strategies primarily from an economic perspective.

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 inferior. 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 has negative MCER and MCUR, meaning it is both cost-saving and more effective. The ranking of scenarios based on MCER and 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 $/LY and 1,971 $/QALY, respectively. As the most intensive scenario, [A40-74] has the highest values, at 37,884 $/LY and 276,058 $/QALY, respectively.

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	Marginal Life Years	Marginal Quality-adjusted Life Years	Marginal Cost-Effectiveness Ratio (MCER)	Marginal Cost-Utility Ratio (MCER)
[A40-74]	80,302	11,020	37,884	276,058
[A45-74]	67,500	12,433	33,060	179,483
[A50-74]	49,862	9,449	31,349	165,421
[B40-74]	21,113	5,102	30,521	126,288
[B45-74]	12,129	3,773	24,771	79,630
[B50-74]	0	0	-	-
[T40-74]	-8,087	-2,818	Inferior	Inferior
[T45-74]	-14,974	-4,443	Inferior	Inferior
[T50-74]	-25,401	-8,659	Inferior	Inferior
[A40-49, B50-74]	75,271	19,905	25,463	96,286
[A45-49, B50-74]	49,905	20,822	11,840	28,376
[T40-49, B50-74]	-6,158	-5,991	Inferior	Inferior
[T45-49, B50-74]	-5,859	-6,081	Inferior	Inferior
[A40-49, T50-74]	72,517	22,427	20,561	66,483
[A45-49, T50-74]	40,644	21,532	1,044	1,971
[B40-49, T50-74]	19,137	7,808	12,428	30,460
[B45-49, T50-74]	3,825	5,433	-73,446	-51,705

3.2.3. Incremental Cost Effectiveness and Utility Ratios (ICER and ICUR)

In this analysis, we assume that policymakers aim to balance competing priorities within limited resources. Therefore, we examine the harm associated with the last LY gained or death averted to assess the trade-offs between benefits and harms. In such a setting, we first define the baseline as the scenario with the lowest total cost. We then identify the scenario with the lowest cost per additional life year and health-adjusted life year gained, corresponding to the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR), respectively. Once the first incrementally efficient scenario is identified, we proceed by selecting the next most efficient scenario among those with higher total costs than the previously chosen scenario, continuing this process iteratively. Some scenarios are classified as weakly dominated if their incremental costs are close to those of the most efficient scenario. Scenarios with substantially higher incremental costs are considered strongly dominated. We used the average incremental benefits of dominated scenarios as a threshold to categorize dominated scenarios into weakly and strongly dominated. Additionally, scenarios that provide lower benefits than the baseline are labeled as inferior. For both the marginal and incremental cost ratio analyses, we follow the approach used by Mittmann et al. [25].

Discounted total costs, LYs, QALYs, and the corresponding ICER and ICUR values are presented in Table 6. This table is the consolidated version of two tables, see Table A4 and Table A5 in the Appendix for the original versions of ICER and ICUR tables. 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 $/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 $/LY, 45,449 $/LY, 154,555 $/LY, and 223,726 $/LY, respectively. The only dominated scenario is [A45-49, B50-74], which 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 $/QALY. Only two additional scenarios

remain incrementally efficient, [A45-49, T50-74] and [A40-49, T50-74], with ICUR values of 20,089 $/QALY and 1,617,874 $/QALY, respectively. A key observation is that two scenarios, [A40-49A, B50-74] and [A40-74], are no longer efficient under ICUR, as they now become inferior to [A40-49A, T50-74].

Table 6. Consolidated incremental 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%.

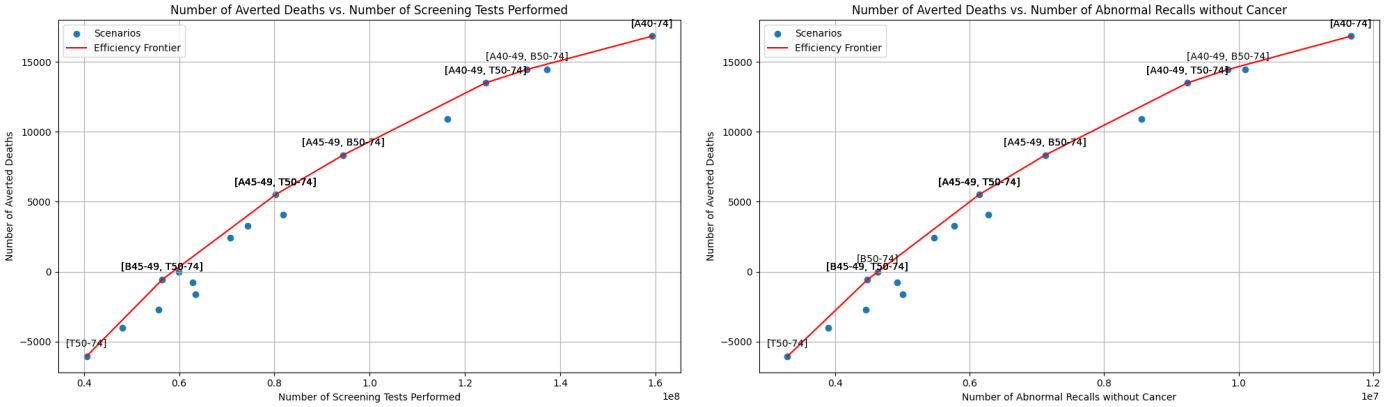
Scenario	Incremental Life Years	Incremental Quality-adjusted Life Years	Incremental Cost-Effectiveness Ratio ($/LY)	Incremental Cost-Utility Ratio ($/QALY)
[A40-74]	5,031	-11,408	223,726	Inferior
[A45-74]	-7,771	-9,995	Inferior	Inferior
[A50-74]	-22,655	-12,978	Inferior	Inferior
[B40-74]	-16,430	-16,430	Inferior	Inferior
[B45-74]	-28,516	-17,759	Inferior	Inferior
[B50-74]	-3,825	-5,434	Inferior	Inferior
[T40-74]	-11,913	-8,251	Inferior	Inferior
[T45-74]	-18,799	-9,877	Inferior	Inferior
[T50-74]	0	0	–	–
[A40-49,B50-74]	2,753	-2,522	154,555	Inferior
[A45-49,B50-74]	9,261	-710	W. Dominated	Inferior
[T40-49,B50-74]	-46,803	-27,523	Inferior	Inferior
[T45-49,B50-74]	-46,503	-27,613	Inferior	Inferior
[A40-49,T50-74]	31,873	895	45,449	1,617,874
[A45-49,T50-74]	36,819	16,099	8,784	20,089
[B40-49,T50-74]	-21,507	-13,724	Inferior	Inferior
[B45-49,T50-74]	29,226	14,093	5,487	11,378

3.2.4. Harm-to-Benefit Efficiency Frontiers

This analysis follows a similar approach to ICER and ICUR analysis, with the key difference that, instead of monetary cost, we consider the number of screens and the number of abnormal recalls without cancer as measures of harm. As measures of benefit, we use the number of averted deaths. This approach follows the methodology used in CISNET's study [24] and as defined in Knudsen et al. [26]. See Section B.6 and Figure A3 for a detailed illustration of the efficiency frontier. Each scenario is represented as a point in a two-axis plot, where the x-axis corresponds to harm, and the y-axis represents benefit. The scenarios that lie on the efficiency frontier represent the incrementally most efficient options, while those positioned near and far below the frontier are classified as weakly and strongly dominated options, respectively

Figure 2 (a) and Figure 2 (b) illustrate the averted number of deaths gained versus the number of screens and the number of abnormal recalls without cancer, respectively. All scenarios identified as efficient in the ICER analysis also appear on the efficiency frontiers. For the averted number of deaths versus the number of screens in Figure 2 (a), one additional scenario (than ICER analysis), [A45-49A, B50-74], appears on the efficiency frontier, indicating its effectiveness in reducing cancer-related mortality. In Figure 2 (b), when using the averted number of deaths as the benefit measure and abnormal recalls without cancer as the harm measure, two additional scenarios (than ICER analysis), [B50-74] and [A45-49A, B50-74], emerge as efficient. This suggests that these scenarios perform efficiently in reducing cancer-related mortality when we ignore the number of screens and consider abnormal recalls without cancer as the only harm measure. The data underlying these figures are also presented in Table A6 and Table A7 in the Appendix, with the

same logic as the consolidated ICER and ICUR table (Table 6). We also illustrate the efficiency frontiers of ICER and ICUR in Figure A4 (a) and Figure A4 (b) in the Appendix. These figures illustrate the shape and structure of trade-offs between benefits, harms, and costs. Notably, all the efficiency frontier figures (Figure 2 and Figure A4) 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])



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

Figure 2. (**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.

3.3. 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), participation rates, the discount factor, and per-case treatment costs by stage (see Table 7 for parameter ranges used in each sensitivity analysis experiment). For the per-case treatment costs, we draw on external evidence to update the model's parameters. 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 life time per case treatment cost for Stage 0, Stage I, Stage II, Stage III, and Stage IV, we considered $14,505, $39,263, $76,446, $97,668, $370,398 (CAD), respectively. See Table S2 in supplementary for a detailed description of each sensitivity analysis experiment. 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 dramatically. 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 QALYs decreases while total costs remain unchanged. (2) When the rescreen rate is reduced from 0.8 to 0.4, total costs remain relatively stable in less intensive scenarios, as screening and diagnostic costs account for a relatively small proportion of 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 scenarios [T40-49, B50-74] and [T40-74], the only more intensive scenarios that involve triennial screening for women under age 50, the reduced frequency of screening mitigates disutility associated with initial screening, leading to a net benefit. As a result, these scenarios exhibit negative MCURs instead of being inferior. (3) When the discount rate is adjusted from 3% to 1.5% and 4.5%, the MCUR slightly decreases and increases, respectively. This suggests that the denominator of the MCUR, QALY, is more sensitive to changes in the discount rate than 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], total costs increase for all scenarios, which is expected. However, the rate of increase varies across scenarios due to differences in stage distribution and total treatment costs. In most cases where QALYs are higher than the baseline scenario, MCUR decreases, indicating that incorporating more realistic treatment costs strengthens the relative benefits of more intensive screening strategies.

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%.

	Marginal Cost-Utility Ratio ($/QALY)					
Scenario	**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]	Inferior	Inferior	-197,428	Inferior	Inferior	Inferior
[T45-74]	Inferior	Inferior	Inferior	Inferior	Inferior	Inferior
[T50-74]	Inferior	Inferior	Inferior	Inferior	Inferior	Inferior
[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]	Inferior	Inferior	-162,734	Inferior	Inferior	Inferior
[T45-49, B50-74]	Inferior	Inferior	Inferior	Inferior	Inferior	Inferior
[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

4. Discussion

This study evaluates the economic and health implications of alternative breast cancer screening strategies using the OncoSim-Breast microsimulation model. By examining multiple dimensions of cost-effectiveness, cost-utility, and harm-to-benefit ratios across an extensive set of 17 screening scenarios, this study provides a broad perspective on the trade-offs involved in revising current screening guidelines in Canada.

Our findings 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]. Among the screening strategies analyzed, hybrid scenarios that include screening before age 50 while maintaining longer intervals for women over 50, particularly [A45-49, T50-74] and [B45-49, T50-74], exhibit superior cost-effectiveness compared to the baseline. These findings suggest that screening initiation before age 50, particularly at 45, while maintaining a biennial or triennial interval after 50, provides a favorable balance between benefits and costs. Conversely, scenarios with triennial screening for women under 50 perform poorly in both marginal and incremental analyses, reinforcing that this approach is 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. Importantly, our sensitivity analyses indicate that the primary qualitative findings remain robust under variations in key input parameters. This consistency strengthens the reliability of the conclusions and underscores the value of conducting economic evaluations when considering adjustments to screening policies. 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, 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 before, adding to the existing body of literature that had not considered this aspect. 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. Furthermore, we explore the effect of varying key OncoSim input parameters, including participation rates and treatment costs, to assess the robustness of our findings.

However, this study has some limitations. We did not evaluate screening strategies tailored to higher-risk groups, nor did we incorporate OncoSim's risk-based screening modules. We plan to study risk-based screening scenarios in another work. 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, 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 costs, harms, and benefits of screening. The decisions on how to design screening strategies largely depend on policymakers' willingness to pay and on how they weigh different aspects of the trade-offs associated with harms and benefits. 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 into account

all dimensions of our analysis, we recommend hybrid strategies that initiate screening before age 50 while maintaining longer intervals for women aged 50 and older, particularly the scenario that offers annual screening for women aged 45–49 and triennial screening for those aged 50–74, due to its cost savings and higher health benefits.

Appendix A. OncoSim

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

The following figure is adapted from Yong et al. [21].

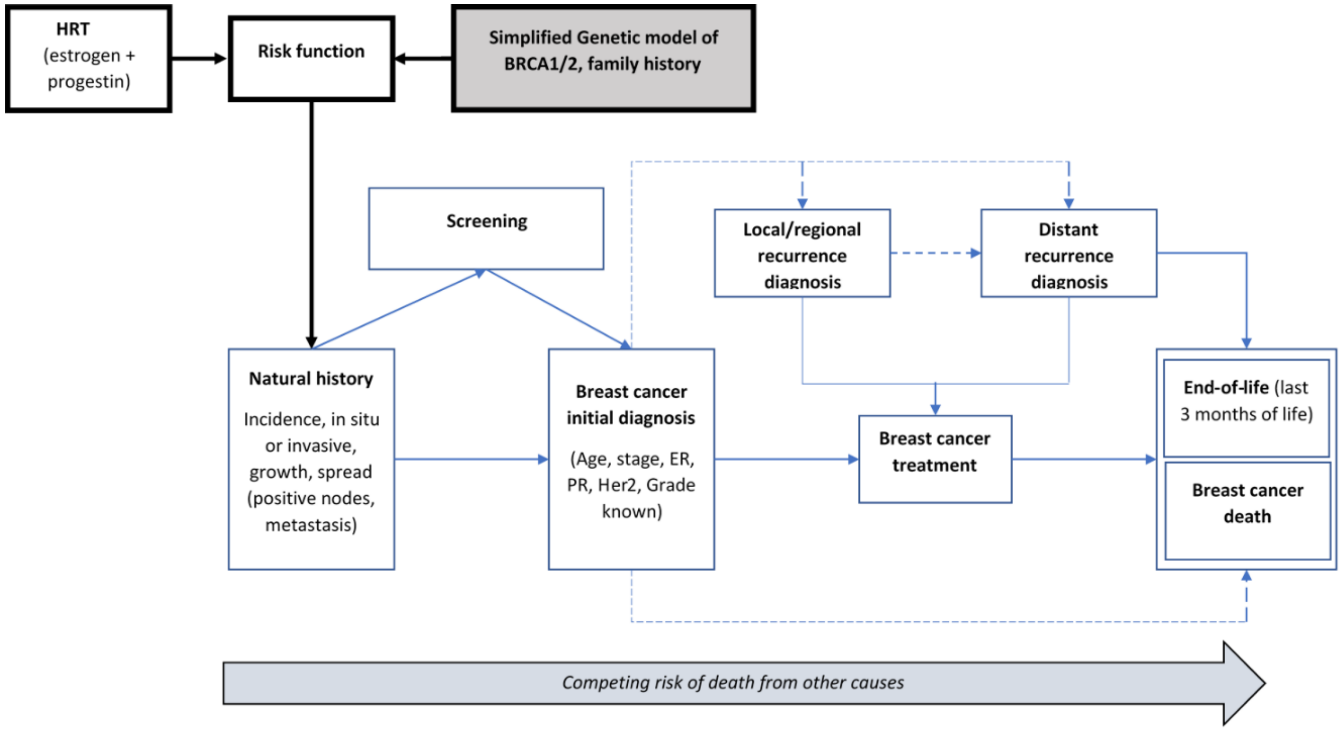


Figure A1. Schematic diagram of the OncoSim-Breast model

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) tumours. Tumours are initiated at 2 mm diamter, 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 tumour onset, scaled according to the maximum diameter allowed for a tumour type. Invasive tumorus have the potential to spread to lymph nodes and other parts of the body. The likelihood of lymph node involvement is a function of tumour size, growth rate, and the time since tumour 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 tumours. 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, tumour size, and the number of positive lymph nodes. In OncoSim, screening can detect tumours in their sojourn time

earlier than they would have been detected clinically (see Figure A2 in Appendix). The model incorporates various screening modalities (e.g., digital mammography, ultrasound, MRI), allowing for adjustments in sensitivity and specificity based on age group, tumour size, and screening sequence.

Appendix A.3. Timeline of cancer progression and detection

The following figure is adapted from Yong et al. [21].

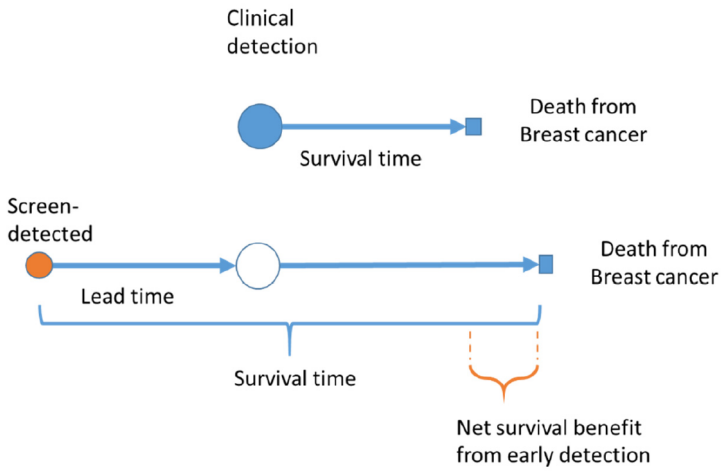


Figure A2. Diagram to show how screening affects survival

Appendix B. Detailed Numerical Results

Appendix B.1. Detailed Total Number of Economic Outcomes

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

Scenario	Women Screened	Screening Test Performed	Abnormal Recalls without Cancer	Biopsy Test Performed	Benign Biopsy Results	Total Cost	Total Treatment Cost
[A40-74]	158,398,440 (+166.12)	159,337,941 (+165.74)	11,672,110 (+151.56)	1,550,976 (+103.28)	1,038,817 (+151.56)	52,337,137,379 (+7.85)	39,863,215,284 (-8.81)
[A45-74]	136,324,125 (+129.04)	137,228,229 (+128.86)	10,098,076 (+117.64)	1,389,008 (+82.06)	898,728 (+117.64)	51,313,896,851 (+5.74)	40,543,546,716 (-7.25)
[A50-74]	115,473,355 (+94.00)	116,344,853 (+94.03)	8,560,442 (+84.50)	1,218,712 (+59.74)	761,879 (+84.50)	50,493,640,296 (+4.05)	41,337,751,364 (-5.44)
[B40-74]	81,353,378 (+36.68)	81,828,955 (+36.47)	6,283,072 (+35.42)	945,829 (+23.97)	559,193 (+35.42)	49,299,353,384 (+1.59)	42,790,552,473 (-2.11)
[B45-74]	70,214,945 (+17.97)	70,671,984 (+17.86)	5,472,047 (+17.94)	857,618 (+12.41)	487,012 (+17.94)	48,877,279,549 (+0.72)	43,229,844,050 (-1.11)
[B50-74]	59,520,868 (0.00)	59,960,875 (0.00)	4,639,834 (0.00)	762,958 (0.00)	412,945 (0.00)	48,529,124,587 (0.00)	43,713,652,309 (0.00)
[T40-74]	55,304,052 (-7.08)	55,622,910 (-7.23)	4,463,363 (-3.80)	704,637 (-7.64)	397,239 (-3.80)	48,462,656,093 (-0.14)	43,972,566,105 (+0.59)
[T45-74]	47,718,837 (-19.83)	48,024,953 (-19.91)	3,899,521 (-15.96)	643,206 (-15.70)	347,057 (-15.96)	48,237,787,062 (-0.60)	44,335,415,712 (+1.42)
[T50-74]	40,269,853 (-32.34)	40,563,921 (-32.35)	3,293,992 (-29.01)	573,322 (-24.86)	293,165 (-29.01)	48,035,863,988 (-1.02)	44,715,508,410 (+2.29)
[A40-49, B50-74]	132,315,589 (+122.30)	133,001,331 (+121.81)	9,842,432 (+112.13)	1,327,880 (+74.04)	875,976 (+112.13)	50,657,089,915 (+4.38)	40,213,548,171 (-8.01)
[A45-49, B50-74]	93,899,478 (+57.76)	94,436,483 (+57.50)	7,125,984 (+53.58)	1,033,071 (+35.40)	634,212 (+53.58)	49,154,949,593 (+1.29)	41,681,419,272 (-4.65)
[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)	49,119,636,593 (+1.22)	44,021,652,475 (+0.70)
[T45-49, B50-74]	62,343,804 (+4.74)	62,773,906 (+4.69)	4,923,080 (+6.10)	792,405 (+3.86)	438,154 (+6.10)	49,020,925,153 (+1.01)	43,980,439,880 (+0.61)
[A40-49, T50-74]	123,685,709 (+107.80)	124,290,029 (+107.29)	9,238,510 (+99.11)	1,240,370 (+62.57)	822,227 (+99.11)	50,019,978,034 (+3.07)	40,249,209,728 (-7.93)
[A45-49, T50-74]	79,831,221 (+34.12)	80,246,634 (+33.83)	6,142,750 (+32.39)	892,014 (+16.92)	546,704 (+32.39)	48,449,957,939 (-0.16)	42,071,206,861 (-3.76)
[B45-49, T50-74]	56,084,695 (-5.77)	56,421,239 (-5.90)	4,482,712 (-3.39)	715,057 (-6.28)	398,961 (-3.39)	48,139,488,817 (-0.80)	43,591,508,032 (-0.28)
[B40-49, T50-74]	73,990,309 (+24.31)	74,392,907 (+24.07)	5,768,789 (+24.33)	868,359 (+13.81)	513,422 (+24.33)	48,682,114,723 (+0.32)	42,747,778,904 (-2.21)

Note: 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].

Appendix B.2. Detailed Total Number of Health Outcomes

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

Scenario	Invasive Cancer Incidences	DCIS Incidences	Screen Detected Incidences	Cancer-caused Deaths	Life Years	Quality-adjusted Life Years	Mortality Rate (per 1000 women)
[A40-74]	667,531 (+2.47)	749,052 (+4.85)	512,159 (+46.33)	103,853 (-13.95)	407,925,338 (+0.02925)	348,995,267 (+0.00724)	0.25574 (-13.69)
[A45-74]	666,911 (+2.38)	746,370 (+4.48)	490,279 (+40.07)	106,225 (-11.99)	407,906,317 (+0.02459)	348,995,145 (+0.00721)	0.26147 (-11.76)
[A50-74]	663,740 (+1.89)	740,313 (+3.63)	456,833 (+30.52)	109,789 (-9.03)	407,879,945 (+0.01812)	348,988,488 (+0.00530)	0.27003 (-8.87)
[B40-74]	654,080 (+0.41)	719,714 (+0.75)	386,635 (+10.46)	116,606 (-3.39)	407,837,532 (+0.00772)	348,980,090 (+0.00289)	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 (+0.00442)	348,976,827 (+0.00196)	0.29052 (-1.95)
[B50-74]	651,439 (0.00)	714,378 (0.00)	350,013 (0.00)	120,693 (0.00)	407,806,037 (0.00000)	348,970,000 (0.00000)	0.29630 (0.00)
[T40-74]	644,205 (-1.11)	700,661 (-1.92)	307,397 (-12.18)	123,409 (+2.25)	407,794,036 (-0.00294)	348,965,604 (-0.00126)	0.30282 (+2.20)
[T45-74]	643,217 (-1.26)	698,734 (-2.19)	296,149 (-15.39)	124,726 (+3.34)	407,783,793 (-0.00545)	348,962,411 (-0.00217)	0.30600 (+3.27)
[T50-74]	640,915 (-1.62)	695,826 (-2.60)	280,157 (-19.96)	126,748 (+5.02)	407,768,415 (-0.00923)	348,955,376 (-0.00419)	0.31086 (+4.91)
[A40-49, B50-74]	649,223 (-0.34)	723,228 (+1.24)	451,903 (+29.11)	106,241 (-11.97)	407,917,434 (+0.02732)	349,008,545 (+0.01105)	0.26130 (-11.81)
[A45-49, B50-74]	645,872 (-0.85)	713,460 (-0.13)	398,858 (+13.96)	112,358 (-6.91)	407,878,718 (+0.01782)	349,004,275 (+0.00982)	0.27591 (-6.88)
[T40-49, B50-74]	653,563 (+0.33)	714,160 (-0.03)	341,373 (-2.47)	122,335 (+1.36)	407,797,027 (-0.00221)	348,960,893 (-0.00261)	0.30033 (+1.36)
[T45-49, B50-74]	655,911 (+0.69)	718,274 (+0.55)	354,250 (+1.21)	121,468 (+0.64)	407,797,984 (-0.00197)	348,961,481 (-0.00244)	0.29832 (+0.68)
[A40-49, T50-74]	638,602 (-1.97)	708,999 (-0.75)	418,143 (+19.46)	107,202 (-11.18)	407,913,174 (+0.02627)	349,012,333 (+0.01213)	0.26355 (-11.05)
[A45-49, T50-74]	632,962 (-2.84)	694,897 (-2.73)	345,309 (-1.34)	115,190 (-4.56)	407,864,328 (+0.01429)	349,004,096 (+0.00977)	0.28262 (-4.62)
[B40-49, T50-74]	644,356 (-1.09)	706,304 (-1.13)	354,937 (+1.41)	117,432 (-2.70)	407,834,482 (+0.00698)	348,984,262 (+0.00409)	0.28839 (-2.67)
[B45-49, T50-74]	641,777 (-1.48)	699,646 (-2.06)	316,096 (-9.69)	121,272 (+0.48)	407,811,042 (+0.00123)	348,977,927 (+0.00227)	0.29754 (+0.42)

Note: 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].

Appendix B.3. Total number and percent change of cancer cases by stage

Table A3. Total number and percent change of cancer cases by stage

Scenario	Number of Stage 0	Number of Stage I	Number of Stage II	Number of Stage III	Number of Stage IV
[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)

Note: 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.

Appendix B.4. Original table of Incremental cost-effectiveness ratios (ICER)

Table A4. Incremental cost-effectiveness ratios (ICER)

Scenario	Total Cost	LYs	Incremental Cost	Incremental LYs	ICER
[T50-74]	36,330,207,746	309,713,265	0	0	–
[B45-49, T50-74]	36,490,561,268	309,742,491	160,353,522	29,226	5,487
[T45-74]	36,508,123,144	309,723,692	17,561,876	-18,799	Inferior
[T40-74]	36,692,551,383	309,730,579	201,990,114	-11,913	Inferior
[B50-74]	36,771,515,974	309,738,666	280,954,706	-3,825	Inferior
[A45-49, T50-74]	36,813,963,301	309,779,310	323,402,033	36,819	8,784
[B40-49, T50-74]	37,009,354,346	309,757,803	195,391,045	-21,507	Inferior
[B45-74]	37,071,951,976	309,750,795	257,988,674	-28,516	Inferior
[T45-49, B50-74]	37,131,921,790	309,732,807	317,958,489	-46,503	Inferior
[T40-49, B50-74]	37,139,669,869	309,732,508	325,706,568	-46,803	Inferior
[A45-49, B50-74]	37,362,372,213	309,788,571	548,408,912	9,261	Dominated
[B40-74]	37,415,916,687	309,759,779	601,953,385	-16,430	Inferior
[A40-49, T50-74]	38,262,576,975	309,811,183	1,448,613,674	31,873	45,449
[A50-74]	38,334,665,285	309,788,528	72,088,310	-22,655	Inferior
[A40-49, B50-74]	38,688,134,074	309,813,937	425,557,099	2,753	154,555
[A45-74]	39,003,041,788	309,806,166	314,907,714	-7,771	Inferior
[A40-74]	39,813,670,477	309,818,968	1,125,536,403	5,031	223,726

Appendix B.5. Original table of Incremental cost-utility ratios (ICUR)

Table A5. Incremental cost-utility ratios (ICUR)

Scenario	Total Cost	QALYs	Incremental Cost	Incremental QALY	ICUR
[T50-74]	36,330,207,746	265,218,058	0	0	-
[B45-49, T50-74]	36,490,561,268	265,232,150	160,353,522	14,093	11,378
[T45-74]	36,508,123,144	265,222,274	17,561,876	-9,877	Inferior
[T40-74]	36,692,551,383	265,223,899	201,990,114	-8,251	Inferior
[B50-74]	36,771,515,974	265,226,717	280,954,706	-5,434	Inferior
[A45-49, T50-74]	36,813,963,301	265,248,249	323,402,033	16,099	20,089
[B40-49, T50-74]	37,009,354,346	265,234,525	195,391,045	-13,724	Inferior
[B45-74]	37,071,951,976	265,230,490	257,988,674	-17,759	Inferior
[T45-49, B50-74]	37,131,921,790	265,220,636	317,958,489	-27,613	Inferior
[T40-49, B50-74]	37,139,669,869	265,220,726	325,706,568	-27,523	Inferior
[A45-49, B50-74]	37,362,372,213	265,247,539	548,408,912	-710	Inferior
[B40-74]	37,415,916,687	265,231,819	601,953,385	-16,430	Inferior
[A40-49, T50-74]	38,262,576,975	265,249,144	1,448,613,674	895	1,617,874
[A50-74]	38,334,665,285	265,236,166	72,088,310	-12,978	Inferior
[A40-49, B50-74]	38,688,134,074	265,246,622	425,557,099	-2,522	Inferior
[A45-74]	39,003,041,788	265,239,150	740,464,813	-9,995	Inferior
[A40-74]	39,813,670,477	265,237,737	1,551,093,502	-11,408	Inferior

Appendix B.6. Harm-to-Benefit Efficiency Frontiers Method

To define the efficiency frontier, we begin with the scenario that has the lowest harm (point A in Figure A3). We then identify the next point that forms the steepest connecting line with the first scenario (point B in Figure A3). 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 A3), while those positioned near and far below the frontier are classified as weakly and strongly dominated options, respectively (orange color points in Figure A3).

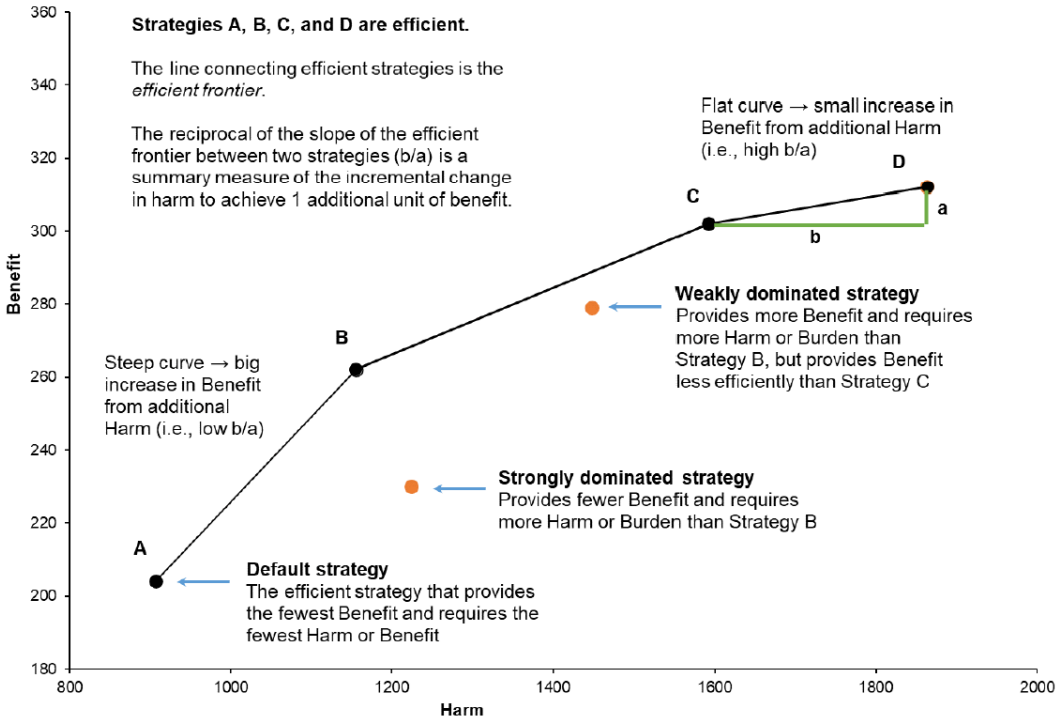
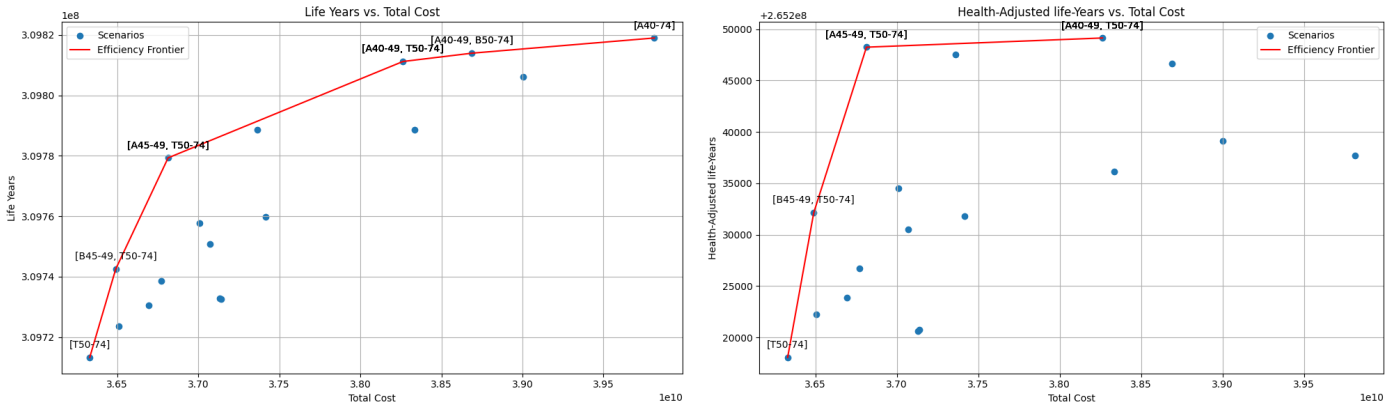


Figure A3. Illustration of Harm-to-Benefit efficiency frontiers method.



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

Figure A4. (**a**) Visual illustration of efficiency frontier for incremental cost-effectiveness ratios. (**b**) Visual illustration of efficiency frontier for incremental cost-utility ratios.

Table A6. Incremental Harm to Benefit (Number of Screening Tests to Number of Averted Deaths) Ratio

Scenario	Number of Screening Tests	Number of Averted Deaths	Incremental Number of Screening Tests	Incremental Number of Averted Deaths	Incremental Harm to Benefit Ratio
[T50-74]	40,563,922	-6,055	0	0	-
[T45-74]	48,024,954	-4,033	7,461,032	2,022	W. Dominated
[T40-74]	55,622,911	-2,716	15,058,989	3,338	S. Dominated
[B45-49, T50-74]	56,421,239	-579	15,857,317	5,476	2,896
[B50-74]	59,960,875	0	3,539,636	579	S. Dominated
[T45-49, B50-74]	62,773,907	-775	6,352,667	-197	Inferior
[T40-49, B50-74]	63,491,656	-1,642	7,070,417	-1,063	Inferior
[B45-74]	70,671,984	2,407	14,250,745	2,986	W. Dominated
[B40-49, T50-74]	74,392,908	3,260	17,971,668	3,839	W. Dominated
[A45-49, T50-74]	80,246,635	5,503	23,825,396	6,082	3,918
[B40-74]	81,828,955	4,087	1,582,321	-1,416	Inferior
[A45-49, B50-74]	94,436,484	8,335	14,189,849	2,832	5,010
[A50-74]	116,344,853	10,904	21,908,370	2,568	W. Dominated
[A40-49, T50-74]	124,290,029	13,491	29,853,545	5,156	5,790
[A40-49, B50-74]	133,001,331	14,452	8,711,302	961	9,064
[A45-74]	137,228,229	14,468	4,226,898	16	W. Dominated
[A40-74]	159,337,941	16,840	26,336,610	2,388	11,029

Table A7. Incremental Harm to Benefit (Number of Abnormal Recalls without Cancer to Number of Averted Deaths) Ratio

Scenario	Number of Abnormal Recalls without Cancer	Number of Averted Deaths	Incremental Number of Abnormal Recalls without Cancer	Incremental Number of Averted Deaths	Incremental Harm to Benefit Ratio
[T50-74]	3,293,993	-6,055	0	0	
[T45-74]	3,899,522	-4,033	605,529	2,022	W. Dominated
[T40-74]	4,463,364	-2,716	1,169,371	3,338	S. Dominated
[B45-49,T50-74]	4,482,713	-579	1,188,720	5,476	217
[B50-74]	4,639,835	0	157,122	579	271
[T45-49,B50-74]	4,923,080	-775	283,246	-775	Inferior
[T40-49,B50-74]	5,009,353	-1,642	369,519	-1,642	Inferior
[B45-74]	5,472,048	2,407	832,213	2,407	W. Dominated
[B40-49,T50-74]	5,768,790	3,260	1,128,955	3,260	S. Dominated
[A45-49,T50-74]	6,142,750	5,503	1,502,916	5,503	273
[B40-74]	6,283,073	4,087	140,322	-1,416	Inferior
[A45-49,B50-74]	7,125,985	8,335	983,234	2,832	347
[A50-74]	8,560,442	10,904	1,434,457	2,568	W. Dominated
[A40-49,T50-74]	9,238,511	13,491	2,112,526	5,156	410
[A40-49,B50-74]	9,842,432	14,452	603,921	961	628
[A45-74]	10,098,077	14,468	255,645	16	W. Dominated
[A40-74]	11,672,111	16,840	1,829,679	2,388	766

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