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Markov Models in Health Technology Assessment: Cost-Effectiveness Analyses Using Literature- and Trial-Based Data in Breast and Ovarian Cancer

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Abstract

Background: Cancer is one of the leading causes of death worldwide and a major driver of health system costs. Advances in prevention and treatment have improved survival rates, but the rising prevalence and escalating costs of new therapies intensify pressure on healthcare systems. Economic evaluation within Health Technology Assessment provides an evidence-based framework to guide the allocation of resources. Markov modelling is widely used to capture long-term costs and outcomes in oncology; however, its robustness relies on the type of data used.

Methods: This thesis employed Markov modelling in two case studies in oncology to assess the cost-effectiveness of preventive and therapeutic strategies, and to investigate how data sources impact outcomes and transferability. Case Study A assessed risk-reducing surgery versus surveillance and no intervention in women with pathogenic BRCA variants in Italy, using literature and registry data. Case Study B evaluated a single dose versus a standard six-monthly zoledronic acid regimen in early breast cancer in Canada, based on pragmatic randomized controlled trial data.

Results: Case Study A found that surgery was cost-effective compared to alternative strategies, although the results were sensitive to assumptions regarding uptake and treatment costs. Case Study B suggested that a single dose of zoledronic acid may be a cost-effective alternative; however, the short follow-up period limited the ability to draw longer-term conclusions. Across both cases, the type and quality of data sources strongly influenced model design, robustness, and transferability.

Conclusion: This thesis shows how economic modelling can inform cancer prevention and treatment policy, while highlighting that outcomes are shaped by the evidence base. Using distinct data sources, the case studies illustrate the strengths and limitations of Markov models in guiding cost-effective, patient-centred care.

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Abbreviation

AI	Aromatase Inhibitor
APR	Acute Phase Reaction
BC	Breast Cancer
BMD	Bone Mineral Density
BMFS	Bone Metastasis-Free Survival
BRCA 1/2	Breast Cancer Gene 1/2
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Analysis Curve
CIHI	Canadian Institute for Health Information
CUA	Cost-Utility Analysis
EBC	Early Breast Cancer
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	Emergency Room
GnRH	Gonadotropin-Releasing Hormone
HR+	Hormone Receptor-Positive
HRT	Hormone Replacement Therapy
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INB	Incremental Net Benefit
ITT	Tntention-To-Treat
IV	Intravenous
MCS	Monte Carlo Simulation
MRI	Magnetic Resonance Imaging

NI	No-Intervention
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
OC	Ovarian Cancer
ONJ	Osteonecrosis of the Jaw
OS	Overall Survival
OSB	Ontario Schedule of Benefits
OWSA	One-Way Sensitivity Analysis
PSA	Probabilistic Sensitivity Analysis
PV	Pathogenic Variants
QALY	Quality-Adjusted Life-Years
QoL	Quality of Life
RCT	Randomized Controlled Trial
REaCT BTA	Rethinking Clinical Trials Bone-Targeted Agents
REaCT ZOL	Rethinking Clinical Trials Adjuvant Zoledronate
RFS	Recurrence-Free Survival
RM	Risk-Reducing Bilateral Mastectomy
RWE	Real-World Evidence
SA	Surgery Alone
SO	Salpingo-Oophorectomy
SRE	Skeletal-Related Event
SS	Surveillance-Surgery
WTP	Willingness-To-Pay
ZA	Zoledronic Acid

1. Introduction

Cancer is one of the leading causes of death worldwide and a major driver of health system costs, with great social and economic consequences [1,2]. Advances in prevention, early detection, and treatment have improved survival, although the number of people living with cancer continues to rise [1,3,4]. In high-income countries, such as Italy and Canada, demographic changes and population aging are expected to drive a progressive increase in incidence over the coming decades, intensifying the burden on patients, families, and healthcare systems [4,5]. Nowadays, cancer care reflects a paradox, while mortality has declined thanks to progress in screening and therapeutics, the overall societal and economic burden is increasing, driven by rising prevalence, long-term survivorship needs, and escalating treatment costs [3,4].

In Italy, cancer accounts for more than 23% of all deaths, making it the second leading cause of mortality after cardiovascular diseases. Although age-standardised mortality has fallen by 15% between 2011 and 2021, incidence is projected to increase by 18% between 2022 and 2040 [4]. Breast, colorectal, lung, and prostate cancers together represent nearly half of all new diagnoses, with breast cancer (BC) alone accounting for 31% of female cases [4]. Alongside these epidemiological pressures, costs have grown substantially; the Italian Medical Oncology Association estimated the national burden of cancer to be €20 billion in 2022, equal to 12% of total health expenditure, with oncology drug spending more than doubling in the past decade [4,6,7].

The Canadian situation is similar. In 2024, an estimated 247,100 new cases and 88,100 deaths were expected, with 9 in 10 diagnoses occurring in people over age 50 [8]. Prostate cancer in men and BC in women remain the most common diagnoses, while lung cancer continues to cause nearly one-quarter of all cancer deaths [8]. Despite modest declines in incidence and mortality rates, absolute numbers of cases and deaths are rising due to demographic change [3].

Cancer is now the leading cause of death in Canada, with a lifetime risk estimated at 45%, followed by cardiovascular diseases deaths [9,10]. The economic toll is equally severe as in 2021, the societal burden of cancer reached CAD $26.2 billion, with almost one-third borne directly by patients and families through out-of-pocket costs, lost income, and caregiving responsibilities [11]. Annual expenditure on cancer medicines has also increased by approximately 15% per year over the past decade, reaching CAD$ 1.7 billion in 2021-22, raising concerns about long-term sustainability [12].

These trends highlight the challenge facing modern cancer care as improved survival has led to more people living longer with cancer, but this has caused an increased financial strain for health systems and households. In both Italy and Canada, where universal health coverage aims to ensure equity of access, the growing incidence and escalating costs of therapies demand careful choices about how to allocate resources.

Health Technology Assessment (HTA) is a structured, multidisciplinary process used to evaluate the value of health technologies across their lifecycle [13]. By combining clinical, economic, ethical, social, organizational, and legal evidence, HTA supports decisions that promote efficient, fair, and high-quality care [13]. It considers not only relative clinical effectiveness and safety but also cost, organizational aspects, and broader societal impacts, helping decision-makers evaluate whether an intervention offers meaningful benefit compared with alternatives [13].

Economic evaluation plays a central role in this process. Health systems continually face challenging decisions about how to allocate scarce resources effectively. In fact, by comparing the costs and outcomes of different options, economic evaluation highlights which ones bring the most value [14]. It ensures that preventive strategies and established interventions are assessed alongside new technologies, and that different perspectives, from hospital budgets to long-term societal costs, are considered [14].

Cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA) are among the most widely applied methods, used by agencies such as the National Institute for Health and Care Excellence (NICE) in the UK, to ensure that limited public resources are directed to where they provide the greatest benefit [15–17].

A key modelling tool in economic evaluations is the Markov model, which is especially suited to chronic diseases such as cancer, where outcomes and costs develop over years or decades [18]. Unlike simple decision trees, Markov models capture disease progression as transitions between health states, such as stable disease, recurrence, or death, allowing for the estimation of cumulative outcomes, including total costs and quality-adjusted life years (QALYs) [18]. They are particularly useful when trial data provide only short-term follow-up, as they allow the extrapolation of long-term risks and benefits based on available evidence and assumptions [18].

This thesis applies Markov modelling to two oncology case studies to explore how economic evaluation can inform cancer policy. The first case focuses on prevention in women with pathogenic BRCA1 and BRCA2 variants, comparing surveillance plus risk-reducing surgery, surgery alone, and no intervention using literature and registry data. The second case examines treatment in postmenopausal women with early breast cancer (EBC), evaluating the cost-effectiveness of adjuvant zoledronic acid (ZA) given as a single dose compared with standard six-monthly dosing, based on patient-level data from a randomized controlled trial (RCT). Together, these cases demonstrate how different data sources shape model design, results, and policy relevance, and highlight the role of CEA in supporting resource allocation in oncology.

The aim of this thesis is to apply Markov modelling to these two case studies to evaluate the cost-effectiveness of preventive and therapeutic strategies, and to examine how data sources influence outcomes and the transferability of findings. The thesis is structured as follows: the background introduces Markov models in HTA, their strengths, applications, and data

requirements, followed by an overview of the two case studies. The methods section details model construction in Microsoft Excel, including setting and design. Results are presented for each case, with base-case findings and sensitivity analyses. The discussion reflects on the main findings, methodological insights into data sources, and policy implications, before assessing limitations and strengths. The thesis concludes by synthesizing insights across both applications, emphasizing the role of Markov modelling in informing oncology decision-making.

2. Background

2.1 Health Economics Modelling in Oncology

Decision-analytic models are increasingly used in HTA to evaluate the cost-effectiveness of healthcare interventions [19,20]. They provide a framework to synthesize evidence from multiple sources and extrapolate short-term trial results into long-term outcomes, making them particularly valuable when direct evidence is lacking [18]. By combining clinical outcomes with resource use, these models help estimate both health and economic consequences of competing strategies, informing decisions from local funding choices to national drug approval and pricing policies [15,16,18,20]. Agencies such as NICE in the UK rely on such analyses to ensure that limited healthcare resources are directed toward interventions that provide the greatest benefit [15].

Among the different approaches (CEA, CUA, and CBA), Markov models are among the most widely applied in economic evaluation [17,18,20]. Markov models have a long tradition in medical decision-making, especially for chronic and recurrent diseases, and remain central to health economics [18,20]. Their strength lies in modelling disease processes that evolve over time by representing them as distinct, mutually exclusive health states [18,20]. Patients transition between states at regular intervals (cycles), with probabilities reflecting disease progression, treatment effects, or mortality risk [18,20]. By attaching costs and quality-of-life (QoL) weights to states and transitions, Markov models estimate both costs and outcomes, typically expressed as QALYs [18,20].

This makes them particularly suited for oncology, where interventions influence both survival and QoL but trial follow-up rarely captures lifetime outcomes [18,20]. Markov models have been widely used to evaluate treatment effectiveness, disease progression, toxicity risks, and long-term survival in cancer, providing evidence that supports both clinical and policy decisions [21–24]. They are also flexible, while simple models assume constant transition

probabilities, more advanced versions incorporate time-dependent risks that vary with age, disease history, or duration in a given state [18,20,22].

A fundamental assumption of standard Markov models is the "memoryless" property, meaning that transitions depend only on the current state, not on prior history [18,22]. Although this simplifies modelling, it can limit realism in clinical settings. To mitigate this, modelers may use "post-event" or tunnel states, or apply time-dependent transition probabilities, to better approximate patient history [22].

The reliability of a Markov model depends heavily on the quality and type of input data. RCTs are often considered the gold standard, as their rigorous design, standardized follow-up, and controlled environment support strong internal reliability [25]. However, their strict eligibility criteria and idealized settings often reduce external validity, making it difficult to generalize results to broader patient populations [25–27], while larger multicentre RCTs may improve representativeness by recruiting more diverse patients across multiple sites [28,29]. Evidence shows that participants in oncology and other chronic disease RCTs are often younger, healthier, and less complex than real-world patients, limiting the applicability of findings to everyday clinical practice [30–32]. Missing data, limited follow-up, and high costs also restrict the ability of RCTs to capture long-term outcomes relevant for economic modelling [33].

In contrast, literature-based and real-world evidence (RWE) sources, including observational studies, registries, electronic health records, and administrative claims, capture larger and more heterogeneous populations, longer follow-up, and routine clinical practice [34,35]. This approach enhances external validity and can provide valuable insights into subgroups underrepresented in RCTs, such as older patients or those with comorbidities [34–37]. RWE is also useful in oncology, where prospective trials may be unfeasible or unethical for rare cancers or certain preventive strategies [38]. However, RWE comes with its own limitations as heterogeneity in patient populations, outcome definitions, and data quality can increase

uncertainty and complicate model assumptions, while confounding, immortal time bias, and misclassification remain important risks [39–41].

Recent initiatives, such as target trial emulation and systematic RCT-RWE comparisons, demonstrate that, under rigorous design and analysis, RWE can sometimes reproduce trial results and enhance decision-making [42–44].

For health economic modelling, both RCT and RWE data have complementary roles. RCTs provide robust estimates of treatment efficacy under controlled conditions, while RWE offers effectiveness data that reflect real-world adherence, resource use, and costs. In practice, the choice of data source shapes model structure, assumptions, and the interpretation of results. For example, literature- and RWE-based models can improve generalizability, but introduce heterogeneity and uncertainty, while trial-based models maximize internal validity, but risk limited transferability to other healthcare systems. Balancing these options is important, as the choice of input data not only determines model reliability but also influences the policy relevance of cost-effectiveness analyses in oncology [42,43,45].

2.2 Case Study A - Ovarian Cancer Prevention Strategy

Pathogenic variants (PV) in the BRCA1 and BRCA2 genes account for about 5% of BC [46] and 15% of epithelial ovarian cancers (OC) [47]. Both cancers pose major clinical and socioeconomic challenges, representing significant public health concerns [48,49]. BC is the most common cancer in women worldwide, responsible for one in four cancer cases and one in six cancer-related deaths [50]. OC, while the third most common gynaecological cancer, is the fifth leading cause of cancer-related death in women [51].

Women carrying BRCA1 or BRCA2 PV face noticeably elevated lifetime risks of both cancers, estimated at 17-44% for OC and 69-72% for BC [52]. As a result, they are typically advised to undergo surveillance and consider risk-reducing surgery. BC surveillance typically includes

clinical breast examination, magnetic resonance imaging (MRI), and mammography, with the option of risk-reducing bilateral mastectomy (RM), which substantially reduces both incidence and mortality [53–55].

For OC prevention, guidelines recommend risk-reducing salpingo-oophorectomy (SO), usually between ages 35-40 for BRCA1 carriers and 40-45 for BRCA2 carriers [55]. However, uptake remains suboptimal [56]. Surveillance strategies such as transvaginal ultrasound and CA125 testing have not shown effectiveness in reducing OC incidence or mortality, either in the general population [57,58] or in high-risk women [59], and are therefore not recommended in international guidelines [55,60,61]. Still, participation in these surveillance programs has been linked to increased acceptance of prophylactic surgery [62].

Management of BRCA-associated cancer risk differs between countries. In settings such as Germany and France, breast surveillance and risk-reducing surgery are routinely offered, while OC surveillance is generally discouraged [63,64] or reserved for women declining surgery after counselling [65]. In contrast, Italian guidelines recommend a combination of biannual OC surveillance with ultrasound and CA125 from age 30, followed by surgery at the appropriate age [66].

Previous studies have shown that risk-reducing surgeries are cost-effective [67], but to date, no economic evaluations have examined OC surveillance programs when combined with preventive surgery. Such analyses are critical for determining the value of these strategies and guiding health policy.

The aim of this study is to evaluate the cost-effectiveness of a combined OC surveillance-surgery strategy in BRCA PV carriers from the perspective of the Italian healthcare system, using real-world data where possible. Results are compared with two alternative strategies: risk-reducing surgery alone and no intervention.

2.3 Case Study B - Zoledronic Acid Injections in Early Breast Cancer Patients

Intravenous (IV) ZA is recommended as adjuvant therapy for postmenopausal patients with EBC, supported by evidence from RCTs and meta-analyses [68–75]. ZA has been shown to improve BC survival, but the optimal dosing schedule remains debated. Most patients currently receive ZA every six months for a period of two to three years. However, the drug is associated with side effects such as acute phase reactions (APRs), bone pain, kidney impairment, and, in rare cases, osteonecrosis of the jaw (ONJ) [76]. While alternative dosing schedules have been explored to maximize benefit and reduce harms, their cost-effectiveness is an equally important consideration.

Evidence suggests that lower ZA exposure may provide similar benefits to standard dosing. Reduced dosing has been shown to be as effective as higher dosing [77], and ZA persists in bone for several years even after a single infusion [78,79], suggesting that further dose reductions could maintain efficacy. The Rethinking Clinical Trials (REaCT) adjuvant zoledronate (ZOL) trial was therefore designed to compare a single ZA infusion against the standard six-monthly regimen (seven doses over three years) in 211 postmenopausal patients with EBC [80]. Over a three-year follow-up, no significant differences were found between the two groups in QoL, recurrence-free survival (RFS), bone metastasis-free survival (BMFS), overall survival (OS), bisphosphonate-related toxicities, or bone health outcomes [80]. Although APRs were more common in the multiple-dose arm, the rate of medical intervention was similar, and APRs were the leading cause of treatment discontinuation. Given the lack of meaningful clinical differences, economic evaluation of these two regimens is essential to guide treatment policy.

Most previous cost-effectiveness studies of ZA have focused on broader comparisons rather than dosing strategies. In the adjuvant setting, ZA has been evaluated against no treatment [81,82] and in combination with other agents [83–85]. In metastatic disease, studies have

compared ZA with alternatives such as oral ibandronate [86] and denosumab, another bone-targeted agent [87–90]. Only a few analyses have examined the cost-effectiveness of different ZA dosing schedules, and these were limited to metastatic disease [91–93]. Simulation-based models generally suggest that lower or less frequent dosing is more cost-efficient, but no study has directly assessed the cost-effectiveness of single-dose versus six-monthly ZA using RCT data.

This study addresses that gap by evaluating the cost-effectiveness of a single ZA infusion compared with a six-monthly regimen over three years, using patient-level data from the REaCT-ZOL trial. The findings will provide economic evidence to inform clinical and policy decisions on optimal ZA dosing strategies, supporting the adoption of cost-effective and patient-centred approaches in EBC care.

3. Methods

3.1 General Modelling Approach

Markov models were used to evaluate the cost-effectiveness of preventive and therapeutic strategies in oncology. These models are particularly suited for conditions that evolve over time, where the timing and recurrence of events affect both costs and outcomes [14,22]. Unlike decision trees, which are limited in representing long-term or recurrent processes, Markov models describe disease progression as transitions between mutually exclusive health states, such as "disease-free," "recurrence," or "death" [24]. Transitions occur in discrete cycles, governed by transition probabilities that reflect natural history, treatment effects, or mortality risk [24]. By attaching costs and QoL weights to each health state, Markov models simultaneously estimate total costs and outcomes over a defined time horizon [18].

Both case studies applied Markov models that produced standard outcomes for cost-effectiveness analysis: QALYs, Incremental Cost-Effectiveness Ratios (ICERs), and Net Monetary Benefit (NMB).

The ICER quantifies the additional cost per additional QALY gained by comparing two interventions and is calculated as:

$$ICER = \frac{Cost_A - Cost_B}{QALY_A - QALY_B} = \frac{\Delta Cost}{\Delta QALY}$$

where A represents the intervention of interest and B represents the standard of care or comparator.

An intervention is considered cost-effective if its ICER falls below a predefined willingness-to-pay (WTP) threshold, which reflects the maximum amount society is willing to pay for one additional QALY [94,95].

The NMB converts both health outcomes and costs into a single monetary value, calculated as:

$$NMB = (WTP * \Delta QALY) - \Delta Cost$$

A positive NMB indicates that the intervention is cost-effective at the given threshold, and the option with the highest NMB provides the greatest net value for money [96,97]. NMB facilitates comparison across multiple alternatives and simplifies interpretation under uncertainty [96].

The Markov models were constructed in Microsoft Excel, following standard methods [14,18]. A parameter sheet defined transition probabilities, costs, and utilities, which were linked by named ranges to the transition matrix [98]. The Markov trace was generated using Excel's matrix multiplication function to project the cohort across health states over the model horizon [98]. Costs and QALYs were accumulated at each cycle, with final outputs including total costs, total QALYs, and ICERs [98].

Uncertainty is inherent in economic modelling, as parameters often come from heterogeneous or limited evidence bases [14,99,100]. Deterministic and probabilistic sensitivity analysis were therefore performed to test the robustness of the results. As defined by Saltelli (2002), sensitivity analysis explores how "uncertainty in the output of a model can be apportioned to different sources of uncertainty in the model input" [101].

One-way sensitivity analysis (OWSA), a deterministic approach, varied key parameters within plausible ranges, based on confidence intervals or literature values. The impact on ICERs was illustrated using a tornado diagram, which highlighted the assumptions that most strongly influenced model outcomes [14,99,100].

While, to capture overall parameter uncertainty, probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulation (MCS). Each parameter was assigned an appropriate probability distribution [14,102]. A macro in Microsoft Excel sampled data from these distributions across 1,000 runs, recalculating costs and health outcomes each time. Results were summarized in cost-effectiveness acceptability curves (CEACs), which show the probability of a strategy being cost-effective at different WTP thresholds. CEACs offer a clear method for

quantifying decision uncertainty and informing policy [14,99,100]. Together, deterministic analysis highlights the most influential inputs, while PSA quantifies the likelihood that results remain stable under uncertainty.

Although the two case studies were based on Markov model and produced the same outcomes and performed the same sensitivity analyses, they differed in their data sources. The BRCA prevention model relied on literature-based and registry data, while the ZA treatment model was parameterized using patient-level data from the REaCT-ZOL trial.

3.2 Case Study A - Ovarian Cancer Prevention Strategy

Model Overview

A Markov cohort simulation model was built in Microsoft Excel to evaluate BC and OC progression in women with BRCA1 and BRCA2 PVs. The model estimated long-term costs and outcomes under three disease surveillance strategies:

1. Surveillance-Surgery (SS): yearly surveillance with two gynaecological visits, two transvaginal ultrasounds, and two CA125 tests, until bilateral SO was proposed; RM was also proposed at the recommended age.
2. Surgery Alone (SA): bilateral SO and RM without annual surveillance.
3. No-Intervention (NI): no preventive surgery or surveillance.

The model was run separately for BRCA1 and BRCA2 carriers. Each simulation started with a cohort of 30-year-old women without prior BC or OC. It ran for 80 one-year cycles, covering ages 30-110 or until death.

The SS and SA strategies included 15 health states (Fig.1). All women began in the "Well" state. They could undergo RM at age 35 or SO at age 40 (BRCA1) or 45 (BRCA2) (Tab.1). After surgery, women moved to "Post-RM", "Post-SO", or "Post RM-SO". Despite

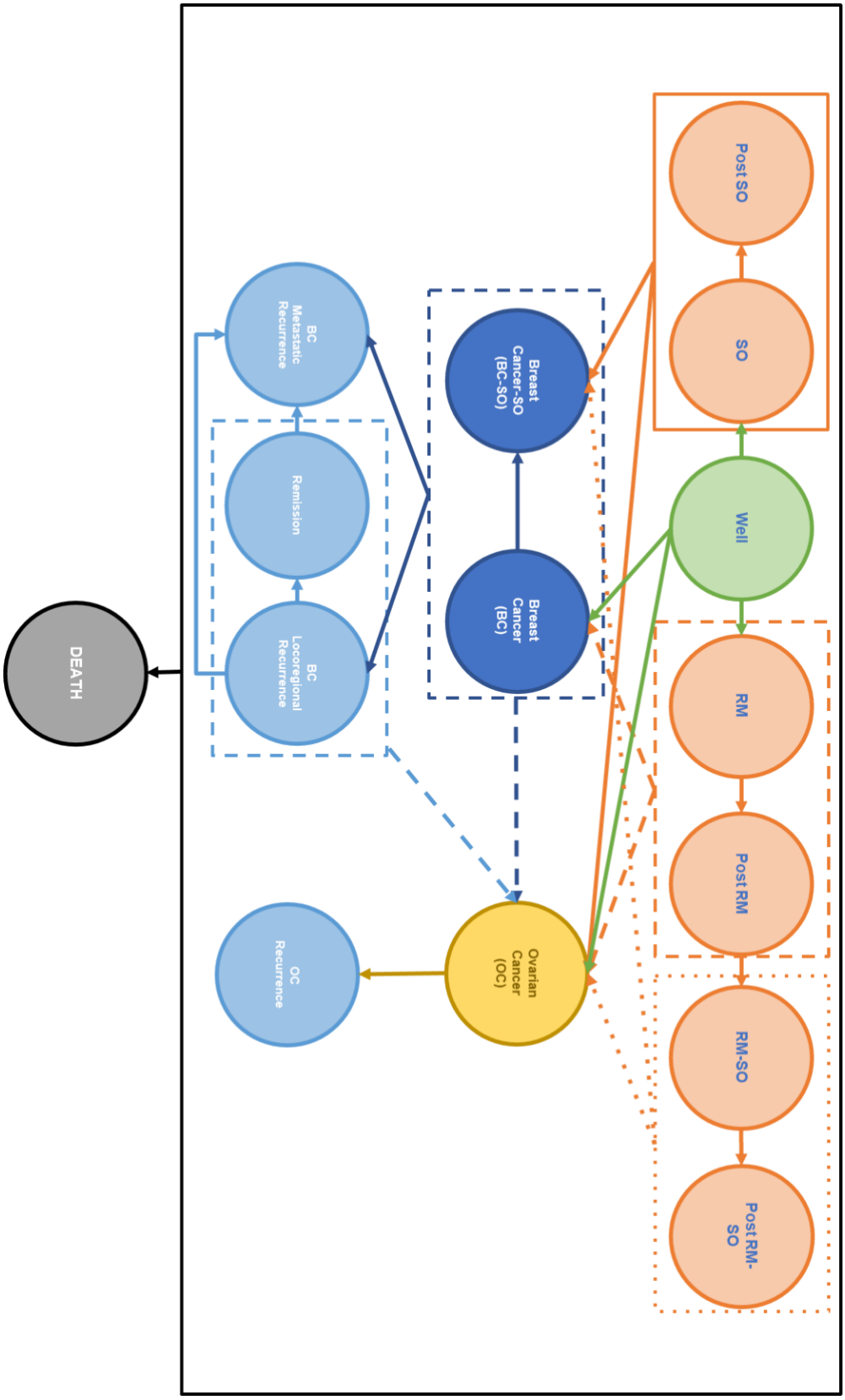
intervention, residual risks of BC and OC remained, allowing transitions to “BC”, “BC-SO”, or “OC”. Women could also develop BC or OC before interventions.

From “BC” or “BC-SO”, patients could experience locoregional recurrence, metastatic recurrence, or OC, or move into “Remission”. Those in “Remission” could later relapse with metastatic BC or develop OC. The “Metastatic Recurrence” state only transitioned to “Death”. Women with OC could experience recurrence or death; otherwise, they remained in the same state. Because of the high mortality rate, recurrent OC was modelled as a direct path to death, and no transition from OC to BC was included (Fig.1). From any state, women could also die from other causes, based on Italian life tables [103].

The NI model excluded intervention-related states and included nine health states. Women began in “Well” and could transition to BC or OC, with subsequent progressions identical to those in the SS and SA models.

The model was conducted from the perspective of the Italian healthcare system, including direct medical costs. Outcomes were expressed as QALYs, ICERs, and NMB. Interventions were considered cost-effective if ICERs were below €33,000 per QALY, the Italian threshold suggested by Russo et al. (2023) [104]. This threshold was also used for NMB estimation.

Figure 1: Case A - Markov Model Structure



The SS and SA Strategies include all the 15 health statuses, while the NI Strategy excludes preventive interventions such as “SO”, “Post-SO”, “RM”, “Post-RM”, “RM-SO”, and “Post RM-SO”.

Data Sources

The model reflected an Italian cohort of women with BRCA1 and BRCA2 mutations. Whenever possible, input data came from Italian studies; otherwise, European or international evidence and expert opinion were used. Clinical practice data on the SS strategy, intervention uptake, and post-intervention follow-up were provided by the Department of Gynaecology, at Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy (Tab.1).

Table 1: Case A - General Clinical Input Parameters.

Parameter	Annual Value	Lower Value	Upper Value	SE	Reference
Cohort mean age	30	24.12	35.88	3.000	NCCN (2019) [105]
SO proposal age					
BRCA1	40	40.00	40.00	4.000	NCCN (2019) [105]
BRCA2	45	45.00	45.00	4.500	NCCN (2019) [105]
RM propo l age	35	28.14	41.86	3.500	NCCN (2019) [105]
Probabilities					
Accepting SO / RM at proposal age					
Italy	0.950	0.76	1.00	0.095	Internal data[a]
Canada	0.718	0.58	0.86	0.072	Metcalfe et al. (2019) [56]
Accepting RM at proposal age					
Italy	0.778	0.63	0.93	0.078	Metcalfe et al. (2019) [56]
Canada	0.767	0.62	0.92	0.077	Metcalfe et al. (2019) [56]
Accepting SO after BC	0.950	0.76	1.00	0.095	Internal data[a]
OC residual risk after SO	0.040	0.00	0.10	0.030	Grann et al. (2011) [106]
BC residual risk after RM	0.100	0.00	0.20	0.050	Grann et al. (2011) [106]
Probabilities					
From BC to BC locoregional recurrence	0.038	0.03	0.05	0.004	Mavaddat et al. (2013) [107]
From BC to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al. (2018) [108]
From BC locoregional to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al. (2018) [108]

From BC remission to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al. (2018) [108]
From BC metastatic recurrence to death	0.219	0.18	0.26	0.022	La Verde et al. (2021) [109]
From OC to OC recurrence	0.135	0.11	0.16	0.014	Mangone et al. (2022) [110]
From OC to death	0.173	0.14	0.21	0.017	Mangone et al. (2022) [110]
From OC recurrence to death	0.178	0.00	0.00	0.018	Mangone et al. (2022) [110]

[a] Department of Gynaecology at Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy.

Probabilities

Age-specific incidence rates for BC and OC were drawn from a large cohort of 6,036 BRCA1 and 3,820 BRCA2 carriers from 18 European cancer centres, plus centres in Canada, Australia, and the US [52]. Rates were available up to age 80; the "71-80" rate was applied beyond age 80 (Tab.2). Incidence rates were expressed as events per 1,000 person-years [52], and converted into annual probabilities based on the observed number of events divided by the person-years at risk, multiplied by 1,000. This approach allowed direct estimation of yearly probabilities without applying an exponential transformation, as rates already reflected annual risk. Prognosis, recurrence, and mortality rates for BC and OC were derived from the literature (Tab.1) [107–110].

Table 2: Case A - Rsik Proability of Ovarian and Breast Cancer in BRCA1 and BRCA2 PV-Carriers.

	BRCA1		**BRCA2**	
Age Class	**Breast Cancer**	**Ovarian Cancer**	**Breast Cancer**	**Ovarian Cancer**
≤20	0.000000	0.000000	0.000000	0.000000
21-30	0.005849	0.000000	0.004780	0.000000
31-40	0.023489	0.001816	0.010767	0.000339
41-50	0.028332	0.007026	0.027484	0.000000
51-60	0.025710	0.013756	0.030615	0.006534
61-70	0.024957	0.029365	0.022943	0.010267
71-80	0.016461	0.005698	0.021850	0.002299

>80*	0.016461	0.005698	0.021850	0.002299

*The risk of the 71-80 age class was used also for the >80 age class.

Source: Kuchenbaecker et al. (2017) [52]. Rates are reported for one person year.

Background mortality in the "Well" state matched that of the Italian general population [103]. Preventive SO and RM were assumed safe, with no procedure-related mortality [111,112]. Cancer-specific deaths were limited to "OC", "OC Recurrence", and "BC Metastatic Recurrence", reflecting their aggressive course (Tab.1) [109,110].

Efficacy

Efficacy estimates for SO and RM came from a comparative effectiveness simulation study of BRCA carriers [106]. The risk reduction of OC after SO and BC after RM was applied in the model (Tab.1). SO was modelled as equally effective whether performed in the "Well" state, after RM, or after a BC diagnosis.

Acceptance rates for SO and RM in the SS strategy were based on data from Fondazione IRCCS San Gerardo dei Tintori (Tab.1). Acceptance rates for the SA strategy were obtained from the literature [56].

Utility Data

Utilities captured health-related quality of life by age group for the "Well" state: 18-35 (0.994), 36-45 (0.935), 46-55 (0.906), 56-65 (0.889), 66-75 (0.868), ≥76 (0.829) [113]. Disutilities for SO and RM were applied based on Müller et al. (2018) [108].

Utilities for BC (during year 1 and after), locoregional and metastatic BC recurrences, and OC (first diagnosis or recurrence) were sourced from Zambelli et al. (2023) [114], adjusted for age (Tab.3). Utilities for BC remission were assumed equal to those for women with BC beyond one year post-diagnosis (Tab.3).

Table 3: Case A - Utility and Cost Input Parameters.

Parameters	Annual Value	Lower Value	Upper Value	SE	Reference
		Utility			
SO intervention	-0.060	-0.0718	-0.0482	0.006	Müller et al. (2018) [108]
RM intervention	-0.040	-0.0478	-0.0322	0.004	Müller et al. (2018) [108]
BC					
1st year	0.829	0.6665	0.9915	0.083	Zambelli et al. (2023) [114]
from 2nd year	0.840	0.6754	1.0046	0.084	Zambelli et al. (2023) [114]
locoregional recurrence	0.720	0.5789	0.8611	0.072	Zambelli et al. (2023) [114]
remission	0.840	0.6754	1.0046	0.084	Zambelli et al. (2023) [114]
metastatic recurrence	0.629	0.5057	0.7523	0.063	Müller et al. (2018) [108]
OC	0.490	0.3940	0.5860	0.049	Müller et al. (2018) [108]
OC recurrence	0.160	0.1286	0.1914	0.016	Müller et al. (2018) [108]
		Cost (€)			
Surveillance – Italy	162.46	131.00	194.00	16.25	Prestazioni Di Assistenza Specialistica Ambulatoriale (n.d.) [115]
Surveillance – Canada	0.00	0.00	0.00	0.00	-
No-Surveillance	0.00	0.00	0.00	0.00	-
SO intervention*	3 108.00	2 499.00	3 717.00	310.80	Ministero della Salute (2013) [116]
RM intervention*	3 385.87	2 722.00	4 050.00	338.59	Ministero della Salute (2013) [116]
Post-SO intervention	81.23	65.00	97.00	8.12	Prestazioni Di Assistenza Specialistica Ambulatoriale (n.d.) [115]
Post-RM intervention	44.87	36.00	54.00	4.49	Prestazioni Di Assistenza Specialistica Ambulatoriale (n.d.) [115]
BC					
1st year	7 577.00	6 092.00	9 062.00	757.70	Francisci et al. (2020) [117]
from 2nd year	1 507.00	1 212.00	1 802.00	150.70	Francisci et al. (2020) [117]
locoregional recurrence	10 143.00	8 155.00	12 131.00	1 014.30	Francisci et al. (2020) [117]
metastatic recurrence	9 784.00	7 866.00	11 702.00	978.40	Francisci et al. (2020) [117]
OC	15 280.00	12 285.00	18 275.00	1 527.98	Lazzaro et al. (2015) [118]
OC recurrence	22 204.00	17 852.00	26 556.00	2 220.43	Lazzaro et al. (2015) [118]

*It includes post-intervention costs.

Cost Data

Healthcare costs were estimated from the perspective of the Italian healthcare system. Costs of visits and tests for the SS strategy were provided by Fondazione IRCCS San Gerardo dei Tintori and valued using Lombardy regional tariffs [115]. SO and RM interventions were costed using national DRG rates 359 and 258, respectively [119]. Post-intervention follow-up included one gynaecological visit, ultrasound, and CA125 annually after SO, or yearly mammography after RM.

BC management costs were taken from Francisci et al. (2020) [117], which reported real-world Italian data. First-year costs were applied after diagnosis, and subsequent-year costs represented long-term management, with and without SO. Stage III costs were used for locoregional recurrence, while Stage IV costs were used for metastatic recurrence. Remission costs after locoregional recurrence equalled continuing care costs. These included hospitalizations, outpatient visits, and prescribed drugs (Tab.3).

OC management costs were based on Lazzaro et al. (2015) [118]. First-line costs included surgery, chemotherapy, cytoreduction, and the creation of an ostomy. Second-line costs, including secondary surgery and chemotherapy, were applied to OC recurrence (Tab.3).

Sensitivity Analysis

OWSA tested how varying one parameter at a time affected model results. Parameter ranges were based on reported distributions and confidence intervals. Deviations in NMB were ranked by absolute magnitude, and the 15 most influential parameters on the value of the technology were displayed in a tornado diagram for both BRCA1 (Fig.3) and BRCA2 carriers (Fig.5).

An additional scenario analysis examined the impact of higher OC management costs, which reflect newer therapies not included in the reference studies. Two scenarios were modelled:

costs 50% higher (OC €22,920; OC recurrence €33,306) and 100% higher (OC €30,560; OC recurrence €44,408) (Tab.6).

PSA assessed the effect of parameter uncertainty when multiple inputs varied simultaneously. Parameters were assigned probability distributions, and 1,000 MCS were run. Results were summarized in CEACs, showing probabilities of cost-effectiveness across WTP thresholds from €0 to €100,000, separately for BRCA1 and BRCA2 carriers (Fig.4).

3.3 Case Study B - Zoledronic Acid Injections in Early Breast Cancer Patients

Study Design and Participants

This cost-effectiveness analysis was based on the REaCT-ZOL trial, a pragmatic, multi-centre, open-label study comparing two ZA regimens in postmenopausal patients with EBC. The trial was conducted across six cities in Ontario, Canada [80,120].

Eligible patients were postmenopausal women, either naturally or treatment-induced, with histologically confirmed EBC and deemed suitable for adjuvant ZA therapy. Key criteria included starting ZA within three months of completing chemotherapy, or within three months of initiating endocrine therapy if chemotherapy was not given. Additional requirements included a creatinine clearance of at least 30 mL/min and normal serum calcium levels, as defined by institutional standards. Patients with metastatic disease or a history of ONJ were excluded.

Participants who met eligibility criteria and provided informed consent were randomized 1:1 to either a single ZA infusion (4 mg) at baseline or ZA infusions every six months for three years, totalling seven infusions (months 0, 6, 12, 18, 24, 30, and 36). In total, 211 patients were recruited: 107 in the single-dose arm and 104 in the six-monthly arm [80]. The trial was registered on ClinicalTrials.gov (NCT03664687) and funded by The Cure Foundation (Montreal, Quebec, Canada) and the Ottawa Hospital Foundation (Ottawa, Ontario, Canada).

It was conducted in accordance with the Declaration of Helsinki and approved by the Ontario Cancer Research Ethics Board (CTO 1446, approved May 9, 2018).

Acute Phase Reactions, Recurrence-Free Survival, Bone Metastasis-Free Survival, and Overall Survival

APRs were defined according to Reid et al. (2010) [121], and categorized into five categories: fever, musculoskeletal, gastrointestinal, ocular, and general symptoms. APRs typically peaked one day after infusion and lasted a median of three days. To assess them, patients were contacted by phone 5-14 days after treatment and asked if they had experienced symptoms within three days of infusion and whether these required medical attention, such as a visit to a family physician, oncologist, or the emergency room (ER). This information was used to estimate the proportion of patients needing additional care.

RFS was defined as the time from randomization to the first ipsilateral invasive recurrence, local/regional invasive recurrence, distant recurrence, or death from any cause [122]. BMFS was the time to radiologically confirmed bone metastases. OS was defined as survival regardless of cancer status, as previously reported by Awan et al. (2024) [80]. To derive these outcomes, descriptive statistics were applied to summarize patient, treatment, and outcome characteristics for the overall cohort and by intervention arm. RFS and OS were estimated using the Kaplan-Meier method, and group comparisons were performed using Fisher's exact test for categorical variables, the Wilcoxon rank-sum test for continuous variables, and the log-rank test for time-to-event outcomes [80]. Confidence intervals were calculated for all key outcomes. Analyses followed the intention-to-treat (ITT) principle, with results considered statistically significant at a two-sided p-value ≤ 0.05. Missing data were not imputed, and no adjustments were made for multiple testing [80].

Direct Costs

Cost estimates were derived from the Ontario Schedule of Benefits (OSB) [123], Ontario Health Formulary [124], Statistics Canada [125], Canadian Institute for Health Information (CIHI) [126], and published literature [127,128]. The total cost per infusion included the ZA drug cost (4 mg), intravenous administration, nursing and pharmacy workload, and required laboratory tests (serum calcium, albumin, and creatinine clearance).

For patients experiencing APRs that require medical attention, additional costs for physician and/or emergency room visits were added. End-of-life costs were included for patients who died of BC, defined as the final 12 months of life [127] (Tab. 4).

Table 4: Case B - Direct Costs.

Direct Costs			
Service	**Cost (CAD $)**	**Notes**	**Reference**
Laboratory	80.00	Laboratory Cost per BC Patient per Year	Statistics Canada (2024) [125]
Zoledronate 4mg/5mL Injection	506.74	Zoledronate 4mg/5mL Injection: $415.56 IV Injection fee: $54.25 Nursing Cost per ZA Injection*: $23.33 Pharmacist Cost per ZA Injection**: $13.60	Government of Canada (n.d.); OSB (n.d.); Marr et al. (2010); Ontario Health Formulary (n.d.) [123,124,128–130]
Oncologist Visit	105.25	Medical Oncology Repeat Consultation	OSB (n.d.) [123]
Family Physician Visit	87.90	General Consultation	OSB (n.d.) [123]
ER Visit	410.80	ER Physician on Duty Consultation: $106.80 Full Hospital Cost per ERVisit: $304.00	OSB (n.d.); CIHI (n.d.) [123,126]
Terminal Care BC	18,593.00	Terminal Care per BC Patient in Ontario (Final 12 Months of Life)	de Oliveira et al. (2016) [127]

*Median Wages of Registered Nurse in Ontario: $40.00 per hour (0.67 $/min) [129]; Average Nurse Workload per ZA Administration: 35 minutes [131].

**Median Wages of Pharmacist in Ontario: $51.00 per hour (0.85 $/min) [130]; Average Pharmacist Workload per ZA Administration: 16 minutes [131].

Outcomes: Quality-Adjusted Life Years

QoL was assessed using the EQ-5D-5L questionnaire, which measures five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has five response levels ranging from “no problems” to “extreme problems/unable to”. [132,133].

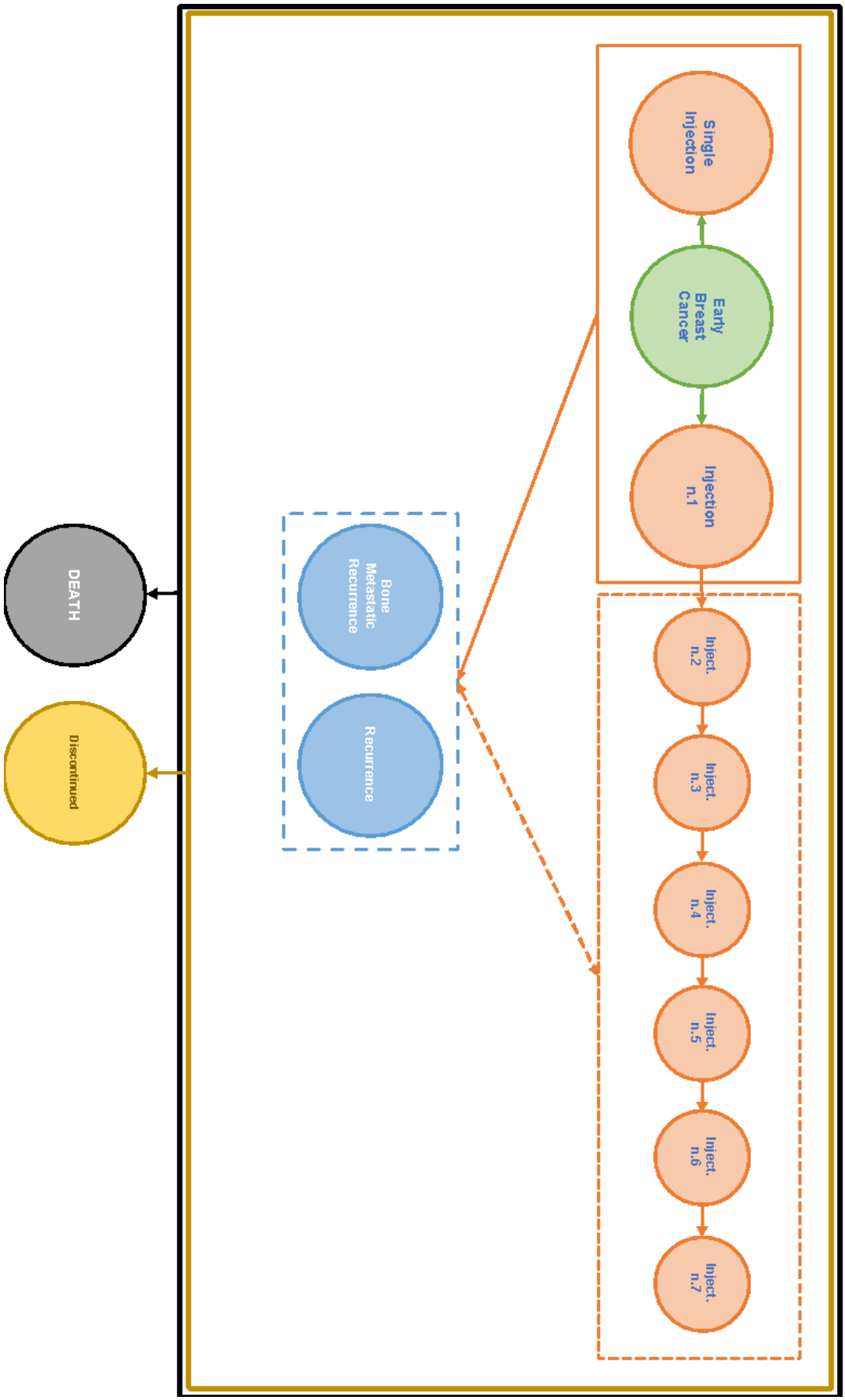
In the six-monthly group, participants completed the questionnaire 5-7 days before each infusion and 5-14 days afterwards. In the single-infusion group, questionnaires were completed 5-7 days before infusion, 5-14 days afterwards, and annually for three years [80]. Only pre-infusion scores were used in this analysis.

EQ-5D-5L scores were converted to utilities using the Canadian Value Set [134]. Linear interpolation was applied in the single-infusion group to align assessments with six-month cycles, standardizing all intervals to six months, and was used to estimate missing values. QALYs were calculated using the trapezoid method for each six-month cycle and the rectangular method for the final available follow-up, ensuring comparability across groups.

Analysis - Markov Model and Sensitivity Analysis

A Markov model was developed in Microsoft Excel to simulate disease progression and compare costs and QALYs for the two treatment strategies over a three-year time horizon, consistent with the trial follow-up. The single-infusion group received a single dose at baseline, while the six-monthly group received seven infusions over a 36-month period. The model consisted of seven six-month cycles, aligned with treatment intervals. Health states are shown in Figure 2 (Fig. 2).

Figure 2: Case B - Markov Model Structure



Deterministic sensitivity analysis varied one parameter at a time to assess its impact on the ICER. The 15 most influential parameters are displayed in a tornado diagram (Fig. 6).

PSA used 1,000 MCS, varying all parameters simultaneously according to predefined probability distributions.

The primary outcome was QALYs. ICER and incremental net benefit (INB) were used to assess cost-effectiveness at a WTP threshold of CAD $100,000 per QALY. CEACs were generated to illustrate the probability of each treatment being cost-effective across WTP thresholds from CAD $0 to $100,000 (Fig. 7).

4. Results

4.1 Case Study A - Ovarian Cancer Prevention Strategy

BRCA1 Carriers

For women with BRCA1 PV, the lifetime healthcare cost of the SS strategy was €17,893 per patient, or €17,893,440 for a cohort of 1,000 patients. This strategy yielded an average of 22.25 QALYs per patient. In comparison, the SA strategy cost €19,902 per patient and generated 21.80 QALYs, whereas the NI strategy cost €26,276 per patient and resulted in 19.60 QALYs (Tab.5).

Table 5: Case A - Cost, QALY, and Cost-Effectiveness of Surveillance and Preventive Strategies in BRCA1 Carriers.

	BRCA1		
	SS	**SA**	**NI**
Cost (€) *	17,893	19,902	26,276
QALY *	22.25	21.80	19.60
Reference SS strategy			
Δ Cost (€)	-	2,008	8,382
Δ QALY	-	-0.45	-2.65
ICER **	-	-4,428	-3,161
NMB (€) ***	-	-16,974	-95,894

*Cost/QALY per patient.

**ICER = ΔCost/ΔQALY.

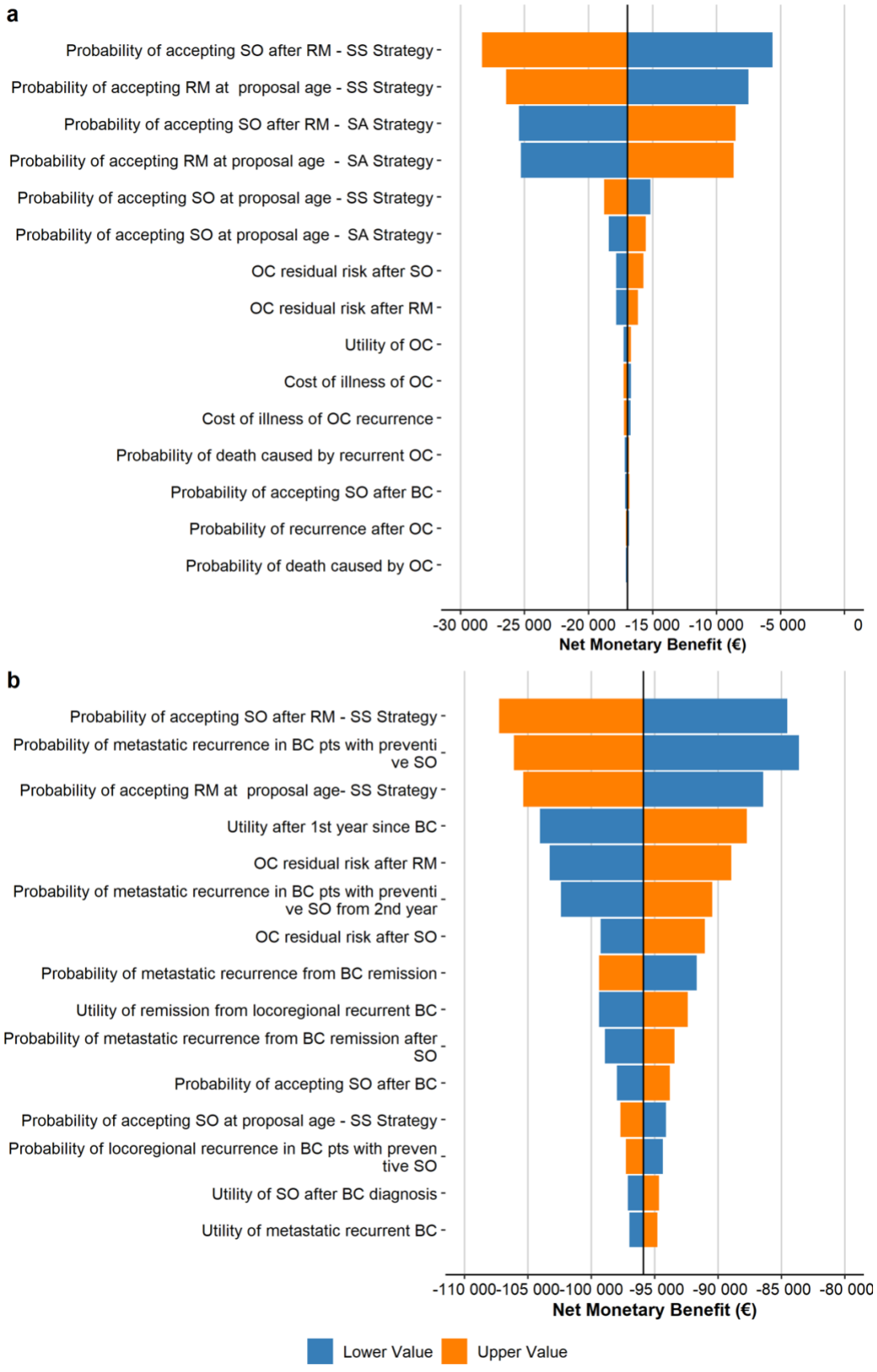
***NMB = (λ*ΔQALY) - ΔCost, with λ = WTP threshold is set at €33,000 per QALY gained (Russo et al. (2023) [104]).

Relative to NI, the SS strategy saved €8,382 per patient and gained 2.65 QALYs. Compared to SA, it saved €2,008 and gained 0.45 QALYs per patient (Tab.5). The SS strategy was therefore dominant over both SA and NI, offering lower costs and improved health outcomes (ICER < 0). At a WTP threshold of €33,000 per QALY gained, the NMB for SA and NI were -€16,974 and -€95,894, respectively, when compared to SS (Tab.5).

In OWSA, the parameters with the greatest impact on NMB at WTP = €33,000 were the probability of accepting preventive interventions, residual OC risk after SO, costs of ovarian cancer management, and disease-related mortality (Fig.3a). For the NI vs SS comparison,

intervention acceptance, residual OC risk, and BC progression were the key drivers (Fig.3b). Across all variations, however, the SS strategy remained dominant.

Figure 3: Case A - Tornado Graphs of Net Monetary Benefit (NBM) of SA (a) and NI (b) Strategies vs SS Strategy in BRCA1 Carriers.



Scenario analyses evaluating increases in OC management costs confirmed the robustness of these findings: the SS strategy continued to dominate both SA and NI even when costs were raised by 50% and 100% (Tab.6).

Table 6: Case A - Sensitivity Analysis of Surveillance and Preventive Strategies in BRCA1/2 Carriers, Varying Annual Ovarian Cancer Costs.

		BRCA1			BRCA2		
		SS	**SA**	**NI**	**SS**	**SA**	**NI**
OC Cost Variation (+50%)[a]	Cost (€) *	19,213	22,574	32,172	14,004	14,877	19,400
	QALY *	22.25	21.80	19.60	23.15	22.98	21.49
	Reference SS strategy						
	Δ Cost (€)	-	3,362	12,959	-	873	5,396
	Δ QALY	-	-0.45	-2.65	-	-0.16	-1.65
	ICER **	-	-7,413	-4,887	-	-5,299	-3,263
	NMB (€) ***	-	-18,328	-100,471	-	-6,309	-59,969
OC Cost Variation (+100%)[b]	Cost (€) *	20,532	25,247	38,069	14,364	15,761	21,428
	QALY *	22.25	21.80	19.60	23.15	22.98	21.49
	Reference SS strategy						
	Δ Cost (€)	-	4,715	17,537	-	1,397	7,064
	Δ QALY	-	-0.45	-2.65	-	-0.16	-1.65
	ICER **	-	-10,397	-6,613	-	-8,480	-4,272
	NMB (€) ***	-	-19,681	-105,049	-	-6,833	-61,637

[a] OC Annual Cost Variation (+50%) vs Reference (Lazzaro et al. (2005) [118]) - OC €22,920; OC recurrence €30,306.

[b] OC Annual Cost Variation (+100%) vs Reference (Lazzaro et al. (2005) [118]) - OC €30,560; OC recurrence €44,409.

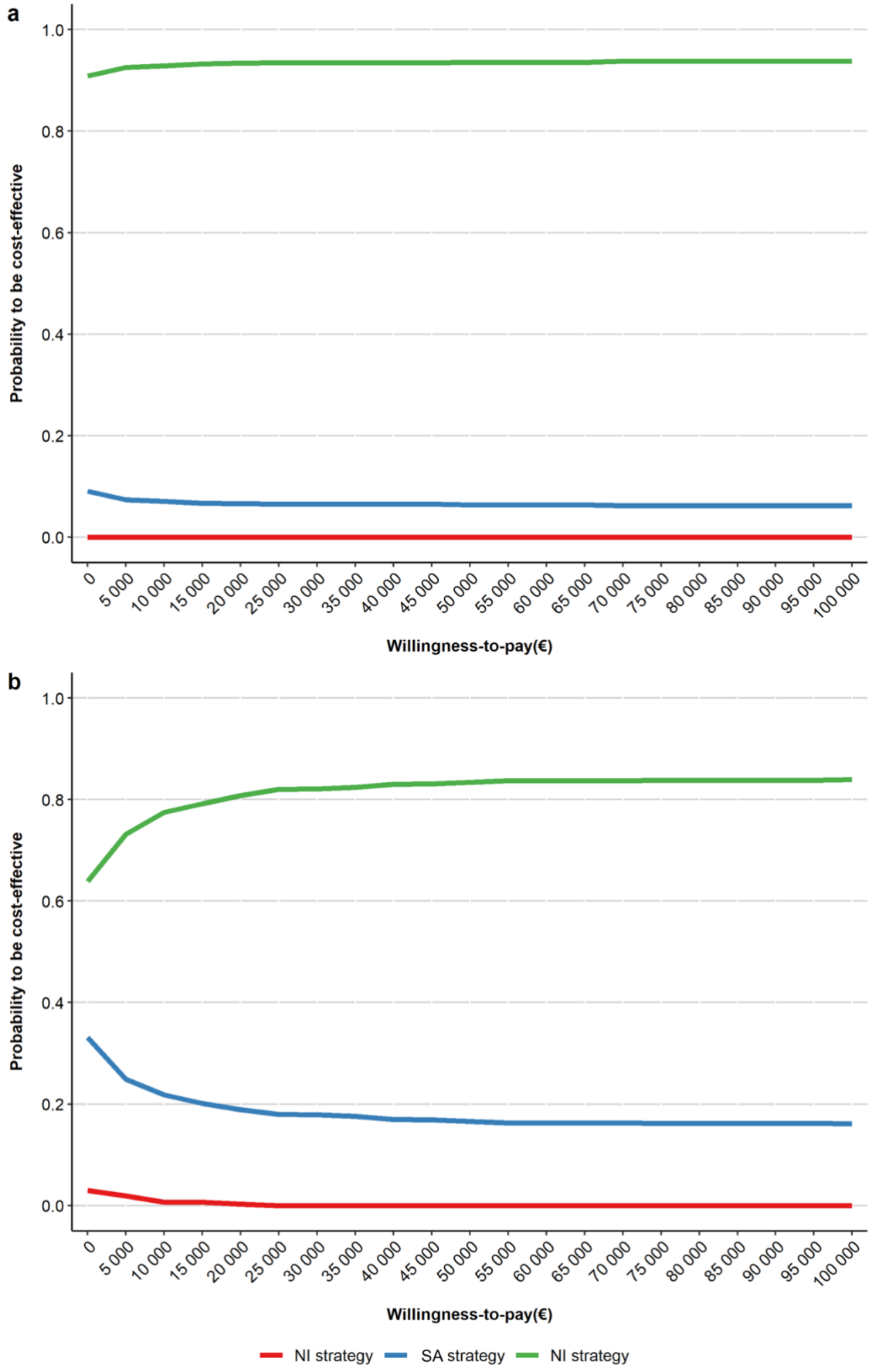
*Cost/QALY per patient.

**ICER = ΔCost/ΔQALY.

***NMB = (λ*ΔQALY) - ΔCost, with λ = WTP threshold is set at €33,000 per QALY gained (Russo et al. (2023) [104]).

The CEAC (Fig.4a) showed that SS consistently remained the most cost-effective option, with a probability exceeding 90% at a WTP threshold of €30,000 per QALY gained.

Figure 4: Case A - Cost-Effectiveness Acceptability Curve for BRCA1 (a) and BRCA2 (b) Carriers.



BRCA2 Carriers

Among BRCA2 carriers, the lifetime cost of the SS strategy was €13,644 per patient, with an average of 23.15 QALYs gained. The SA strategy cost €13,993 per patient and yielded 22.98 QALYs, while the NI strategy cost €17,372 and resulted in 21.49 QALYs (Tab. 7). Compared with NI, SS saved €3,729 per patient and gained 1.65 QALYs. When compared with SA, SS saved €349 and gained 0.16 QALYs per patient (Tab. 7). Therefore, SS was dominant over both comparators (ICER < 0). At a WTP threshold of €33,000, the NMBs for SA and NI were -€5,785 and -€58,302, respectively, relative to SS (Tab. 7).

Table 7: Case A - Cost, QALY, and Cost-Effectiveness of Surveillance and Preventive Strategies in BRCA2 Carriers.

	BRCA2		
	SS	**SA**	**NI**
Cost (€) *	13,644	13,993	17,372
QALY *	23.15	22.98	21.49
	Reference SS strategy		
Δ Cost (€)	-	349	3,729
Δ QALY	-	-0.16	-1.65
ICER **	-	-2,118	-2,255
NMB (€) ***	-	-5,785	-58,302

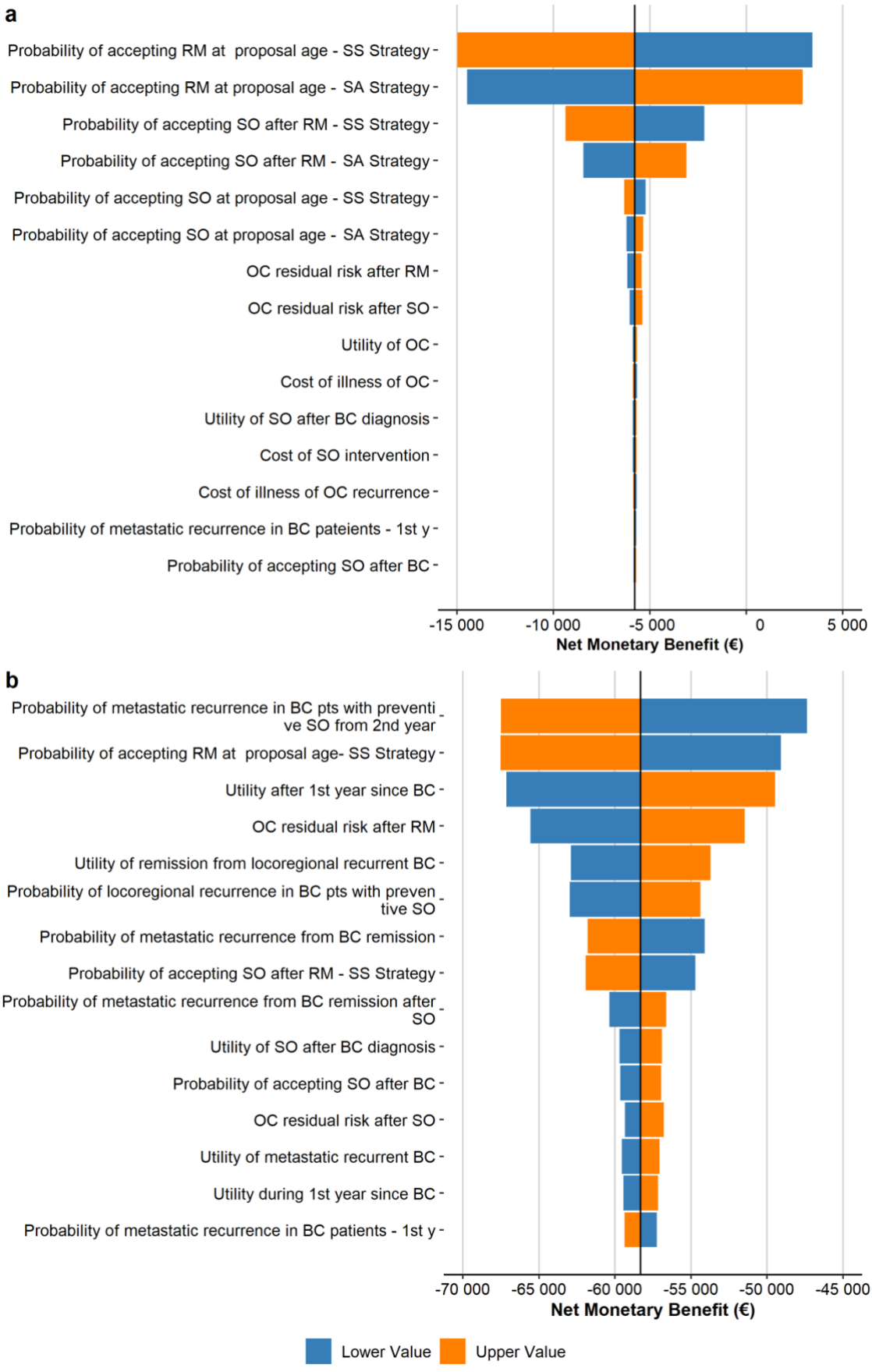
*Cost/QALY per patient.

**ICER = ΔCost/ΔQALY.

***NMB = (λ*ΔQALY) - ΔCost, with λ = WTP threshold is set at €33,000 per QALY gained (Russo et al. (2023) [104]).

The parameters with the greatest influence on the SA vs SS comparison were the probability of accepting preventive interventions, residual OC risk, and OC management costs (Fig. 5a). For NI vs SS, intervention acceptance, residual OC risk, and disease progression were the main drivers (Fig. 5b). In all cases, SS remained the most cost-effective strategy.

Figure 5: Case A - Tornado Graphs of Net Monetary Benefit (NBM) of SA (a) and NI (b) Strategies vs SS Strategy in BRCA2 Carriers.



Scenario analyses that increased OC management costs by 50% and 100% confirmed that SS continued to dominate both comparators (Tab. 6).

The CEAC in Figure 4b (Fig.4b) showed that SS consistently remained the most cost-effective strategy, with a probability greater than 80% at a WTP threshold of €30,000 per QALY gained.

4.2 Case Study B - Zoledronic Acid Injections in Early Breast Cancer Patients

A total of 211 patients were included in the analysis, with 107 randomized to the single-injection arm and 104 to the six-monthly ZA arm.

Over three years, average annual costs were substantially higher in the six-monthly group compared to the single-injection group (CAD $3,430.18 vs CAD $955.16) (Tab.8). The main cost driver in the six-monthly arm was the ZA drug and administration costs (Tab.4).

QALYs were similar between groups, with the single-injection strategy yielding slightly higher QALYs (2.95 vs 2.89). Given its lower costs and comparable effectiveness, the single-injection regimen was identified as the dominant strategy (Tab.8).

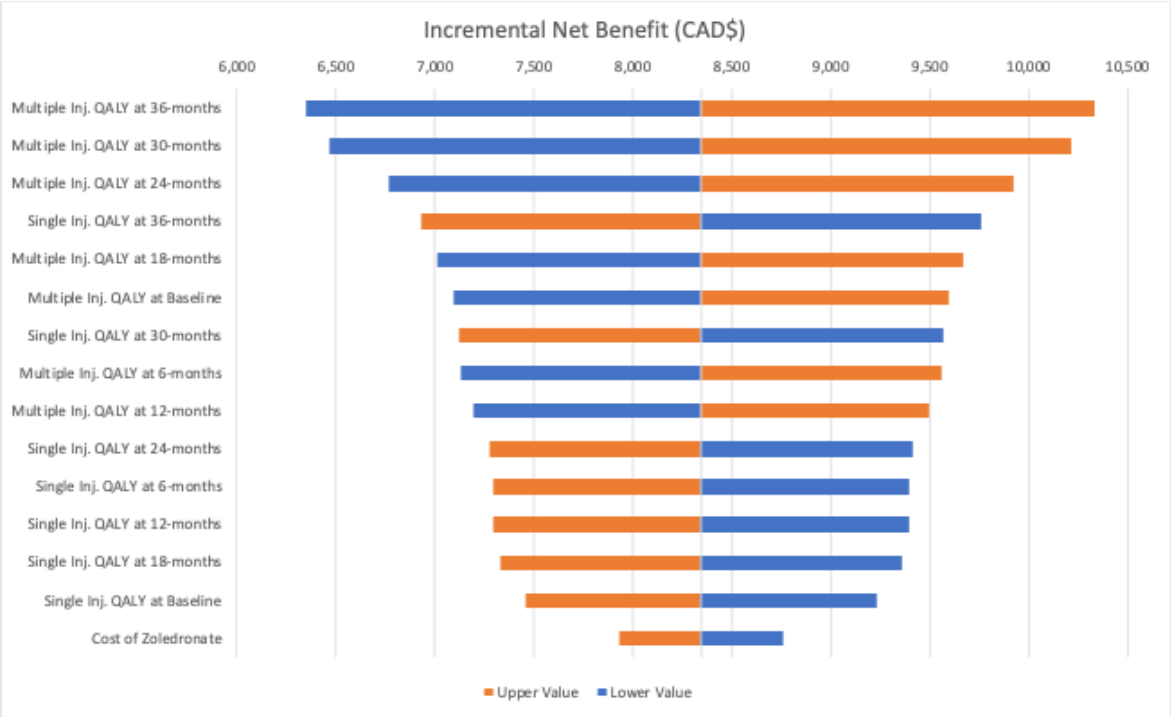
Table 8: Case B - Cost, QALY, and Cost-Effectiveness of Single-Dose vs Six-Monthly ZA Regiments.

	Cost (CAD $)	**QALY**
Single Injection	955.16	2.95
Multiple Injection	3,430.18	2.89
Incremental	2,475.02	-0.06
ICER (ΔCost / ΔQALY)	Single injection arm is dominant	
INB ((WTP × ΔQALY) − ΔCost)*	8,343.87	

*INB is based upon an assumption that the WTP for one QALY is CAD $100,000.

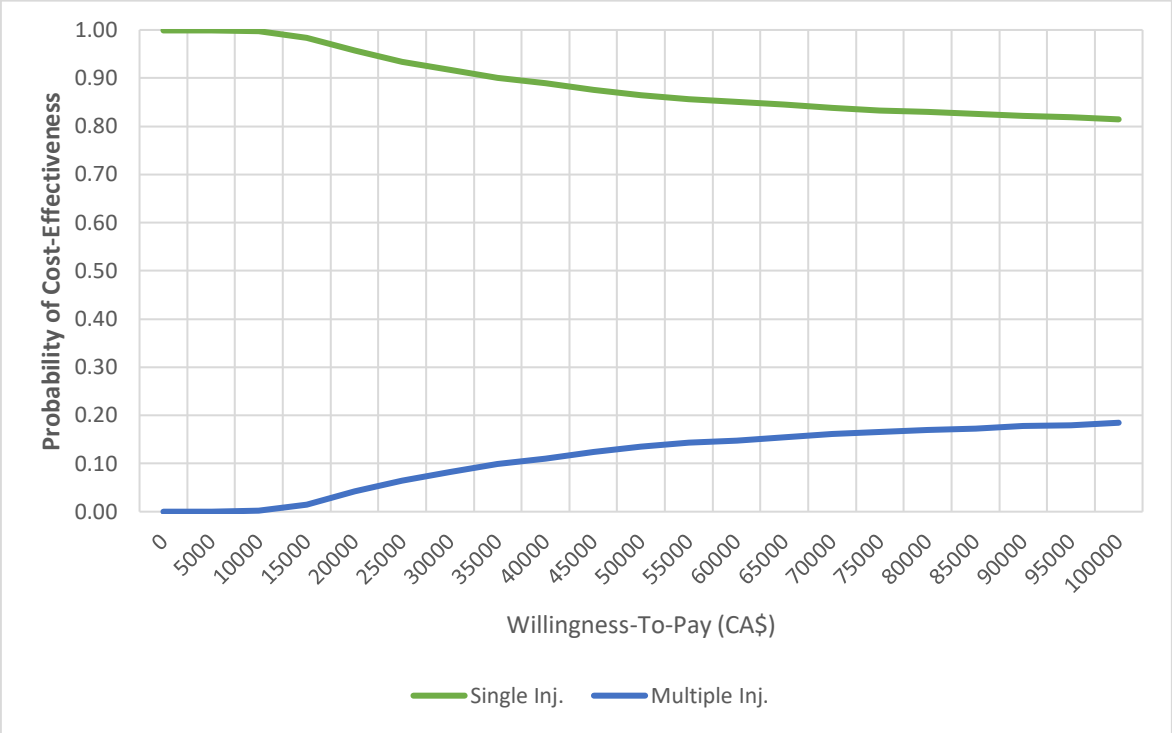
The OWSA confirmed the robustness of these results. The INB was most influenced by variations in QALYs at different time points and by the cost of ZA (Fig.6).

Figure 6: Case B - Tornado Diagram of Incremental Net Benefit (INB) for Single-Injection vs Multiple-Injection ZA Regimens.



PSA further supported these findings. Across all WTP thresholds, the single-injection arm was consistently more cost-effective than the six-monthly regimen. At a WTP threshold of CAD $100,000 per QALY, the probability of cost-effectiveness was 82.2% for the single-injection strategy (Fig.7).

Figure 7: Case B - Cost-Effectiveness Acceptability Curve (CEAC) for Single-Injection vs Multiple-Injection ZA Regimens.



5. Discussion

5.1 Main Findings

The two case studies demonstrate how Markov modelling can identify efficient strategies in both preventive and therapeutic oncology settings. In Case Study A, the strategy SS consistently emerged as the dominant option, yielding more QALYs at lower lifetime costs compared with SA or NI. This advantage was observed for both BRCA1 and BRCA2 carriers and was strongly driven by the higher uptake of risk-reducing surgery facilitated by surveillance. The findings suggest that surveillance, even if not effective for early OC detection, adds value by increasing patient acceptance of preventive interventions, which translates into substantial health gains and long-term savings.

In Case Study B, the single-dose strategy was identified as the dominant option, providing similar QALY outcomes to the six-monthly regimen while reducing costs by over CAD $2,400 per patient. The cost savings were primarily attributable to lower drug and administration expenses. Sensitivity analyses supported the robustness of this result, with the single-dose approach consistently outperforming the standard regimen across a wide range of assumptions.

Both findings highlight opportunities for greater efficiency in oncology care. In prevention, aligning clinical surveillance with surgery can maximize uptake and cost-effectiveness. In treatment, simplifying regimens without compromising outcomes can lower healthcare costs. Both examples underscore the potential of Markov models to inform policy by identifying strategies that deliver comparable or superior outcomes at reduced cost, therefore supporting more sustainable and patient-centred healthcare delivery.

5.1.1 Case Study A - Ovarian Cancer Prevention Strategy

This study shows that a prevention strategy combining clinical surveillance with risk-reducing surgeries at appropriate ages is cost-effective for both BRCA1 and BRCA2 PV carriers. The SS strategy emerged as the dominant option, yielding higher QALYs per patient while reducing costs compared with SA or NI.

Risk-reducing SO is well established to reduce the incidence of OC in BRCA PV carriers by up to 97% [135–137]. Previous studies have found SO, either alone or in combination with risk-RM, to be cost-effective or even cost-saving compared to surveillance [138–140]. However, results vary due to differences in model design, timing of surgery, and healthcare context. RM is also an effective preventive option, significantly reducing the incidence and mortality of BC [53,54,67,141,142]. Because BC tends to occur earlier in BRCA carriers and RM benefits increase with longer life expectancy, the intervention is typically advised at a young age. Its cost-effectiveness is reinforced by reduced BC incidence and lower follow-up costs, as post-RM surveillance generally requires only ultrasound [143].

Although risk-reducing surgeries are effective, they can negatively affect QoL. RM may impact body image and self-confidence [144,145], while SO induces surgical menopause, leading to more severe menopausal symptoms, sexual dysfunction, and long-term health consequences for bone and cardiovascular health [146]. These drawbacks explain why some women decline surgery despite the substantial reduction in cancer risk and anxiety reported after intervention [135–137,139,147].

Encouraging uptake of prophylactic surgery is therefore a major priority in OC prevention. Surveillance, although ineffective in reducing OC incidence or mortality, may play a critical role by increasing the acceptance of surgery. At the Department of Gynaecology at Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy, where surveillance is delivered by a multidisciplinary team that includes a psychologist and a nutritionist, the uptake of SO

among unaffected women reaches 96%. This is markedly higher than the 15-78% range reported in studies offering surgery without surveillance [56,62,148,149].

The higher acceptance of surgery directly contributes to the cost-effectiveness of the combined SS strategy. Petelin et al. (2020) demonstrated the value of multidisciplinary high-risk clinics combining SO, RM, and BC screening, though their model did not include gynaecological surveillance [150]. Uptake of SO was shown to be a key driver of cost-effectiveness [151]. Similarly, in our analysis, acceptance of preventive interventions was the parameter with the greatest influence on incremental cost-effectiveness for both BRCA1 and BRCA2 PV carriers. Factors affecting acceptance include age, mutation type, personal history of BC, clinic attendance, and participation in surveillance programs. Our findings therefore support offering gynaecological surveillance until SO is performed as a cost-effective means of improving preventive outcomes in this population.

This study has limitations. The uptake data for SO were derived from a single centre, which may limit generalizability to other healthcare systems and cultural settings. BC surveillance was not included in the model, so the benefits of earlier BC detection were not assessed. However, BC incidence before the recommended age for RM (35 years) is low, and the model accounted for BC diagnosis by offering SO in the following year. Furthermore, while disutility for surgery was included, the potential mitigating role of hormone replacement therapy (HRT) after SO was not modelled. HRT can reduce menopausal symptoms, but it is contraindicated in women with prior BC, who represent a substantial portion of this population. Lastly, OC cost estimates relied on an older study that did not reflect newer, high-cost therapies. Sensitivity analyses accounting for higher OC management costs confirmed that our base case results remain conservative.

Economic evaluations are essential for assessing the value of current clinical practices and guiding policy on preventive strategies. This study highlights the cost-effectiveness of the

Italian model for managing BRCA1 and BRCA2 PV carriers. With the SS strategy demonstrating dominance, the health benefits and long-term savings outweigh the costs of surveillance and follow-up. Future research should test these findings in other healthcare and cultural contexts and evaluate the impact of linking surveillance with structured screening programs. Such work will help refine public health strategies and ensure effective, patient-centred prevention for high-risk women.

5.1.2 Case Study B – Zoledronic Acid Injections in Early Breast Cancer Patients

This study evaluated the cost-effectiveness of a six-monthly ZA regimen compared with a single one-time dose in patients with EBC enrolled in the REaCT-ZOL Clinical Trial. Results show that a single infusion of ZA is more cost-effective than six-monthly dosing over three years in postmenopausal women with EBC. The main driver of this outcome is the lack of meaningful QALY differences between strategies, combined with substantially higher costs in the multiple-dose arm due to drug expenses and the management of APRs, which require extra visits and medical attention.

These findings align with and expand on previous literature on ZA cost-effectiveness in BC. In the adjuvant setting, Logman et al. (2010) reported that delaying ZA treatment until bone mineral density (BMD) declined was more cost-effective than upfront therapy, with ICERs of £16,069 and £21,973 per QALY gained, respectively [82]. Lamond et al. (2015), evaluating endocrine-sensitive early BC in Canada, found ICERs between $17,007 and $23,093 per QALY gained, indicating cost-effectiveness below the $100,000 threshold [81]. In metastatic disease, results have been mixed. Stopeck et al. (2020) and Cristino et al. (2017) found denosumab to be more cost-effective than ZA, despite higher drug costs, because of reduced skeletal-related events (SREs) and improved QALYs [87,89]. De Cock et al. (2005) suggested oral ibandronate as a lower-cost alternative to ZA with comparable benefits [86].

In contrast, Snedecor et al. (2012) and Xie et al. (2012) concluded that denosumab, although clinically superior in preventing SREs, incurred significantly higher costs per QALY gained, making ZA the more cost-efficient option [88,90].

Other studies have examined six-monthly ZA in combination with other therapies. Lux et al. (2010) reported that adding ZA to gonadotropin-releasing hormone (GnRH) with tamoxifen or anastrozole was cost-effective in premenopausal women with hormone receptor-positive (HR+) BC in Germany, with a 90% probability of an ICER below €22,000 per QALY [85]. Huang et al. (2023) showed that ZA plus aromatase inhibitor (AI) improved OS and reduced bone metastases compared with AI alone, at a cost-effective level in China [84]. Similarly, Delea et al. (2010) found that adding ZA to endocrine therapy in premenopausal HR+ EBC was cost-effective from the US perspective [83].

Several analyses have also considered de-escalation of ZA in metastatic BC to reduce costs while maintaining efficacy [91–93]. Tu et al. (2021), using data from the REaCT bone-targeted agent (BTA) trial, found that extending dosing from 4 weeks to 12 weeks improved QALYs and lowered costs [92]. Shapiro et al. (2017) concluded that ZA every three months was the most cost-effective option compared with monthly ZA or denosumab [91]. Wadhwa et al. (2024) similarly found that ZA every 12 weeks was the most cost-effective option compared with more frequent ZA or denosumab in India [93]. These studies support dose reduction, but most rely on simulation models.

This analysis adds to this evidence by assessing a single-dose strategy using data from a pragmatic RCT rather than a model-based approach. The trial's broad eligibility criteria enhance real-world relevance, reflecting routine clinical practice and diverse patient populations. This design strengthens confidence in the applicability of the findings and provides robust evidence to support major de-escalation of ZA administration.

Several limitations should be noted. The open-label design may have introduced reporting bias, as patients were aware of their treatment allocation, which could have potentially influenced their symptom awareness and reporting. Information on APR severity, duration, and details of medical consultations was not collected, which may have led to an underestimation of APR-related costs. For the single-injection group, QALY data required linear interpolation between collection intervals, which could have introduced inaccuracies if utilities changed between measurement points. The study was conducted entirely in Ontario, which may limit generalizability to healthcare systems with different costs, infrastructure, or clinical practices. Moreover, the three-year follow-up may not fully capture differences in RFS or OS between groups, outcomes that could influence long-term cost-effectiveness. Lastly, while the trial captured broad real-world data, the relatively small sample size may limit the precision of subgroup analyses.

Despite these limitations, this study offers valuable evidence. It is the first to evaluate the cost-effectiveness of adjuvant ZA in Canada using real-world data from an RCT. The findings suggest that a single ZA infusion is both more cost-effective and clinically comparable to the standard regimen administered every six months. Given the lack of significant QALY differences and substantial cost savings, adopting a single-dose strategy could improve the efficiency of adjuvant care in postmenopausal women with EBC. These results support the de-escalation of ZA dosing in routine practice and provide a strong foundation for policy discussions. Future research should validate these findings in larger populations, across different healthcare systems, and with longer-term follow-up to capture survival outcomes.

5.2 Methodological Reflections

A key methodological reflection from this thesis is the use of the same modelling tool, Markov models, across two different evidence bases. In Case Study A, the model used data from the literature and registries, built on assumptions where evidence was incomplete. This approach enabled the capture of a broader range of clinical and economic outcomes, offering greater external validity and longer time horizons. However, reliance on heterogeneous sources and assumptions inevitably introduced more uncertainty into the estimates, making the robustness of results sensitive to input variation [34,41]. In contrast, the ZA case study relied on data from a pragmatic RCT, which provided more standardized inputs and stronger internal validity. This strength came at the cost of limited follow-up and reduced generalizability, as the trial population may not fully represent real-world patients [26,31]. These examples illustrate how the selection of evidence sources influences both the design and the transferability of Markov models in oncology. Literature- and registry-based models can extend analyses across longer horizons and diverse populations, but require careful handling of heterogeneity and uncertainty. Trial-based models, although more precise within their study context, may not translate as well across different healthcare systems or capture long-term dynamics that extend beyond the study period. Balancing them is crucial for enhancing the robustness of cost-effectiveness results and ensuring their relevance to policy decisions [42,43,45].

5.3 Policy Relevance

The findings from both case studies carry important policy implications. In the BRCA model, the combined surveillance and surgery strategy demonstrated clear value by lowering costs and improving outcomes compared with either SA or NI. While surveillance adds some costs, its main benefit lies in improving uptake of preventive surgery, which ultimately reduces

OC risk and treatment expenses. This suggests that policies supporting integrated strategies, linking regular surveillance with timely preventive options, could help maximize both health benefits and system efficiency.

For adjuvant ZA, the results support a move toward treatment de-escalation. A single-dose regimen provided the same health outcomes as the standard six-monthly dosing but at a fraction of the cost, mainly due to lower drug and administration expenses. This suggests that a careful re-evaluation of long-standing treatment protocols can identify opportunities for substantial savings without compromising patient outcomes. These case studies demonstrate how cost-effectiveness models can inform resource allocation in oncology across various healthcare system contexts. By identifying preventive strategies that improve uptake and therapeutic strategies that reduce unnecessary intensity, decision-makers can target investments where they deliver the most value, supporting more efficient and evidence-based cancer care.

5.4 Strengths and Limitations

Both case studies illustrate the strengths of Markov modelling but also highlight important limitations that influence the interpretation and transferability of their findings. Many of these depend on the type and source of data used. In Case Study A, surgical uptake rates were derived from a single Italian centre, which may not accurately reflect rates in other healthcare systems or cultural contexts. In Case Study B, all participants were recruited in Ontario, Canada, which restricts applicability to settings with different costs, infrastructures, or clinical practices. In both cases, generalizability is therefore limited by reliance on data from specific healthcare environments.

Another limitation concerns the scope of outcomes captured. The BRCA model excluded BC surveillance, so potential benefits from earlier detection were not incorporated. In the

ZA model, QALYs in the single-injection arm had to be linearly interpolated between assessment points, which may have reduced the precision of QoL estimates. The BRCA model also did not account for the potential role of HRT in mitigating surgical menopause, while the ZA model lacked detail on the severity and management of APRs. Together, these gaps suggest that some aspects of patient experience and healthcare use may have been underestimated or simplified.

The time horizon and completeness of the evidence posed further challenges. The BRCA model relied on OC cost data from an older source that excluded newer high-cost therapies, although sensitivity analyses supported the conservative nature of base-case estimates. In the ZA model, the three-year follow-up period may not fully capture differences in RFS or OS outcomes that could shift cost-effectiveness over longer horizons. Both cases illustrate how incomplete or time-limited data constrain the ability of Markov models to reflect the full trajectory of disease and treatment.

Furthermore, the two case studies differ in patient populations and outcomes. Case Study A focused on women with pathogenic BRCA variants and preventive strategies for BC and OC, while Case Study B examined postmenopausal women with EBC and treatment de-escalation with ZA. Although both fall under the broader context of BC, the heterogeneity in populations, interventions, and endpoints limits direct comparability between the two case studies. Moreover, the reliance on literature-based and observational data in the BRCA model increases uncertainty, whereas the ZA model, based on RCT data, offers strong internal validity but limited external transferability. These contrasts emphasize the differences between evidence sources and highlight the need for models that integrate multiple data types across healthcare settings.

Despite these limitations, the thesis has several notable strengths. First, it applies a consistent Markov modelling framework to two distinct oncology contexts, demonstrating the

adaptability of the method across the cancer care spectrum. By explicitly comparing models based on literature and observational data with those built on trial-based data, the thesis provides methodological insights into how evidence sources influence cost-effectiveness results, robustness, and policy relevance. The thesis also addresses questions of practical importance, such as improving uptake of preventive strategies and identifying opportunities for treatment de-escalation, both with implications for resource allocation in publicly funded health systems. Furthermore, the focus on the Italian and Canadian settings enhances the relevance, illustrating how economic evaluation and Markov models can support decision-making in diverse healthcare contexts.

6. Conclusion

This thesis applied Markov modelling to two oncology case studies to examine how economic evaluation can inform cancer policy and practice. The first study assessed preventive strategies for women with pathogenic BRCA variants, while the second evaluated treatment de-escalation with ZA in EBC. Both demonstrated that economic modelling is a powerful tool for weighing costs and outcomes, supporting decisions that aim to deliver value for patients and sustainability for health systems.

While the modelling framework was consistent, the outcomes were shaped by the type of evidence available. The BRCA case, built primarily on literature, registries, and assumptions, allowed for a broader perspective and longer time horizon, but might have introduced greater uncertainty. In contrast, the ZA case, which utilized trial-based data, provided stronger internal validity and standardized inputs; however, its shorter follow-up period limited the ability to capture long-term outcomes. These contrasts highlight the importance of selecting evidence sources, as different data types not only influence robustness but also determine the transferability of results across settings.

The two studies illustrate the challenge and opportunity of applying economic models in oncology. Preventive and therapeutic contexts each present unique uncertainties, yet both demonstrate how cost-effectiveness analysis can guide resource allocation, support patient-centred strategies, and inform health policy.

Future research should extend trial follow-up in treatment settings, such as those in ZA, to capture long-term survival and recurrence outcomes. Meanwhile, prevention-focused models, like BRCA, would benefit from multi-country data to reflect different healthcare environments, cultural contexts, and resource structures. Comparative analyses that explicitly test the impact of different data sources, trial-based, registry-based, or hybrid approaches, could strengthen model robustness and improve transferability across systems.

Ultimately, this thesis demonstrates that economic modelling is not only a technical exercise but also a vital link between clinical evidence, patient needs, and policy priorities. By adapting to diverse data sources and contexts, models can play a vital role in ensuring that oncology care remains both effective and sustainable.

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