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ORIGINAL PAPER

Cost-effectiveness analysis (CEA) of ovarian cancer preventive strategies for women with *BRCA1/2* pathogenic variants: the role of surveillance

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Abstract

Background The management of cancer risk for *BRCA* pathogenic variants (PV) carriers varies depending on countries, with different strategies. However, some strategies lack of cost-effectiveness evidence. This study fills this gap assessing the cost-effectiveness of a combined ovarian cancer (OC) surveillance and prevention strategy in *BRCA1/2* PV carriers.

Methods The developed Markov decision model simulated the progression of breast cancer and OC in *BRCA1/2* PV carriers separately. The model estimated benefits and costs associated with three OC surveillance strategies: Surveillance-Surgery (SS), annual surveillance until salpingo-oophorectomy (SO) and radical mastectomy (RM) at appropriate age; Only-Surgery (OS), without surveillance, and No preventive Intervention (NI). Extensive literature review informed the model. The analysis adopted the Italian NHS perspective and a lifetime horizon, with direct healthcare costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio as outcome measures. Base-case, deterministic and probabilistic sensitivity analyses were performed.

Findings In *BRCA1* PV carriers, SS yielded lifetime cost savings of €8 382 and €2 008 compared to NI and OS, respectively, while also gaining 2.65 and 0.45 QALYs per patient. Similar trends were observed for *BRCA2* PV carriers. Sensitivity analyses confirmed SS as the dominant strategy across all scenarios, with a > 80% probability of being most cost-effective at a willingness-to-pay threshold of €20 000 per QALY gained.

Interpretation Combined OC surveillance and prevention strategy for *BRCA1/2* PV carriers at appropriate age represents a highly cost-effective approach compared to surgical prophylaxis alone or no intervention. Periodical counselling in a multidisciplinary team affects high surgical acceptance rates, that are crucial for maximizing the effectiveness of such programs.

Highlights

- Some countries advise transvaginal ultrasound and CA125 tests every 6 months from age 30, along with risk-reducing surgery.
- Annual surveillance until salpingo-oophorectomy and mastectomy saves costs over surgery alone or no preventive measures.
- High surgical acceptance rates are crucial for maximizing the effectiveness of this programs.

Keywords BRCA1 mutation · BRCA2 mutation · Ovarian cancer · Breast cancer · Cost-Effectiveness · Surveillance

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Serena Negri and Carla Fornari contributed equally to this work.

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Introduction

Pathogenic variants (PV) in *BRCA1* and *BRCA2* genes contribute to approximately 5% of breast cancers (BC) [1], and 15% of epithelial ovarian cancers (OC) [2]. Both ovarian and breast cancers impose significant clinical and socio-economic burdens, representing major Public Health issues [3, 4]. Female BC has become the leading cause of cancer globally, constituting one in four cancer cases and one in six cancer-related deaths among women [5]. Additionally, OC ranks as the fifth leading cause of cancer-related death in females [6], despite being the third most prevalent gynaecological cancer.

Women carrying *BRCA1* or *BRCA2* genes PV mutations face elevated lifetime risks of both OC and BC, estimated at up to 17–44% and 69–72%, respectively [7]. Consequently, they are often advised to undergo surveillance programs and consider risk-reducing therapies or surgeries.

BC surveillance typically involves a combination of clinical examination, breast magnetic resonance imaging (MRI), and mammography. Additionally, the option of risk-reducing bilateral mastectomy (RM) should be discussed [8], as it has been shown to significantly reduce the incidence and mortality of BC [9, 10].

For the prevention of OC, *BRCA1* and *BRCA2* PV carriers are advised to undergo risk-reducing salpingo-oophorectomy (SO), typically recommended at ages 35–40 and 40–45, respectively [8]. However, the acceptance rate of SO within this population remains suboptimal [11]. Surveillance strategies, such as routine serum CA125 measurement and transvaginal ultrasound, have not demonstrated efficacy in reducing OC risk or mortality in either the general population [12, 13], or high-risk women [14]. As a result, these approaches are not recommended by guidelines [8, 15, 16]. Despite their ineffectiveness in early OC diagnosis or mortality reduction, these strategies can increase the uptake rates of prophylactic surgery [17].

Furthermore, the management of cancer risk for *BRCA* PV carriers varies depending on the country, with different combinations of strategies offered. In many countries such as Germany and France, surveillance and risk-reducing surgeries for BC are commonly proposed, while routine surveillance for OC is not recommended [18, 19], or it may be considered only if a woman refuses surgery after appropriate counselling [20]. Conversely, in other countries, like Italy [21], a regimen including screening with transvaginal ultrasound and CA125 tests twice a year, starting from age 30, alongside risk-reducing surgery at an appropriate age, is advised [21].

Previous literature has evaluated the cost-effectiveness of risk-reducing surgeries, demonstrating favourable value for money [22]. However, to our knowledge, economic evaluations of OC surveillance programs associated to risk-reducing surgeries have not been conducted. Cost-effectiveness analyses of the combined interventions are essential for assessing their value and supporting healthcare decision-makers in implementing policies and recommendations for implementing surveillance program in this population.

The aim of this study is to assess the cost-effectiveness of a strategy combining OC surveillance and risk-reducing surgery in *BRCA* PV carriers, using the perspective of the Italian healthcare system and incorporating real-world data where available. This approach is compared to a strategy involving only risk-reducing surgery and to a strategy with no interventions proposed.

Methods

Model overview

A Markov cohort simulation model was developed using Microsoft® Excel® 365 to evaluate OC and BC disease progression in women with *BRCA1* and *BRCA2* PV as well as long-term benefits and costs associated with three different disease surveillance strategies. The first strategy, the Surveillance-Surgery (SS) strategy, consisted of yearly surveillance with two gynaecological visits, two transvaginal ultrasound, and two CA125 measurements until bilateral SO prevention intervention proposal managed by a multidisciplinary team that included a clinical psychologist [23]; RM intervention is also proposed at an appropriate age. The second strategy, the Only-Surgery (OS) strategy, included bilateral SO and RM interventions without a yearly surveillance strategy. The third one, the No-Intervention (NI) strategy, did not implement neither preventive surgery nor surveillance.

The Markov model was simulated separately for women with *BRCA1* and *BRCA2* PV and for each previously defined strategy. It started with a cohort of 30 years-old women with *BRCA* mutation and without history of BC or OC. The model lasted 80 cycles, each spanned 1 year (i.e., until age 110 or death).

The model for the SS and OS Strategies included 15 health states (Fig. 1). Women in the simulation started in a state of good health ("well"). They could accept to undergo RM intervention at 35 years-old or SO intervention at 40 and 45 years-old for *BRCA1* and *BRCA2* PV carriers respectively (Table 1). After interventions, women moved to the respective health states of "post SO" or "post RM". The simulation also included the chance to undergo SO intervention after RM intervention ("RM-SO") and then move to the "post RM-SO" health state. Although interventions were performed to reduce the risk of developing BC or OC, there

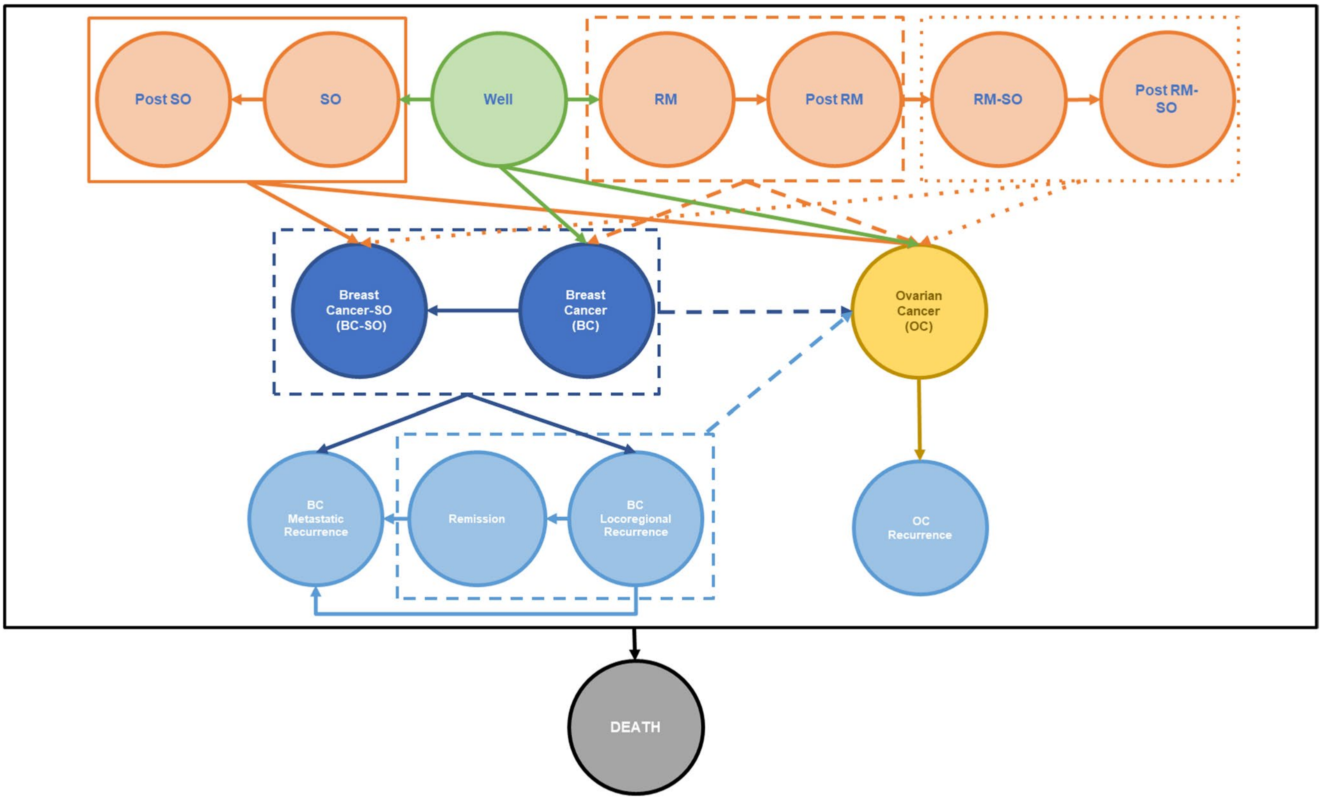


Fig. 1 Markov model structure. The Surveillance-Surgery (SS) and Only-Surgery (OS) Strategies include all the 15 health statuses, while the No-Intervention (NI) Strategy excludes preventive interventions such as "SO", "Post-SO","RM", "Post-RM", "RM-SO", and "Post RM-SO". RM - risk reducing bilateral mastectomy. SO -salpingo oophorectomy

was a residual risk of developing the diseases and shift to the corresponding health states – "Breast Cancer", "Breast Cancer-SO", or "Ovarian Cancer" (Fig. 1). Alternatively, women could develop BC or OC before undergoing interventions and therefore shift to "Breast Cancer" or "Ovarian Cancer" health states. Women in "Breast Cancer" could underdo SO after one year from BC diagnosis. Moreover, women in "Breast Cancer" or "Breast Cancer-SO" health states who did not die could experience locoregional or metastatic recurrences or OC and so move to the respective health states in the next cycle. Women in the "BC Locoregional Recurrence" health state could experience metastatic recurrence or OC or move to "Remission" if they didn't die. Women in "Remission" health state could also experience BC metastatic recurrence or OC. Lastly, from "metastatic recurrence" the only possible transition is to "death" (Fig. 1). Women developing OC could experience recurrence or face death in the following cycles, otherwise they remain in the disease state. In case of recurrent OC, individuals could just progress to death because of the high expected mortality rate of OC [24]. Therefore, the transition from OC to BC was not included (Fig. 1). Finally, the model included the chance to move to death from each health state following Italian life-expectancy data [25].

The NI strategy simulation model did not include health states related to interventions nor post-intervention; it had 9 health states. Women within the model initially began in a state of good health ("well") and could develop either BC or OC. The possible transition to other health states in the following cycles were equal to those previously described (Fig. 1).

The model was constructed using a healthcare system perspective, so it included direct healthcare costs, and it used Quality Adjusted Life-Years (QALYs) as outcome measure. The model computed both Incremental Cost Effectiveness (ICER) and Net Monetary Benefit (NMB) measures of cost-effectiveness. The intervention was considered cost-effective if the ICER was below the threshold of €33 000 per QALY gained indicated by Russo and colleagues for the Italian setting [32]. The same threshold was used to estimate the NMB.

Data sources

The simulation model was designed to reflect an Italian women cohort with *BCRA1* or *BCRA2* mutation and it was populated using data related to the Italian context as far as possible. The Department of Gynaecology of Fondazione

Table 1 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 [26]
SO proposal age					
BRCA1	40	40.00	40.00	4.000	NCCN, 2019 [26]
BRCA2	45	45.00	45.00	4.500	NCCN, 2019 [26]
RM proposal age	35	28.14	41.86	3.500	NCCN, 2019 [26]
Probabilities					
Accepting SO at proposal age					
SS Strategy	0.950	0.76	1.00	0.095	Inzoli et al., 2024 [23]
OS Strategy	0.718	0.58	0.86	0.072	Metcalfe et al., 2019 [11]
Accepting RM at proposal age					
SS Strategy	0.778	0.63	0.93	0.078	Metcalfe et al., 2019 [11]
OS Strategy	0.767	0.62	0.92	0.077	Metcalfe et al., 2019 [11]
Accepting SO after BC	0.950	0.76	1.00	0.095	Inzoli et al., 2024 [23]
OC residual risk after SO	0.040	0.00	0.10	0.030	Grann et al., 2011 [27]
BC residual risk after RM	0.100	0.00	0.20	0.050	Grann et al., 2011 [27]
Probabilities					
From BC to BC locoregional recurrence	0.038	0.03	0.05	0.004	Mavaddat et al., 2013 [28]
From BC to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al., 2018 [29]
From BC locoregional to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al., 2018 [29]
From BC remission to BC metastatic recurrence	0.027	0.02	0.04	0.006	Müller et al., 2018 [29]
From BC metastatic recurrence to death	0.219	0.18	0.26	0.022	La Verde et al., 2021 [30]
From OC to OC recurrence	0.135	0.11	0.16	0.014	Mangone et al., 2022 [31]
From OC to death	0.173	0.14	0.21	0.017	Mangone et al., 2022 [31]
From OC recurrence to death	0.178	0.00	0.00	0.018	Mangone et al., 2022 [31]

BC - breast cancer. OC - ovarian cancer. OS - only-surgery. RM - radical mastectomy. SE - standard error. SO - salpingo-oophorectomy. SS - surveillance -surgery

IRCCS San Gerardo dei Tintori in Monza, Italy, provided valuable information on the SS strategy system, the acceptance rates of preventive interventions, and the post-intervention follow-up plan. Data on incidence, prognosis and healthcare costs related to diseases were taken from the literature, mainly from Italian or European studies. When no data were available, expert opinion were used.

Probabilities

Incidence rates of OC and BC derived from a cohort study which included 6 036 *BRCA1* and 3 820 *BRCA2* PV carriers from 18 European cancer centres, and others in Canada, Australia, and US [7]. The study reported rates by age classes for both types of PV until 80 years; in the model the risk of “71–80” age class was applied also to women > 80 years-old (Table 2). Data pertaining to disease prognosis, incidence of locoregional or metastatic BC recurrences, of OC recurrences and mortality associated with diseases were obtained from the literature (Table 1) [28–31].

Mortality rates of women in the “Well” state were assumed to be equivalent to those of the general population, using life-expectancy data from the Italian National Institute of Statistics [25]. SO and RM interventions were considered safe and were thus not linked to death [33, 34]. Furthermore, it was assumed that cancer-specific deaths would only occur in the health states “Ovarian Cancer,” “OC recurrence” and “BC metastatic recurrence” due to the more aggressive nature of these conditions (Table 1) [30, 31].

Table 2 Incidence rates of ovarian and breast cancer for *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

Data from Kuchenbaecker et al., 2017 [7]. Rates are reported for one person year

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

Efficacy

Data on the efficacy of preventive SO and RM interventions were obtained from a comparative effectiveness simulated cohort study involving women who tested positive for *BRCA1* or *BRCA2* PV. This study compared the outcomes of various interventions, including mammography with and without MRI, prophylactic oophorectomy with and without mastectomy, mastectomy alone, and chemoprevention [27]. Specifically, the risk reduction of OC incidence after SO and BC incidence after RM were derived (Table 1). In the model, women could undergo SO while in the "Well" state, after an RM intervention, or following a BC diagnosis. The model assumed that the efficacy of the SO intervention would remain unchanged throughout these scenarios.

Probabilities of accepting SO or RM intervention for the SS strategy were derived from clinical practice data at the Department of Gynaecology of Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy (Table 1). Acceptance rates for the OS strategy interventions were obtained from the literature [11].

Utility data

Utilities were used to describe patients' quality of life (QoL), which is generally associated with age. The model applied utilities by age group for the "Well" status: 18–35 years (utility = 0.994), 36–45 years (utility = 0.935), 46–55 years (utility = 0.906), 56–65 years (utility = 0.889), 66–75 years (utility = 0.868), and ≥ 76 years (utility = 0.829) [35]. The model also accounted for the potential negative impact of SO and RM interventions on patients' well-being by applying a disutility for each intervention in the year of its occurrence, based on data from Müller et al. (2018) [29].

Utilities for patients with BC during and after the first year since diagnosis, as well as locoregional and metastatic BC recurrences, and OC first diagnosis or recurrence were obtained from Zambelli et al. (2023) [36] (Table 3). Adjustments for ages were made using utilities for "Well" status [35]. Utilities for women in BC remission were assumed to be the same as those for women diagnosed with BC more than one year prior.

Table 3 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 [29]
RM intervention	-0.040	-0.0478	-0.0322	0.004	Müller et al., 2018 [29]
BC					
1st year	0.829	0.6665	0.9915	0.083	Zambelli et al., 2023 [36]
from 2nd year	0.840	0.6754	1.0046	0.084	Zambelli et al., 2023 [36]
locoregional recurrence	0.720	0.5789	0.8611	0.072	Zambelli et al., 2023 [36]
remission	0.840	0.6754	1.0046	0.084	Zambelli et al., 2023 [36]
metastatic recurrence	0.629	0.5057	0.7523	0.063	Müller et al., 2018 [29]
OC	0.490	0.3940	0.5860	0.049	Müller et al., 2018 [29]
OC recurrence	0.160	0.1286	0.1914	0.016	Müller et al., 2018 [29]
Cost (€)					
SS Strategy	162.46	131.00	194.00	16.25	Prestazioni Di Assistenza Specialistica Ambulatoriale, n.d [37].
OS Strategy	0.00	0.00	0.00	0.00	-
NI Strategy	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 [38]
RM intervention*	3 385.87	2 722.00	4 050.00	338.59	Ministero della Salute, 2013 [38]
Post-SO intervention	81.23	65.00	97.00	8.12	Prestazioni Di Assistenza Specialistica Ambulatoriale, n.d [37].
Post-RM intervention	44.87	36.00	54.00	4.49	Prestazioni Di Assistenza Specialistica Ambulatoriale, n.d [37].
BC					
1st year	7 577.00	6 092.00	9 062.00	757.70	Francisci et al., 2020 [39]
from 2nd year	1 507.00	1 212.00	1 802.00	150.70	Francisci et al., 2020 [39]
locoregional recurrence	10 143.00	8 155.00	12 131.00	1 014.30	Francisci et al., 2020 [39]
metastatic recurrence	9 784.00	7 866.00	11 702.00	978.40	Francisci et al., 2020 [39]
OC	15 280.00	12 285.00	18 275.00	1 527.98	Lazzaro et al., 2015 [40]
OC recurrence	22 204.00	17 852.00	26 556.00	2 220.43	Lazzaro et al., 2015 [40]

BC - breast cancer. OC - ovarian cancer. OS - only-surgery. RM - radical mastectomy. SE - standard error. SO - salpingo-oophorectomy. SS - surveillance-surgery

* It includes post-intervention costs

Cost data

Healthcare costs for the three strategies were calculated using outpatient regional service fees provided by the Lombardy region [37]. The number of visits and tests per year for the SS strategy was provided by the Department of Gynaecology at Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy. The annual cost was computed by summing the costs of visits and tests performed each year per patient. Costs associated with SO and RM preventive interventions were determined using national rates from Diagnosis Related Group (DRG) 359 and 258, respectively [41]. After SO intervention, patients received regular follow-up care, which included one gynaecological visit, one transvaginal ultrasound, and one CA125 test per year. Patients who underwent a RM intervention were advised to undergo one mammography per year. Post-interventions costs were calculated using rates from the Italian Ministry of Health (Table 3).

Healthcare costs associated with BC management, both during the first-year post-diagnosis and thereafter, were derived from a real-world data study conducted in Italy by Francisci et al. (2020) [39]. The costs reported for the initial phase of care were used in the model as disease management costs for the first year following a BC diagnosis, while costs for continuing phase of care were considered representative of management costs from the second year, with and without the SO intervention. Stage III disease costs were used as reference for healthcare costs related to BC locoregional recurrence, while cost for BC metastatic recurrences were based on expenses associated with Stage IV disease. Costs associated with remission from BC locoregional recurrence were assumed to be equivalent to those for BC management from the second-year post-diagnosis. These costs included expenses related to hospitalisation, outpatient services, and prescribed medications (Table 3) [39].

The healthcare cost estimation for OC management was derived from a study conducted in Italy focusing on advanced OC by Lazzaro et al. (2015) [40]. Costs associated with first-line treatment were considered as the cost of OC and included initial surgery, adjuvant chemotherapy, cytoreductive revision surgery, and potential ostomy. Expenses for second-line treatment, which included secondary surgery and adjuvant chemotherapy, were used as model inputs for expenses related to OC recurrence (Table 3) [40].

Sensitivity analysis

One-way sensitivity analysis

One-Way Sensitivity Analysis (OWSA) was used to assess the impact of changing one model parameter at a time on predicted costs and outcomes, while keeping all other parameters constant [42]. The range of variation of each parameter was calculated based on the distribution type, with mean and standard error values. Specifically, the lower and upper values of the parameter changes were selected as the limits of its confidence interval. The resulting deviations in the NMB were ranked by their absolute magnitude and presented in a tornado diagram, highlighting the 15 most influential parameters with greatest variation of NMB.

Additionally, an alternative scenario analysis was conducted to evaluate the impact of increased healthcare costs for OC management due to more recent therapeutic options not included in the reference burden of disease studies. Specifically, two scenarios were defined: one with a 50% increase (OC cost=€22 920; OC recurrence cost=€33 306), and another with a 100% increase (OC cost=€30 560; OC recurrence cost=€44 408) in OC management costs.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess how simultaneous changes in multiple parameters affected the NMB. Each parameter was assigned a probability distribution, and a Monte Carlo simulation was conducted, repeatedly sampling sets of all inputs over 1000 simulation runs. The results were summarised in a cost-effectiveness acceptability curve (CEAC), varying Willingness-To-Pay (WTP) thresholds ranging from €0 to €100 000 for both *BRCA1* and *BRCA2* PV-carrier cohorts (Fig. 2).

Results

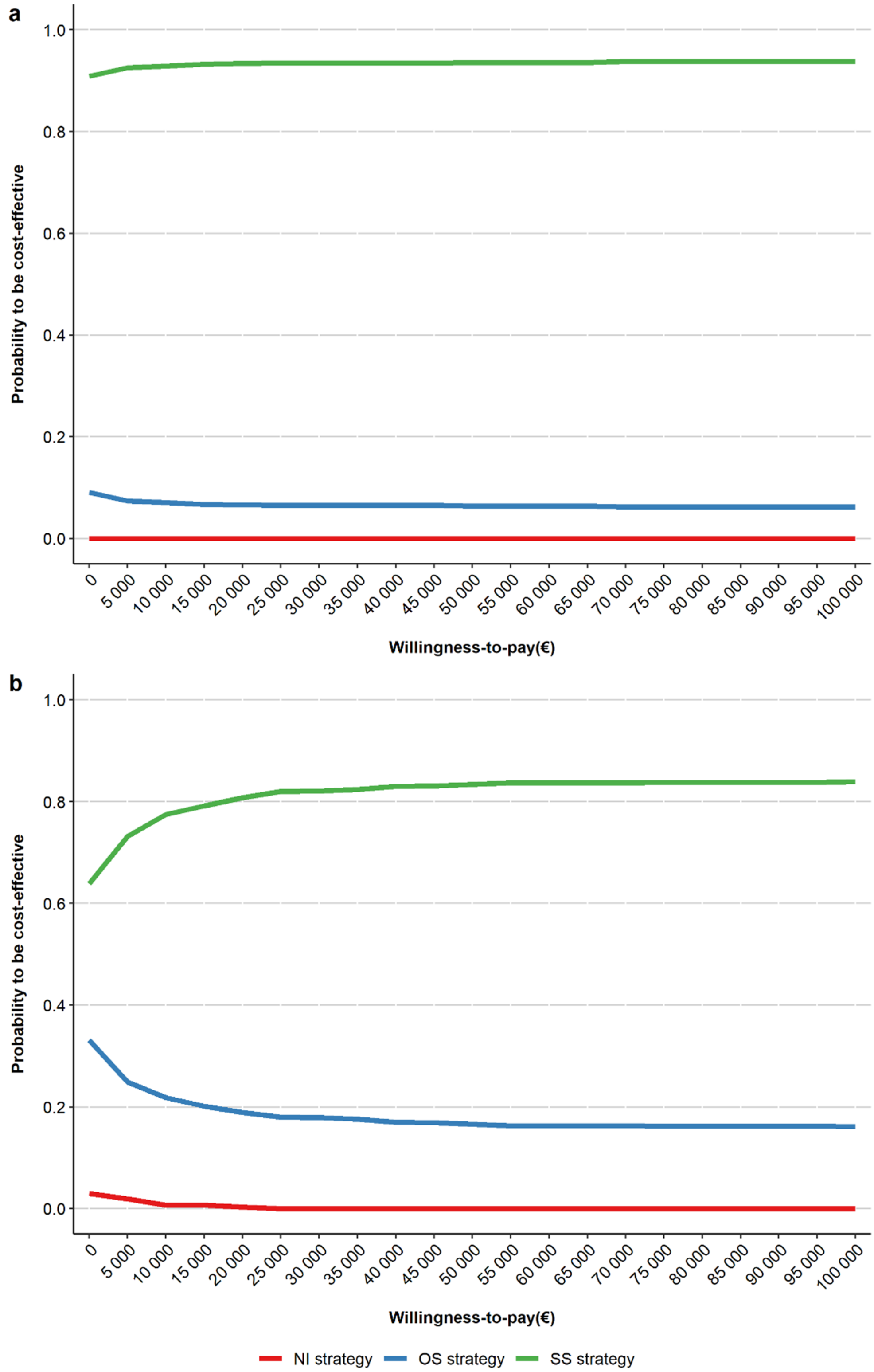
BRCA1 PV-Carriers

The lifetime healthcare cost for managing women with *BRCA1* PV, utilizing the SS strategy, amounts to €17 893 per patient, totalling €17 893 440 for a sample population of 1000 patients. This approach yields an average of 22.25 QALYs per patient. In contrast, the OS strategy costs €19 902 per patient and generates 21.80 QALYs per patient, while the NI strategy incurs €26 276 per patient and results in 19.60 QALYs per patient (Table 4).

Compared to the NI strategy, the SS strategy saves €8 382 per patient and gains 2.65 QALYs per patient. Similarly, compared to the OS strategy, it saves €2 008 per patient and gains 0.45 QALYs per patient (Table 4).

The SS strategy demonstrates dominance over the NI and OS Strategies, indicating that it both saves costs and improves outcomes compared to the other strategies (ICER < 0). The NMB (WTP=€33 000 per QALY gained) for the OS and NI Strategies were -€16 974 and -€95 894 respectively, compared to the SS strategy (Table 4).

Fig. 2 Cost-Effectiveness Acceptability Curve for *BRCA1* (**A**) and *BRCA2* (**B**) PV-carriers cohorts



Sensitivity analysis

The parameters with the most impact on NMB (at WTP=33 000) for the OS vs. the SS strategy comparison include the probability of intervention acceptance, residual risk of OC after SO intervention, healthcare costs associated with OC management, and disease-related mortality (Fig. 3a). Likewise, for the NI vs. SS strategy comparison, key parameters influencing NMB include the probability of intervention acceptance, residual risk of OC, and the progression of BC

Table 4 Cost, QALY and Cost-Effectiveness of surveillance and preventive strategies in *BRCA1* and *BRCA2* PV-carriers

	BRCA1			BRCA2		
	SS	OS	NI	SS	OS	NI
Cost (€) *	17 893	19 902	26 276	13 644	13 993	17 372
QALY *	22.25	21.80	19.60	23.15	22.98	21.49
Reference SS strategy						
Δ Cost (€)	-	2 008	8 382	-	349	3 729
Δ QALY	-	-0.45	-2.65	-	-0.16	-1.65
ICER **	-	-4 428	-3 161	-	-2 118	-2 255
NMB (€) ***	-	-16 974	-95 894	-	-5 785	-58 302

SS - Surveillance-Surgery strategy. OS - Only-Surgery strategy. NI - No-Intervention strategy

*Cost/QALY per patient

**Incremental Cost Effectiveness Ratio ICER = Δ Cost/ Δ QALY

***Net monetary benefit NMB = λΔ QALY - Δ Cost, with λ = Willingness-To-Pay threshold is set at €33 000 per QALY gained (Russo et al., 2023 [32])

diagnosis (Fig. 3b). However, the SS strategy maintained dominance across all simulations.

The sensitivity analysis results, indicating the impact of increasing OC management costs in the model, are presented in Table 4. Notably, the SS strategy continues to dominate other strategies in both scenarios, even with a 50% or 100% increase in OC costs.

The CEAC in Fig. 2a illustrates the probability of each intervention being cost-effective compared to alternatives. The SS strategy consistently emerges as the most cost-effective option, with a probability of being cost-effective exceeding 90% at a WTP threshold of €33 000 per QALY gained.

BRCA2 PV-carriers

The lifetime healthcare cost for managing women with *BRCA2* PV using the SS strategy is €13 644 per patient, yielding 23.15 QALYs per patient. The implementation of the OS strategy costs €13 993 per patient and produces 22.98 QALYs per patient. In contrast, the NI strategy costs €17 372 per patient and results in 21.49 QALYs gained per patient (Table 4).

The SS strategy saves €3 729 per patient and gains 1.65 QALYs per patient compared to the NI strategy. When comparing the SS to the OS strategies, it saves €349 and increases QALYs by 0.16 per patient (Table 4).

The SS strategy is dominant compared to both the NI and OS strategies (ICER < 0). The OS strategy has a negative NMB (with WTP=€33 000 per QALY gained) compared to the SS strategy (-€5 785), while the NMB for the NI strategy compared to the SS strategy is -€58 302 (Table 4).

Sensitivity analysis

The model input parameters with the most significant impact on the NMB of the OS vs. SS Strategies in women with *BRCA2* PV are the probability of accepting RM or SO interventions, residual OC risk, and the OC management cost (Fig. 4a). When comparing the NI vs. SS strategy, the parameters with the greatest impact are the probability of accepting the interventions, residual OC risk, and disease progression (Fig. 4b). The SS strategy remained dominant compared to the NI strategy in all simulations and was more cost-effective in all simulations compared to the OS strategy.

Results of varying model parameters for OC management costs are reported in Table 5. The SS strategy continues to dominate other strategies in both scenarios (OC cost + 50%, + 100%).

The CEAC in Fig. 2b illustrates the probability that an intervention is cost-effective compared to the alternatives. The SS strategy consistently remains the most cost-effective strategy, with a probability of being cost-effective exceeding 80% at a WTP threshold of €33 000 per QALY gained.

Discussion

This study demonstrates that a prevention strategy incorporating both multidisciplinary surveillance and risk-reducing surgeries at an appropriate age is cost-effective for both *BRCA1* and *BRCA2* PV-carriers, compared to risk-reducing surgeries alone or no preventive intervention. Notably, the SS strategy is the dominant approach, yielding higher QALYs per patient and resulting in significant savings compared to the OS strategy and to the NI strategy in both *BRCA1* and *BRCA2* PV-carriers. Risk-reducing SO is well known to reduce the incidence of OC in *BRCA* PV-carriers by up to 97% [43–45]. Some studies have evaluated its cost-effectiveness in unaffected patients, either alone or combined to RM and found it to be cost-effective or even cost-saving for both *BRCA1* and *BRCA2* PV-carriers when compared to surveillance [46–48]. However, the timing of

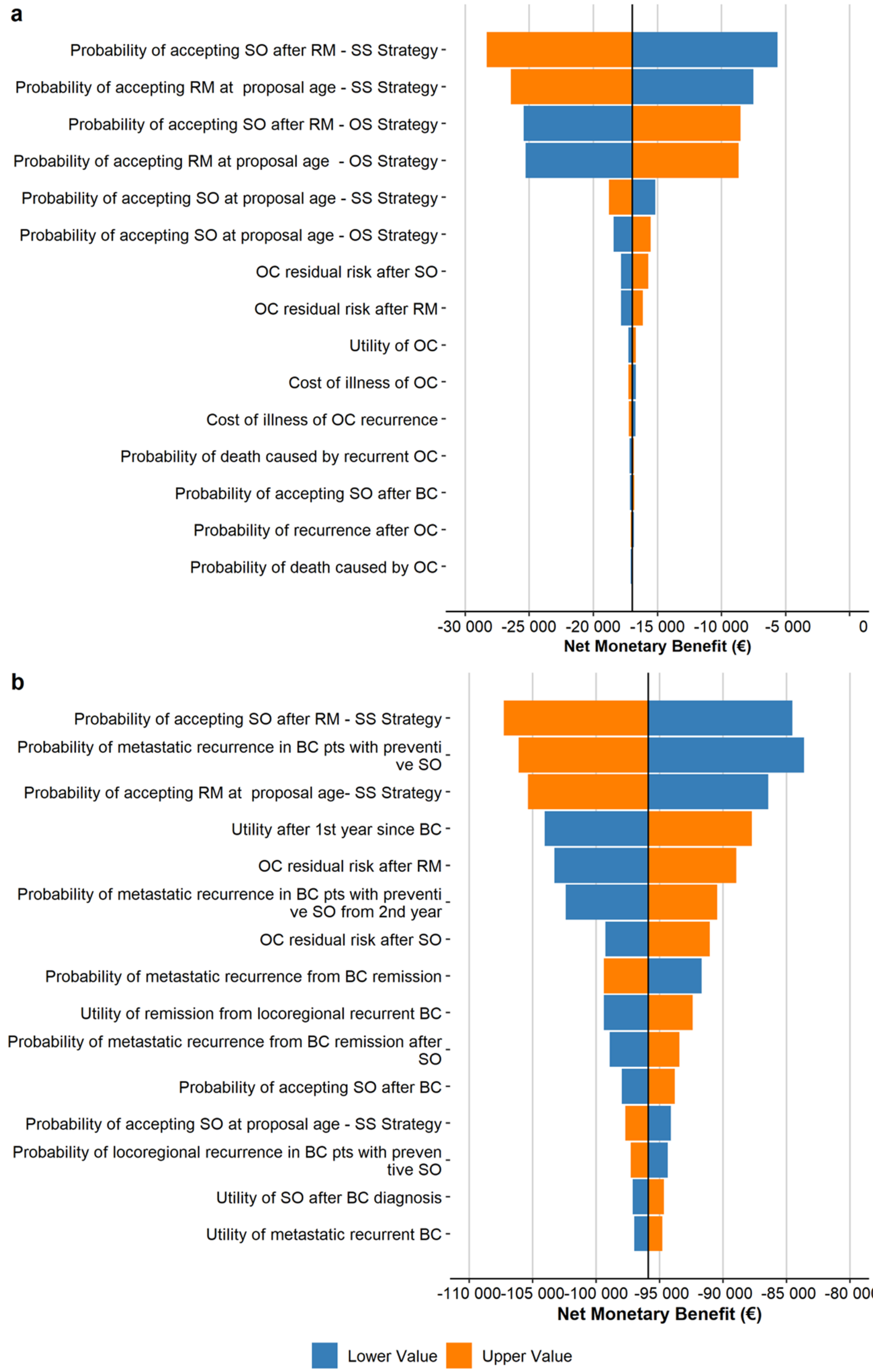


Fig. 3 Tornado Graphs of Net Monetary Benefit (NBM) of OS (**a**) and NI (**b**) Strategies vs. SS Strategy in *BRCA1* PV-carriers cohort simulation. The graphs report the first 15 parameters in descending order of NMB variation (WTP=€33 000). BC - breast cancer. OC - ovarian cancer. OS - only-surgery. RM - radical mastectomy. SO -salpingo-oophorectomy. SS - surveillance-surgery

the surgery proposal, the model, and the setting used for the analysis vary considerably, resulting in heterogeneity of results.

RM is an option for unaffected women to reduce the incidence of BC [49, 50], and has been associated with a reduced mortality [10]. Since BC typically has an early onset in *BRCA* PV-carriers and because the benefit of the surgery partly depends on life expectancy, RM is advised at a young age. This approach is also cost-effective, not only due to the decreased incidence and costs of BC [9, 10, 22],

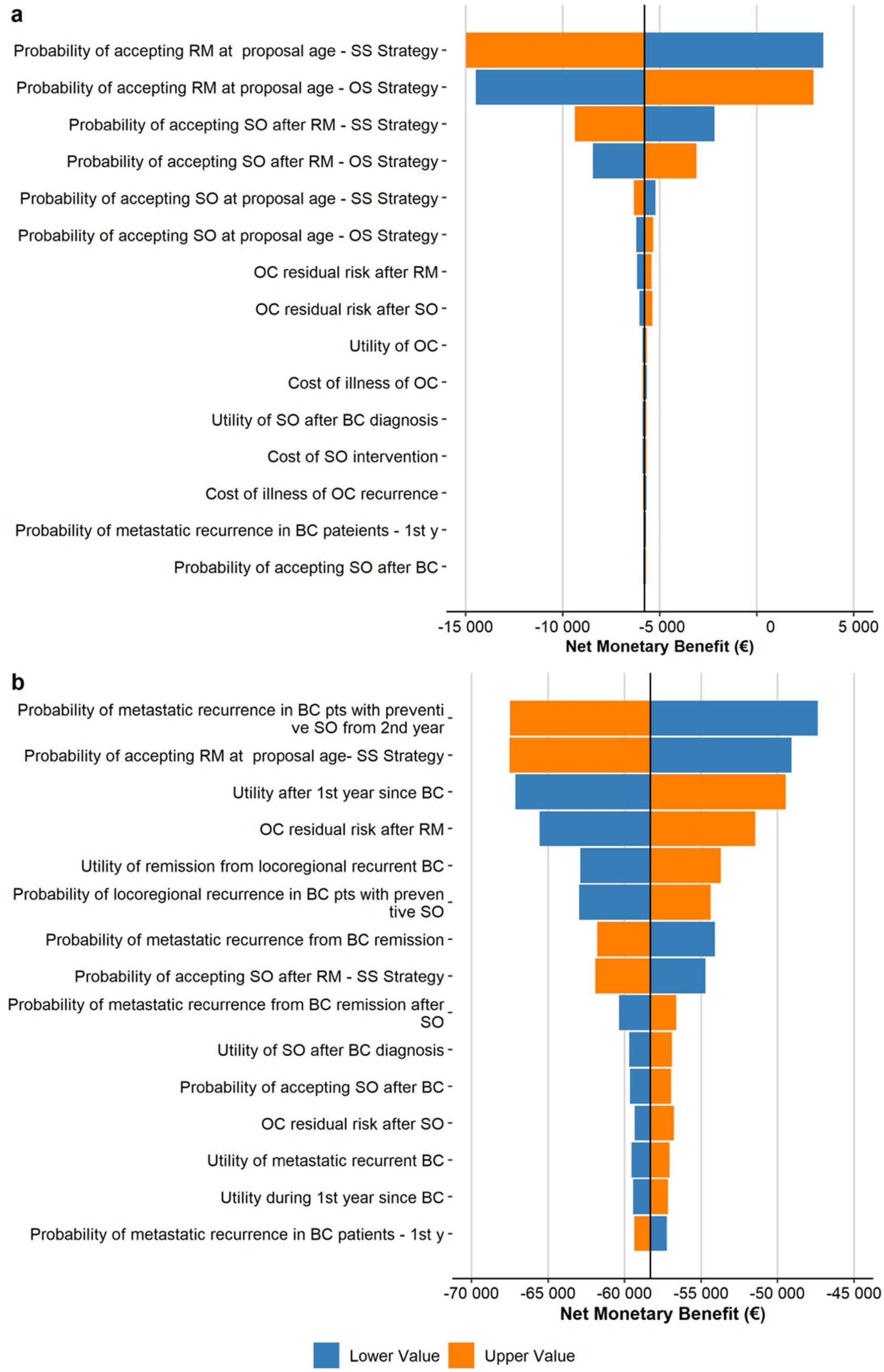


Fig. 4 Tornado Graphs of Net Monetary Benefit (NBM) of OS (**a**) and of NI (**b**) Strategies vs. SS Strategy in *BRCA2* PV-carriers cohort simulation. The graphs report the first 15 parameters in descending order of NMB variation (WTP=€33 000). BC - breast cancer. OC - ovarian cancer. OS - only-surgery. RM - radical mastectomy. SE – standarderror. SO - salpingo-oophorectomy. SS - surveillance-surgery

but also because the follow-up after RM consists only of ultrasounds [51].

Although effective in cancer prevention, risk-reducing surgeries may impair women's quality of life. While RM does not seem to have major health consequences, but it may affect body image and self-confidence [52, 53]. SO leads to surgical menopause, which is associated with more severe menopausal symptoms, and decreased sexual function, and long-term health effects, particularly on bone density and cardiovascular health [54]. These factors can lead

Table 5 Cost, QALY, and Cost-Effectiveness of surveillance and preventive strategies in women with BRCA1 and BRCA2 PV. Sensitivity analysis, varying ovarian cancer annual cost

		BRCA1			BRCA2		
		SS	OS	NI	SS	OS	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

SS - Surveillance-Surgery strategy. OS - Only-Surgery strategy. NI - No-Intervention strategy

[a] OC Annual Cost Variation (+ 50%) vs. Reference (Lazzaro et al., 2005 [40]) - OC €22 920; OC recurrence €30 306

[b] OC Annual Cost Variation (+ 100%) vs. Reference (Lazzaro et al., 2005 [40]) - OC €30 560; OC recurrence €44 409

*Cost/QALY per patient

**Incremental Cost Effectiveness Ratio ICER = Δ Cost/ Δ QALY

*** Net monetary benefit NMB = λΔ QALY - Δ Cost, with λ = Willingness-To-Pay threshold is set at €33 000 (Russo et al., 2023 [32])

some women to refuse the intervention despite the reduction in cancer worry in most women [46, 55], and the overall positive impact on health by significantly reducing cancer incidence [43–45].

Increasing uptake rate of prophylactic surgeries is a major goal for clinicians involved in OC prevention, and surveillance may play a significant role in getting this target. Surveillance may influence the uptake rates of prophylactic surgery increasing the percentage of women accepting the intervention, even if it is ineffective in early diagnosis of OC. The reason why surveillance may drastically increase the uptake rates resides in the presence of a specialized and multidisciplinary team, which allows women to be counselled appropriately twice a year. In fact, at the Department of Gynaecology at Fondazione IRCCS San Gerardo dei Tintori in Monza, Italy, where gynaecological surveillance is conducted by dedicated professionals with the support of a clinical psychologist and a clinical nutritionist, the uptake of SO in unaffected women reaches 95% [23]. This rate is significantly higher than the uptake rates reported in the literature (15%-78%) for strategies offering only prophylactic surgery [11, 17, 56, 57]. The effectiveness of a multidisciplinary strategy is confirmed also by other studies [58–60].

The higher uptake rate of surgery contributes to the cost-effectiveness of the combined approach, as demonstrated in this study. The cost-effectiveness of the SS strategy is primarily attributable to the high SO acceptance rate it facilitates. For the OS strategy to become cost-effective compared to SS (95% uptake), the SO acceptance rate must reach a higher value: 96% for BRCA1 and 98% BRCA2 carriers. Petelin et al. (2020) [61] used real-world clinical data to evaluate the cost-effectiveness of a program involving attendance of a multidisciplinary high-risk clinic, SO, bilateral or contralateral RM, and BC screening with mammography and MRI. A gynaecological surveillance program was not included. This strategy was cost-effective compared to no intervention. However, the uptake rate of SO significantly impacts the incremental ICER estimated [62]. In this study, the likelihood of accepting the interventions is the key parameter that defines the cost-effectiveness of the SS strategy over the alternative approaches in both *BRCA1* and *BRCA2* PV-carriers. The uptake rate of SO was influenced by age, type of mutation, personal history BC, recent clinic attendance, and involvement in surveillance programs.

Given its role in increasing the uptake rate of surgery, proposing gynaecological surveillance for unaffected *BRCA* PV-carriers until SO is performed is a cost-effective intervention.

This study has some limitations that need to be discussed. First, data on SO surgery uptake is based on a single centre, which could limit the generalizability and application of this strategy to other contexts with different healthcare systems, cultures, and practices. A sensitivity analysis (not shown) where the probability of accepting SO was varied demonstrate that the SS strategy remains cost-effective compared to the OS strategy even when the SO uptake rate is lowered to 70% but still greater than or equal to SO uptake in OS strategy. Furthermore, the model did not include a surveillance program for BC, which means the impact of early BC management linked to surveillance was not accounted for. However, the incidence of BC before the age of RM proposal (35 years) is low and should minimally impact the results and the model assumed offering SO in the year after women experienced BC to account for the interaction between BC development and SO risk management in *BRCA1* and *BRCA2* PV-carriers. Moreover, the model does not account for the transition from OC to BC, although the prognosis for OC has recently improved. The decision was made to maintain model simplicity due to the uncertainty of relevant data and the negligible effect this transition would have on the model results. Additionally, the model included a disutility for risk-reducing surgeries, but it did not investigate the use of Hormone Replacement Therapy (HRT). While HRT may partially mitigate the negative effects of surgical menopause and could have reduced the impact of SO, it was omitted primarily due to model complexity constraints and the minimal expected impact on the overall findings. Lastly, data on OC costs are based on a single, outdated study that did not include the costs of new, high-priced treatments. A sensitivity analysis was performed to test the impact of higher costs associated with OC, showing a conservative profile for our base case analysis.

Conclusion

Economic evaluations are essential to assess the cost-effectiveness of a country current clinical practices and can support healthcare decision-makers in implementing preventive healthcare strategies. This study highlights the cost-effectiveness of the management provided in Italy for BRCA1 and BRCA2 PV-carriers. Given the dominant profile of the SS strategy, the future savings and health benefits outweigh the investments in surveillance, including clinical evaluations and exams in a multidisciplinary strategy. Further studies are needed to confirm these results in countries with different healthcare systems and socio-cultural contexts. Additionally, specific assessments of the impact of a screening program linked to surveillance are necessary to define effective public health prevention interventions.

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Data availability All data used in this study are available upon request.

Declarations

Competing interests The authors declare no conflict of interest.

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