Economic modeling of risk-adapted screen-and-treat strategies in women at high-risk for breast or ovarian cancer

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Statement:

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Key Words:

Cost-effectiveness, economic modelling, genetic testing, breast cancer, ovarian cancer, risk-reducing surgery, BRCA

Running Title:

Cost-effectiveness of genetic testing to prevent breast and ovarian cancer

ABSTRACT

Background

The 'German Consortium for Hereditary Breast and Ovarian Cancer' (GC-HBOC) offers women with a family history of breast and ovarian cancer genetic counselling. The aim of this modeling study was to evaluate the cost-effectiveness of genetic testing for BRCA 1/2 in women with a high familial risk followed by different preventive interventions (intensified surveillance, risk-reducing bilateral mastectomy, risk-reducing bilateral salpingo-oophorectomy, or both mastectomy and salpingo-oophorectomy) compared to no genetic test.

Methods

A Markov model with a lifelong time horizon was developed for a cohort of 35-year old women with a BRCA 1/2 mutation probability of ≥10%. The perspective of the German statutory health insurance (SHI) was adopted. The model included the health states ‚well' (women with increased risk), 'breast cancer without metastases', 'breast cancer with metastases', 'ovarian cancer', 'death', and two post (non-metastatic) breast or ovarian cancer states. Outcomes were costs, quality of life years gained (QALYs) and life years gained (LYG). Important data used for the model was obtained from 4380 women enrolled in the GC-HBOC.

Results

Compared with the no test strategy, genetic testing with subsequent surgical and non-surgical treatment options provided to women with deleterious *BRCA 1* or *2* mutations resulted in additional costs of €7256 and additional QALYs of 0,43 (incremental cost-effectiveness ratio of €17,027 per QALY; cost per LYG: €22,318). The results were robust in deterministic and probabilistic sensitivity analyses.

Conclusion

The provision of genetic testing to high-risk women with a BRCA1 and 2 mutation probability of ≥10% based on the individual family cancer history appears to be a cost-effective option for the SHI.

Introduction

The socioeconomic burden caused by breast and ovarian cancer and its treatment is substantial. The four countries with the highest populations in the EU—Germany, France, Italy, and the UK—accounted for €82·9 billion (66% of all costs) [1]. Knowledge about BRCA1 and BRCA2 mutations can be used to estimate the absolute risk reduction from preventive strategies and to inform decisions about the age at which to commence cancer screening [2].

Access to genetic counseling and testing for women with family history across Europe has been highly variable, with many centers using complex criteria to determine which women should be offered testing. Including 17 specialized university hospitals, the 'German Consortium for Hereditary Breast and Ovarian Cancer' (GC-HBOC) collects data on genotype and phenotype from women with an increased familial risk of breast or ovarian cancer. In 1996, the GC-HBOC has defined clinical criteria for BRCA1/2 testing based on familial history of breast and ovarian cancer [3] and evaluated them in 2014 with regard to BRCA1 and 2 mutation prevalence on the data of 21,401 families [4]. In accordance with other countries, , the GC-HBOC currently offers genetic testing to index patients with a BRCA mutation probability of ≥10% based on the individual family cancer history. In case of a deleterious BRCA1 and 2 mutations, the women concerned are offered: (i) intensified surveillance (i.e., breast examination by physicians and sonography every 6 months, yearly mammography and magnetic resonance imaging of the breast until age 69), (ii) prophylactic bilateral salpingo-oophorectomy (BSO), (iii) prophylactic bilateral mastectomy (BM), or (iv) BSO plus BM [5].

This economic modelling study is part of the More-Risk study founded by the Federal Ministry of Education and Research within the framework of ELSA, a multifaceted research branch dealing with the ethical, legal and social aspects of modern life sciences. The model aims to analyze whether genetic testing in women with an increased risk for breast or ovarian cancer followed by several preventive options for women tested positive (BSO, BM, BM plus BSO, or surveillance) is cost-effective compared with a no genetic testing strategy.

Methods

Our Markov model is an extension of a model assessing the cost-effectiveness of different preventive options for women with *BRCA*-mutations [6]. The prior model was extended to estimate the costs and benefits (i.e., quality-adjusted life years (QALYs), and life years gained (LYG)) associated with a genetic test-and-treat strategy compared with no test. The target population of the model was a cohort of 35 year-old women with an increased familial cancer risk but without a history of breast or ovarian cancer. The analysis was performed from the perspective of the German Statutory Health Insurance (SHI). In accordance with the recommendations of the German Institute of Quality and Efficiency in Health Care (IQWiG), costs and benefits were discounted at 3% [7]. In order to reflect the long-term consequences of breast/ovarian cancer, the model had a 1-year cycle length and a time horizon of 65 years. The model was created in TreeAge ProSuite 2010 (TreeAge Software, Inc., Williamstown, MA).

Women with a mutation probability of ≥10% who tested positive for deleterious BRCA1/2 mutations [9] were informed about the preventive options (i) to (iv). In line with previously published data, sensitivity and specificity was assumed to exceed 99%. Therefore, no false-positive and false-negative results were taken into account [53]. Preventive surgeries were offered to all positively tested women at age 35. These women received individual psychological counselling including risk communication and information about benefits and harms of the preventive options. Based on self-reported choice behavior of BRCA positive women in a survey conducted at Cologne University hospital 7% were assumed to choose intensified surveillance only, while the remaining 93% chose either both surgeries (45%) or one of the surgeries (42% oophorectomy only and 6% mastectomy only, table 1, figure 1). [10]. Women with a negative test result were assumed to receive strategy (i). Women in the control group who do not undergo genetic testing were assumed to be unaware of their increased familial risk but to participate in public breast cancer screening programs offered to women aged 50 to 69 years (biennial mammography) [8]. They were assumed to have the same risk of breast and ovarian cancer as women in the intervention group.

Model overview

Women in the model started in the state 'well' and could move to the states 'breast cancer' or 'ovarian cancer'. From there, they could move to the states 'post breast cancer', 'post ovarian cancer', 'metastatic breast cancer', or 'death' (absorbing state) (Figure 2). The breast cancer state included first and contralateral breast cancers. Women with breast or ovarian cancer who did not experience another event moved to the corresponding post-cancer states with gradually increasing utility, and follow-up treatment costs up to year 5. From the sixth year on, women stayed in the post-cancer state unless another event occurred. No further treatment costs were attributed to this state, and women

experienced constant increases in utility. Women with contralateral breast cancer returned to the initial breast cancer state, with treatment costs assumed to be the same as for their first breast cancer. Patients in the 'metastatic breast cancer' state either stayed there or died [11,12]. Because of their increased risk of mortality, women with ovarian cancer, either moved to the post-ovarian-cancer state (and remained in this state) or, they died.

Figure 1. Decision model that shows the test-/no-test-strategies and a woman's options depending on the test result.

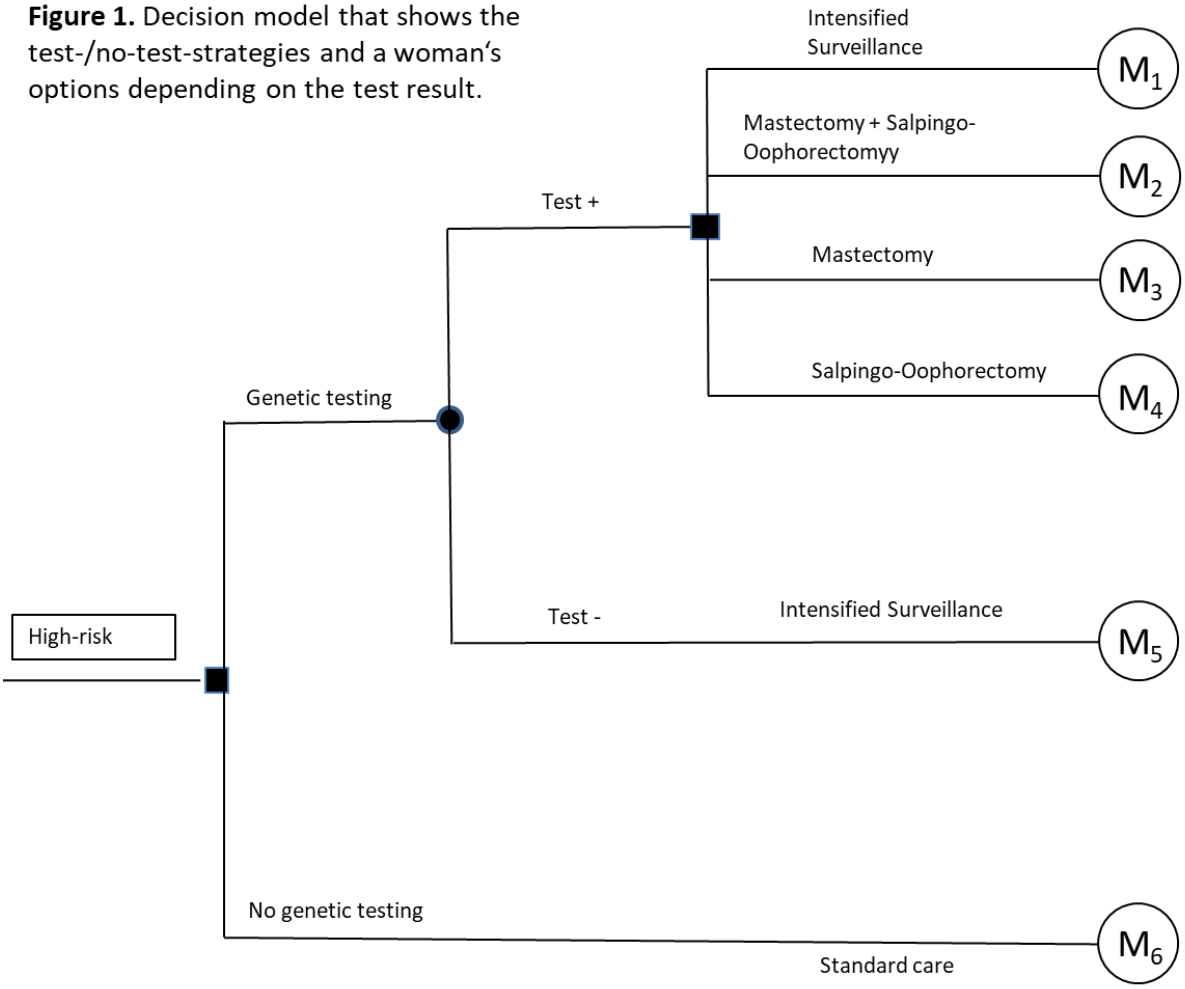
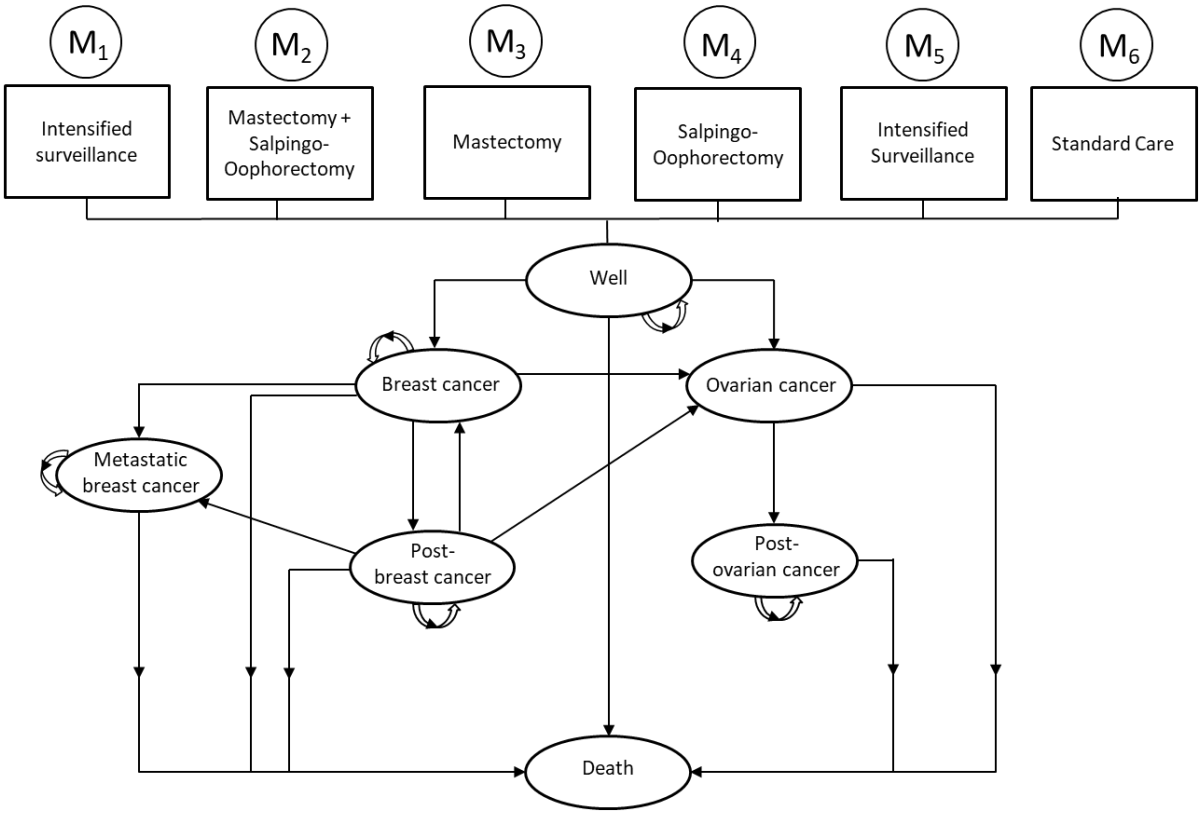


Figure 2. Model overview*



* Using a tunnel state, women were kept in the post-breast cancer states for 5 cycles. From year 6, no further treatment costs and increments in utility incurred and women remained in this state unless a further event occurred.

Data sources

Predominantly, the relevant input data was obtained from the GC-HBOC dataset [13]. However, due to the relatively short follow-up (up to 4 years for first breast cancer and 3.5 years for contralateral breast cancer) and, the partial incompleteness of GC-HBOC data, the model had also to be based on published data and, in some respects, on expert opinion. Therefore, several systematic literature searches in the databases of Medline, Cochrane, guideline databases and public sources were performed to identify complementary input data (e.g., clinical efficacy of surgical treatment options, utilities, and costs) (Table 1). More information about search strategies, inclusion criteria, and quality assurance may be found in the supplementary material.

Probabilities

The incidence of first-time breast cancers was obtained from a dataset of both high-risk women with and without BRCA (BRCA1=959; BRCA2=581, non-carriers = 2840) from the GC-HBOC [14]. Incidence of contralateral breast cancers was based on a follow-up of this cohort [14]. Due to the low number of events data on incidence of ovarian cancer, metastatic breast cancer and mortality had to be taken

from the literature. For high-risk women being in the 'well' state, mortality was assumed to be that of the normal population. The probability of moving from 'breast cancer' to 'death' took into account both the effects of breast cancer and of its treatment on mortality [15]. The majority of cancer-specific death was assumed to occur in the states 'metastatic breast cancer' and 'ovarian cancer' [16]. All transition probabilities are reported in table 1.

Efficacy

In the absence of randomized-controlled trials (RCTs) data on efficacy of surgical treatment options were taken from cohort studies. All treatment options were based on studies including only women with *BRCA1/2* mutations [16-18]. For women without BM or BM/BSO in the case of breast cancer, both therapeutic and prophylactic mastectomy were assumed to have been performed [19]. A risk reduction for breast cancer due to BSO as found in earlier trials was not assumed because a re-analysis of data that maximally eliminated bias found no evidence for a protective effect [20].

Utility data

Utility was assumed to decrease as a result of a positive genetic test, prophylactic surgery and, breast or ovarian cancer. Reported utilities varied depending on which women were asked (e.g., women with or without high risk status) and method used (direct or indirect). To ensure a consistent set of utilities, preference values were obtained from studies including both patients/mutation carriers and healthy women. If utilities for different subgroups were provided, these were combined [21,22]. Decreased utilities following preventive surgery were assumed to increase in a linear manner for 5 years to regain the age-specific utility of an otherwise healthy woman carrying a mutation.

Data on utility in case of breast cancer or metastatic breast cancer was obtained from a meta-regression of studies eliciting utilities in breast cancer patients using a Standard Gamble (SG) approach [23]. Utilities in case of ovarian cancer and end stage ovarian cancer were taken from a single study using the time trade-off (TTO) method [24]. It was assumed that a woman's utility declines as a result of breast or ovarian cancer and then increases linearly for 5 years to reach the age-specific utility of a post-cancer state as defined by Grann [21]. For the states metastatic breast cancer, recurrent ovarian cancer and post ovarian cancer at year 6, a permanent decrease in utility was assumed.

For all states, utilities were age-adjusted. To combine age-specific utility-values in the 'well'-state with utilities in all other states, the multiplicative method was used [25].

Tab. 1: Input data

Variable	Value (SD)	Source
Probabilities		
Genetic testing positive (*BRCA1* or *2*)	0.24 (0.003)	[9]
Choice of prophylactic option: – mastectomy – oophorectomy – both – intensified surveillance	 0.06 (0.02) 0.42 (0.04) 0.45 (0.04) 0.07 (0.02)	[10]
Well – BC	C: 35 – 39: 0.031 (0.002), 40 – 44: 0.021 (0.002), 45-49: 0.023 (0.002), 50-54: 0.027 (0.002), ≥55: 0.033 (0.002) nC: 35 – 39: 0.004 (0.001), 40 – 44: 0.007 (0.001), 45-49: 0.008 (0.001), 50-54: 0.012 (0.002), ≥55: 0 (0.001)	[14]
Well – OC	C: 0.039 (0.005) nC: 0.002 (0.001)	[11] [26]
Well - death	age- and gender-specific	[27]
BC - contralateral BC	C: 0.067 (0.008) nC: 0.015 (0.003)	[14]
BC/Post-BC - death	35-39: 0.00 (0.000), 40-49: 0.001 (0.000), 50-59: 0.002 (0.000), 60-69: 0.004 (0.000), 70-79: 0.007 (0.000), 80-89: 0.028 (0.001), 90-99: 0.139 (0.001), ≥100: 0.404 (0.002)	[15,27]
BC/Post-BC – metastatic BC	all ages: 0.0267 (0.0055)	[28]
BC – OC	0.015 (0.005)	[16]
Metastatic BC - death	30-49: 0.216 (0.046), 50-69: 0.219 (0.046), ≥ 70: 0.313 (0.052)	[12]
OC - death	30-44: 0.060 (0.015), 45-54: 0.103 (0.015), 55-64: 0.142 (0.015), 65-74: 0.180 (0.014), ≥ 75: 0.240 (0.016)	[11]
Relative risk		
BC: Mastectomy Mastectomy + Oophorectomy OC: Oophorectomy Oophorectomy in case of BC Contralateral BC: Mastectomy Oophorectomy	 0.08 (0.01) 0.05 (0.03) 0.28 (0.01) 0.14 (0.01) 0.05 (0.01) 0.59 (0.02)	 [18] [18] [16] [16] [19] [17]
Health-related quality of life*		
Well, at age 35	0.920 (0.002)	[29]

Annual decrease due to age	0.00029	[29]
Well, with positive test result	0.890 (0.02)	[22]
Prophylactic mastectomy, oophorectomy or both	0.850 (0.24), 0.830 (0.24), 0.780 (0.25)	[21]
Annual increase after mastectomy, oophorectomy or both in year 2-5	0.014 (0.006), 0.018 (0.007), 0.028 (0.011)	Assumption based on [22]**
BC	0.679 (0.031)	[23]
Metastatic BC	0.629 (0.045)	[23]
OC OC, end stage	0.52 (0.050) 0.160 (0.250)	[24]
Annual increase after BC in year 2-5	0.028 (0.01)	Assumption based on [21]***
Annual increase after OC in year 2-5	0.054 (0.02)	Assumption based on [21]***

BC = breast cancer, OC = ovarian cancer, SD = Standard deviation, C = carrier of mutation, nC = non-carrier of mutation

* To combine age-specific utility-values in the 'well'-state with utilities in all other states, the multiplicative method was used [25]

** Assumed annual increase to regain the utility of (healthy) women with mutations as described in vignettes by Grann [21]

*** Assumed annual increase to reach the utility of a post-cancer state as described in vignettes by Grann [21]

Cost data

In the intervention group, the costs of ongoing high-risk screening were based on a lump sum data obtained from the GC-HBOC. It includes a breast examination by physicians and sonography every 6 months, plus mammography and magnetic resonance imaging of the breast until age 69 on a yearly basis (costs of public screening in the control group were assumed to be one third of that lump sum). The costs of prophylactic surgeries were calculated via a DRG-Webgrouper [30]. The resource use of (therapeutic) mastectomy or breast conserving surgery in case of breast cancer, therapeutic oophorectomy and delayed prophylactic surgeries due to first cancers (e.g. prophylactic mastectomy in case of ovarian cancer) was estimated according to their proportions in the GC-HBOC data set. Breast cancer drug costs were estimated for specific cancer type subgroups [5,31,32] (table 2). Based on studies suggesting a larger than average proportion of triple negative breast cancers in *BRCA 1* carriers [33], 60% of women were assumed to be triple negative 10% HER2neu+ and 30% hormone-receptor positive (HR+) [12,34]. The latter subgroup was assumed to consist primarily of *BRCA 2* mutation carriers.

Chemotherapy was assumed to be provided mainly to women with triple negative breast cancer, most of which are associated with BRCA1 mutations than to those with HR+ cancers [5,32,31). The chemotherapeutic regimens most frequently prescribed in Germany were assumed to be equally

distributed among women. In addition, targeted therapy was offered to women with HER2neu or metastatic breast cancers (see Table 2). In order to consider non-response to chemotherapy, it was assumed that 2/3 of women with metastatic breast cancer did not respond sufficiently or at all to their first-line chemotherapeutic treatment regimen and needed at least one additional treatment regime [35].

Because of the low number of events on incidence of ovarian cancer in the GC-HBOC, the average total treatment costs in Germany were taken from a recent study at the University Breast Center for Franconia (Germany) [36]. This calculation included the costs of treatment and further surveillance of women with first, recurrent and/or metastatic ovarian cancer. By considering the distribution of tumor stages and biological characteristics (e.g. grading, estrogen receptor, progesterone receptor, and Her2-status) the treatment costs estimated in that study included expenses for surgery, chemotherapy, targeted therapies, laboratory costs, diagnosis, surveillance, and palliative care. The aggregate calculations were based on the assumption that 90% of primary OC patients receive surgery first, while 10% have a tumor stage so advanced that primary cyto-reductive surgery is not performed. Additional costs for potential postoperative complications were not included [36,37].

All data on costs are presented in table 2.

Model validation and sensitivity analyses

In the deterministic sensitivity analysis, we varied all parameters considered uncertain within the respective ranges or confidence limits. In addition, the impact of including the costs of added life years was evaluated [39]. In order to assess how a simultaneous change of several variables affected the cost-effectiveness ratio, a probabilistic sensitivity analysis (10,000 iterations) was conducted. Relying on the model input data listed in Table 1 and Table 2 (except for mortality without cancer and the discount rate), we assumed cost data to be gamma-distributed, probabilities and proportions beta-distributed and relative risks log-normally-distributed.

To validate the model, technical accuracy was checked regarding data entry and potential programming errors (internal validation). For external validation, we assessed the extent to which other models for breast cancer prevention came to different conclusions (cross validation).

Tab. 2: Cost data

Variable	Value in € (SD)[a]	Proportion (SD)
Diagnosis and monitoring		
Genetic testing	2600 (1040) [4]	All women [9]
Ongoing intensified surveillance	560 (224) [13]	T+ without prophylactic mastectomy; T- with a lifetime risk of BC > 20% from age 30-70, women in post-cancer state [13]
Screening control group (age 50-69)	140 (66)*	0.82 of the ‚No test'-group [8]
Surgeries		
Prophylactic mastectomy Prophylactic oophorectomy Prophylactic mastectomy + oophorectomy	8317 (3327) [30] 2854 (1142) [30] 11,171 (4468) [30]	
Breast conserving surgery (in case of BC) Oophorectomy in case of BC Mastectomy in case of OC Mastectomy in case of BC	4318 (1727) [30]	C: 0.56 (0.06), nC: 0.79 (0.08) [13] C: 0.44 (0.06), nC: 0.09 (0.05) [13] C: 0.02 (0.01), nC: - [13] C: 0.44 (0.06), nC: 0.21 (0.07) [13]
Medication BC[b,c,]		
Chemotherapy BC (year 1, proportion of subgroups C/nC) Triple – (0.60/0.15) Her2neu (0.10/0.21) HR + (0.30/0.64) Chemotherapy metastatic BC Triple – (0.60/0.15) Her2neu (0.10/0.21) HR + (0.30/0.64)	 6370 (2550) [38] 26,540 (10,620) [38] 6370 (2550) [38] 19,490 (7800) [38] 48,780 (19,510) [38] 12,200 (4880) [38]	All subgroups: 0.70 C: 0.42 (0.11), nC: 0.10 (0.03) [5,13,31-34] C: 0.07 (0.02), nC: 0.15 (0.04) [5,13,31-34] C: 0.21 (0.05), nC: 0.45 (0.11) [5,13,31-34] T-: 0.85, HER2neu: 0.75, HR+: 0.40 C: 0.51 (0.13), nC: 0.13 (0.03) [5,13,31-34] C: 0.08 (0.02), nC: 0.16 (0.04) [5,13,31-34] C: 0.12 (0.03), nC: 0.26 (0.07) [5,13,31-34]
Medication OC		
Year 1 (state OC) Year 2-5 (state post OC)	91,530 (36,610) [36,37] 2000 (400) [36]	All women*
Palliative care		
End-of-life treatment	11,150 (4460) [37]	Women in 'post state OC' OC who died in that cycle or, women with metastatic BC (each cycle)*

Ca=Cancer, C= carrier of genetic mutation, nC = non-carrier of genetic mutation, BC = breast cancer, OC = ovarian cancer, T = test, triple - = triple negative, HR = hormone receptor, +=positive, _-=negative, SD = Standard error

*Expert opinion

[a]Standard deviation of all costs and proportions of medication intake were assumed to be 40%.

[b]Calculated (assumed an equal share of prescription) for three chemotherapy regimens that were frequently prescribed: 5-fluorouracil / epirubicin/ cyclophosphamide (FEC), Taxane/Antracycline / Cyclophosphamide (TAC), and 5-epirubicin or Doxorubicin / cyclophosphamide plus Taxane (ECT).

[c]According to the consortium about 70% of women with early or recurrent BC received chemotherapy (C, nC). In metastatic women costs of chemotherapy were calculated in relation to the subgroups

Results

Results of base case analysis

With total costs of €22,253, the provision of genetic testing for women at increased risk of developing breast or ovarian cancer resulted in additional costs of €7256 compared with the no test strategy. For women receiving genetic testing, the added gain in QALYs was 0.425, compared with those without genetic testing. Assuming an a priori *BRCA1/2*-mutation probability of ≥10%, the screen and treat strategy resulted in an ICER of €17,027 per QALY (costs per LYG: € 22,318) (Table 3). Compared to the no test-strategy the provision of a genetic test followed by the strategies (i) to (iv) would avoid almost one third of cancers and 20% of deaths at the age of 75 (table A3).

Table 3. Results of the base-case

Strategy	Costs (€)	Δ costs (€)	QALYs	Δ QALYs	LYG	Δ LYG	ICER	
							Cost (€) /QALY	Cost (€) /LYG
No test strategy	14,997		17.07		19.20			
BRCA – (0.76)	8084		17.68		19.64			
BRCA+ (0.24)	36,888		15.12		17.81			
Test strategy	22,253	7256	17.49	0.42	19.53	0.33	17,027	22,318
BRCA - (0.76)	18,329		17.68	0	19.64			
BRCA + (0.24)	34,682		16.89	1.77	19.16			
Mastectomy	30,566		17.25		19.16			
Oophorectomy	44,095		15.94		18.69			
Mastectomy + oophorectomy	24,800		17.94		19.76			
Intensified surveillance	45,256		15.62		18.12			

QALY = quality-adjusted life years
ICER = incremental cost-effectiveness ratio
LYG = life year gained
BRCA+=deleterious BRCA1 or 2 mutation

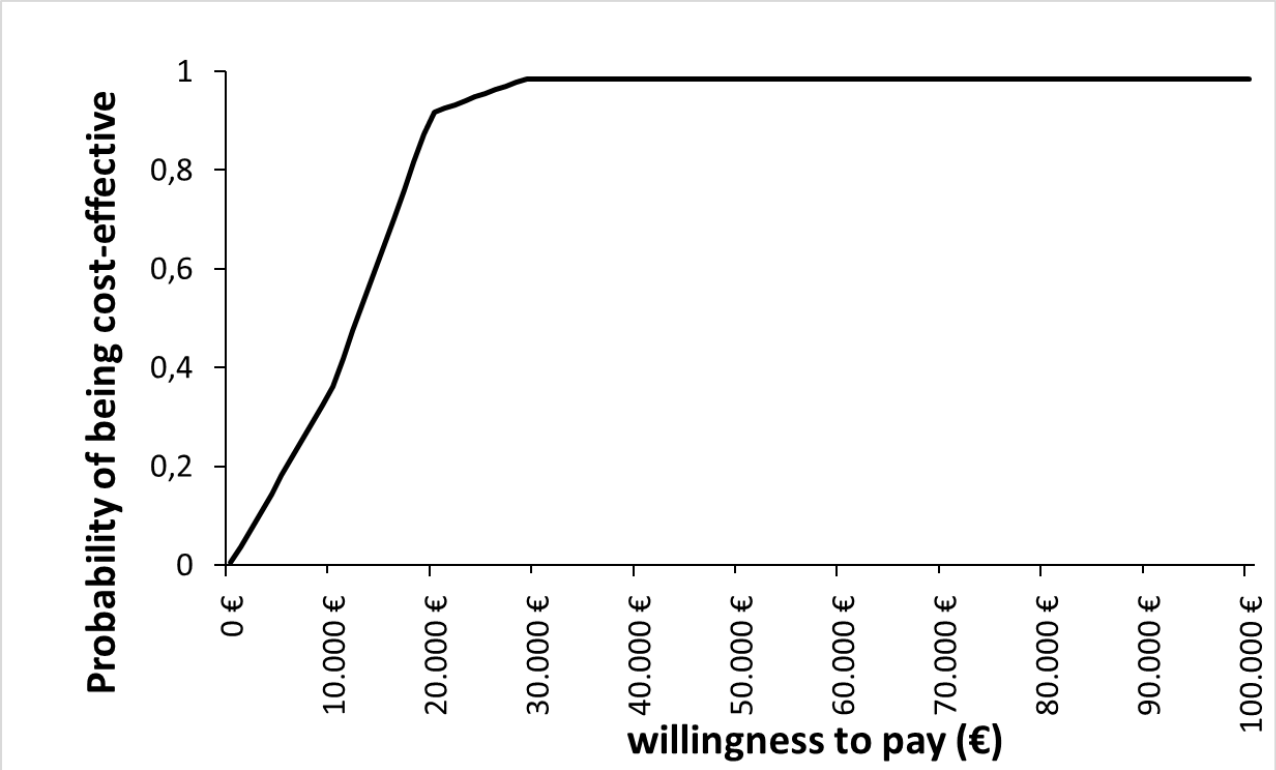
Results of sensitivity analyses

Variables with the largest impact on the ICER were the incidence of first breast cancer, the choice of prophylactic surgery, and the discount rate. Assuming a lower incidence of first breast or ovarian cancer increased the ICER by 85% and 25%, respectively. Similarly, less women choosing surgical prophylaxis increased the ICER by two thirds. In contrast, a higher incidence of breast cancer and a lower discount rate improved the ICER by 45% and 65%, respectively. Overall, the cost-effectiveness

ratio was less sensitive to changes of cost parameters. Including the costs of added life years, the cost–effectiveness ratio increased to 21,000 €/QALY (appendix, table A4).

In the probabilistic sensitivity analysis, 99% of the iterations were in the northeast quadrant, indicating an almost certain gain in QALYs with additional costs. The cost-effectiveness acceptability curve showed a probability of genetic testing being cost-effective of 36%, 92% and 99% at a willingness to pay WTP of €10,000, €20,000 and €30,000 €/QALY, respectively (Figure 3 and appendix, Figure A1).

Figure 3. Cost-effectiveness acceptability curve for the genetic testing strategy (versus no testing)



Discussion

The current GC-HBOC recommendation to test women with a probability of a pathogenic mutation of more than 10% results in a cost-effectiveness ratio of €17,000 per QALY. Based on the inclusion criteria for offering genetic testing within the centers of the GC-HBOC (i.e., expected BRCA mutation probability is ≥10% based on the individual family cancer history) [4,40], close to one quarter of our model population will have a deleterious BRCA1 or BRCA2 mutation. From both a clinical and economic point of view, these women should be tested and – in case of a confirmed BRCA mutation - receive BM plus BSO as the treatment option with the highest gain of QALYs/LYG at the lowest costs.

The model has a considerable number of strengths. First, important clinical data was based on the GC-HBOC (e.g., data on mutation probability, first and contralateral breast cancer incidence and the choice of treatment options). This increased the representativeness of the results of our analysis for German women. The GC-HBOC prospectively follows a cohort of women, avoiding the problem of ascertainment bias which is characteristic of family-based retrospective studies. In addition, incidence data was in accordance with recently published retrospective German data [41, 42] and with the so far largest prospective study based on internationally pooled data conducted by Kuchenbaecker et al [2].

Second, resource use and costs of breast cancer treatment were based on the GC-HBOC, German public data sources and evidence-based guidelines. In order to reflect a realistic scenario of the resource use, medication costs were estimated separately for the subgroups HER2neu, HR+, and triple negative, who considerably differ, especially with respect to targeted drug treatments. In order to determine the costs of ovarian cancer, we used estimates from a recent German study [36]. The average total treatment costs for the treatment and surveillance of women with first, metastatic, and recurrent ovarian cancer in German women appeared to be a realistic scenario as the costs of breast cancer calculated in that study were relatively similar to the costs calculated for women in the GC-HBOC (18,000€ versus 14,000€ in the GC-HBOC for first, 39,000€ versus 45,000€ in the GC-HBOC for metastatic breast cancer).

Third, the treatment options include fair evidence for risk-reduction strategies, i.e. evidence from well-designed (prospective or retrospective) cohort studies, preferably from more than one center or research group. Such studies can contribute to the body of evidence in meaningful ways, and provide useful information when an RCT is unethical or not feasible. A risk reduction for breast cancer due to BSO as found in earlier trials was conservatively not assumed because a recently performed re-analysis of data revealed no evidence for a protective effect [20]. Therefore, a less conservative assumption about a risk reduction of breast cancer due to oophorectomy would further improve the cost-effectiveness ratio.

Finally, the model structure separated between first and metastatic breast cancer. As a result, reported differences in treatment costs and utilities could be specifically assigned to these states. In addition, a gradual increase of utilities after prophylactic surgery was also taken into account just as an initial decrease of utility due to a positive test result or preventive surgery.

As for other modeling studies, there are several limitations which might have affected the results. Although data from GC-HBOC was preferred, several model inputs regarding resource consumption had to be obtained from alternative sources including guideline, bibliographic and public databases. With regard to bibliographic databases our search was restricted to Medline and Cochrane.

Because of the low rates of subsequent events in the GC-HBOC, data on metastatic breast cancer or death from cancer had to be taken from published international studies. Although the GC-HBOC-based incidence rates of first or contralateral breast cancer were similar to those of other studies [18], the usage of published data for metastatic breast cancer and ovarian cancer might deviate to the risk of women in the consortium. Because data recorded in the GC-HBOC did not include information about recurrent ipsilateral breast cancer, a disease progress was restricted to contralateral or metastatic breast cancer. Evidence from the literature supports this assumption because the probability of recurrent ipsilateral breast cancer in women with *BRCA1/2*-associated stage I/II breast cancer only slightly increases the risk of the general population [43]. The inclusion of recurrent breast cancers at the same site might result in an even lower cost-effectiveness ratio as demonstrated in the sensitivity analysis. Doubling the incidence of recurrent breast cancer slightly improves the cost-effectiveness ratio by about 10% (table A4).

Due to a lack of appropriate data, the model also did not include a transition from ovarian cancer to breast cancer. However, according to the literature the risk of breast cancer after ovarian cancer is lower in mutation carriers than in unaffected BRCA mutation carriers [44].

The proportion of women assumed to choose either preventive option was based on hypothetical decisions of 142 women at different ages following individual prevention counseling [10]. Although the relatively small observations in specific age-groups did not allow statistically significant inferences, a 35-year-aged woman may decide to postpone surgery due to still being at childbearing age or for other reasons. Similar preferences for the uptake of preventive surgical options as observed in the 142 German women were reported for older women [45]. In detail, after genetic testing and counseling, the use of BSO was 45% for BRCA1 and 34% for BRCA2 by age 40, whilst the use of BM was estimated to be 46% by age 70 in both BRCA1 and BRCA2 carriers [45]. However, in the sensitivity analyses, changing the proportion of women choosing different preventive options did not alter the conclusions of our analysis.

Our search for data on utilities resulted in heterogeneous findings from studies conducted in different target groups: women with a present mutation/breast cancer or women from a healthy reference group. For example, women at increased risk of breast/ovarian cancer reported an increase of utility in case of BSO, whilst women obtained from a (healthy) reference group reported a substantial decrease due to the procedure [21,22]. Similarly, there were remarkable differences in the decrease of utilities as a result of positive genetic testing or from having new-onset breast or ovarian cancer, i.e., healthy women obtained from a reference group reported lower utilities than women at high risk of cancer [22,46]. In order to ensure consistent utility estimates for this analysis, we used data either from mixed populations [23] or from women at high risk or with cancer [21,22,24]. However, in these studies utilities were elicited using either a TTO or a SG. A comparison of the cross-sectional construct validity between TTO and SG revealed that the SG more accurately reflects health-related quality of life and patient preferences compared to the TTO [47].

A further drawback is in the use of utilities obtained from studies that were published between 1999 and 2009. Because therapies and prognosis of breast and ovarian cancers have improved over time, utility estimates might be higher if more recent studies had been available.

In our model a decrease in utility from preventive surgeries was assumed to last for 5 years only. Because the ambiguity on this issue [48-50] our assumption may be controversially discussed. Negative long-term physical and psychological effects of surgery going beyond the 5year time frame have been reported in some studies [48,49]. After a median follow-up period of 7 years, psychological distress is decreased after PM/BR, at the cost of persistent problems regarding body image [48,49]. A long-term prospective study suggests that women undergoing surgery are satisfied with their decision and have an increasing quality of life over time [50]. However, changes not measured or controlled for in the intervening time periods (e.g. in the clinical care and follow up of study participants) could have confounded this effect [50]. In accordance with the principles of Nyman, the potential costs of these effects were also excluded, even though these costs are causally associated with the intervention [51].

To summarize, the available data on utility is far from being homogeneous. However, in contrast to other parameters, the sensitivity analysis did not reveal a considerable impact of the rather heterogeneous utility data on the cost-effectiveness ratio.

In contrast to earlier modeling studies that have evaluated the cost-effectiveness of genetic testing, we do not believe the results of this model be affected by inconclusive test results such as impaired sensitivity or specificity [52]. The reason being the development of next-generation sequencing (NGS) technologies with very robust statistics about the sensitivity (100% [95% confidence interval, 99.71%-100%] and specificity (99.99% [95% confidence interval, 99.99% -100%] of the assays [53].

There are two previous Markov models that evaluated the cost-effectiveness of genetic BRCA-testing for breast or ovarian cancer in high-risk women compared to no test [52,54]. Both models differed from our model in some methodological aspects. In the model regarding familial breast cancer developed for NICE, a transition from existing ovarian cancer to breast cancer was included and, a potential delay of preventive surgery by up to 5 years after genetic testing was simulated [54]. Holland et al. performed a Markov model from the societal perspective without including the preventive option of BM/BSO [52]. Additionally, in contrast to our model the authors assumed an increase in utility due to a negative test result. They found that an increasing probability of mutation decreased the cost-effectiveness of the test strategy. However, despite these methodological discrepancies in the model structure and input data all analyses showed very similar results.

As a result of avoiding incident breast and ovarian cancer, a comprehensive genetic test-and-screen strategy for German high-risk women results in a substantial gain of QALY/LYG at moderate additional costs. In the future, the cost-effectiveness of multigene-gene test strategies for hereditary breast cancer should be evaluated for the GC-HBOC. Nevertheless, while genetic testing followed by preventive surgery appears to be the most economically advantageous option, a woman's preferences and her personal life situation should always be elicited and drive the final treatment decision.

Conflict of interest statement

The analysis was part of the More-Risk Study, an evaluation of the economical, legal, ethical and risk-communicative implications of a risk-adapted screening strategy to detect mamma- and ovarian cancer. The More-Risk Study was funded by the "Federal Ministry of Education and Research" (NKP-332-019).

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Appendix

Tab. A1: Additional cost data used for the analysis

Variable	Value (SD)[a]	Proportion (SD) [ref.]
Medication BC[b,c,d]		
Endocrine therapy (Her2neu/HR +) BC, year 1/year 2-5 metastatic BC	 1120 (448) / 320 (128) / 1120 (448)	 C: 0.42 (0.11), nC: 0.70 (0.18) [13,32] C: 0.28 (0.07), nC: 0.47 (0.12) [13,32]
Neutropenic sepsis (DRG T60C)	5782 (2313)	0.15 (0.04) of women receiving chemotherapy [30]
Neulasta (Pegfilgrastim)	9852 (3941)	0.50 (0.13) of women receiving chemotherapy [5]
Antiemetics	495 (198)	All women receiving chemotherapy [5]
Bisphosphonates	421 (168)	All women with metastatic BC [5]
Other treatment BC[c,d,e]		
Local surgeries	8381 (3328)	0.05 (0.01) of women with metastatic BC [30]
Adjuvant radiotherapy	1791 (716)	C: 0.60 (0.06), nC: 0.30 (0.10) [5]
Psychological advice and treatment Positive test result BC	 415 (166) 1231 (492)	 0.27 (0.04) [13] 0.36 (0.06) [13]
Lymphatic drainage (BC)	1160 (464)	0.25 (0.06) [5]
Physiotherapy	320 (128)	0.25 (0.06) [5]

C= carrier of genetic mutation, nC = non-carrier of genetic mutation, BC = breast cancer, OC = ovarian cancer, T = test, HR = hormone receptor, SD = Standard error, ref. = reference

[a]Standard deviation of all costs and proportions of medication intake were assumed to be 40%.

[b]Additional medication calculated (assumed an equal share of prescription) for three chemotherapy regimens that were frequently prescribed: 5-fluorouracil / epirubicin/ cyclophosphamide (FEC), Taxane/Antracycline / Cyclophosphamide (TAC), and 5-epirubicin or Doxorubicin / cyclophosphamide plus Taxane (ECT).
[c]Cost for drugs obtained from a German database for pharmaceutical prices [38]

[d]Calculated with a DRG-Webgrouper [30]

[e]Except for local surgeries data on costs were obtained from public available sources (National Association of Statutory Health Insurance Physicians, remuneration lists of health insurances)

Table A2. Additional information about assumptions used for the model

Parameter	Assumption
Ovarian cancer	No transition to breast cancer possible due to high fatality [11]
Transition from 'well' to 'mortality'	Same transition as in the normal population
Transition from 'breast cancer' to 'death'	Increased due to breast cancer- and treatment-related comorbidities [15]
Cancer-specific death	Only in the states 'metastatic breast cancer' and 'ovarian cancer'
Treatment in case of breast cancer for women without BM or BM/BSO	Therapeutic/contralateral prophylactic mastectomy or breast-conserving surgery [5]
Re-increase of utility after prophylactic surgery	Linearly for 5 years to regain the age-specific utility of (healthy) women carrying a mutation
Re-increase of utility after breast or ovarian cancer	Linearly for 5 years to regain the age-specific utility of a woman in the post-cancer state
Monitoring costs of women undergoing BM (with or without BSO)	Half of the lump sum cost for high risk women without surgery and for women undergoing BSO alone
Monitoring costs of women after BC or OC	Same costs as assumed for intensified surveillance
Distribution of cancer type subgroups	60% triple negative, 10% HER2neu+, 30% hormone-receptor positive (HR+). Rationale: 71% of all mutation carriers are BRCA1 carriers; of those, 85% were assumed to be triple negative, the remaining were distributed 1 (HER2neu):3 (HR+) [31-34]
Hormone-receptor positive (HR+)	BRCA 2 mutation carriers
Chemotherapy: FEC, TAK and ECT	Equally distributed
Additional costs due to non-response to chemotherapy	2/3 of women suffering from metastatic breast cancer [35]
Targeted therapy with Bevacizumab	8% of women with HR+ (triple neg.) and metastatic breast cancer [5, 31]
Targeted therapy with Trastuzumab	90% of women with HER2neu (metastatic and non-metastatic breast cancers who received chemotherapy including taxanes [5, 31]
Costs of recurrent BC or OC or, OC following BC	Causes the same costs as the initial BC/OC
Palliative care	Women with metastatic breast cancer (each year) and women with ovarian cancer state (year of dying)

BC=breast cancer, OC=ovarian cancer, HR=hormone receptor, BSO=bilateral Salpingo-oophorectomy, BM=bilateral prophylactic mastectomy

Table A3. Number of cycles spent in different cancer states over lifetime of cancer and death in a cohort of 1000 women with a mutation probability of ≥10% (genetically tested or not)

	Genetic test (n = 1000)*						No genetic test (n = 1000)
	BRCA + (n = 240)						
Health state	**Mastectomy + oophorectomy (n = 108)**	**Mastectomy (n = 14)**	**Oophorectomy (n = 101)**	**Surveillance (n = 17)**	**BRCA – (n = 760)**	**∑**	
Breast cancer**	15	3	143	19	127	307	458
Metastatic breast cancer***	10	2	93	10	165	280	392
Ovarian cancer	7	3	10	4	36	60	101
Total	**32**	**8**	**246**	**33**	**328**	**647**	**951**
Deceased at age 50	2	1	4	5	17	29	34
Deceased at age 75	17	3	33	1	140	194	247

* choice of preventive strategy according to data used for the base-case analysis [10], n describes the number of women choosing the preventive option

** refers to first and/or ipsilateral recurrent breast cancer resulting in more cancer cases than women choosing oophorectomy (because for women in this group no risk reduction of breast cancer was assumed and therefore multiple breast cancers were counted)

*** refers to the number of cycles women spent in the metastatic breast cancer state (i.e. developing plus surviving a metastatic breast cancer)

Tab. A4: Deterministic sensitivity analyses

Number	Variable		Costs per QALY			Costs per life year gained		
			Δ costs (in €)	**Δ QALYs**	**ICER**	**Δ costs (in €)**	**Δ LYGs**	**ICER**
	Base case		7256	0.43	17,027	7256	0.33	22,318
A1	Incidence first BC	lb ub	9208 5176	0.30 0.56	31,100 9302	9208 5232	0.23 0.42	39,205 12,532
A2	Incidence first OC	lb ub	7711 6232	0.36 0.57	21,563 10,960	7711 6232	0.26 0.47	30,056 13,315
A3	Relative risk due to prophylactic surgeries in state 0	lb ub	7002 8041	0.45 0.36	15,558 22,638	7011 8042	0.34 0.28	20,528 29,198
A4	Proportion mutation carrier	lb ub	7331 7182	0.42 0.44	17,642 16,442	7331 7184	0,32 0.33	23,124 21,576
A5*	Choice of prophylactic surgery	lb ub*	8347 7200	0.30 0.44	28,210 16,487	8347 7200	0.22 0.34	37,784 21,130
A6	Costs of prophylactic surgeries	lb ub	6357 8155	0.43 0.43	14,918 19,136	6357 8158	0.33 0.33	19,553 25,092
A7	Costs of chemotherapy for women with BC	lb ub	7761 6751	0.43 0.43	18,212 15,842	7761 6751	0.33 0.33	23,871 20,764
A8	Costs of palliative care	lb ub	7460 7049	0.43 0.43	17,505 16,542	7457 7049	0.33 0.33	22,936 21,682
A9	First-year costs of treatment for women with OC	lb ub	7844 6669	0.43 0.43	18,406 15,648	7844 6669	0.33 0.33	24,125 20,511
A10	Screening and monitoring costs	lb ub	5998 8514	0.43 0.43	14,075 19,979	6339 8167	0.33 0.33	19,498 25,120
A11	Utilities	lb ub	7256 7256	0.44 0.41	16,548 17,558	-	-	-
A12	Discount rate	0% 7%	6212 7226	1.10 0.16	5649 44,811	4572 7226	1.71 0.10	2673 71,424
A13	Genetic testing at the age of 40		6371	0.40	16,089	6371	0.30	21,250
A14	Costs of added life years included		9301	0.43	21,826	9301	0.33	28,608
A15	Assumed risk reduction for BC due to oophorectomy		6234	0,52	11,904	6234	0.38	16,452
A16**	Doubling the probability of ipsilateral recurrent breast cancer*		6747	0.43	15,632	6747	0.32	20,791

BC = breast cancer, OC = ovarian cancer, lb = lower bound, ub = upper bound, QALY = quality-adjusted life year, LYG = life years gained, ICER = incremental cost-effectiveness ratio

*For the upper bound 50% of oophorectomy and oophorectomy plus mastectomy were assumed

** by multiplying the probability used for the base-case

Figure A1. Scatterplot for the incremental cost-effectiveness (genetic