Eur J Health Econ
DOI 10.1007/s10198-017-0887-5

ORIGINAL PAPER

Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation

Dirk Müller[1] · Marion Danner[1] · Kerstin Rhiem[2] · Björn Stollenwerk[3] · Christoph Engel[4] · Linda Rasche[5] · Lisa Borsi[1] · Rita Schmutzler[2] · Stephanie Stock[1]

Received: 6 May 2016 / Accepted: 14 March 2017

Abstract
Background Women with a *BRCA1* or *BRCA2* mutation are at increased risk of developing breast and/or ovarian cancer. This economic modeling study evaluated different preventive interventions for 30-year-old women with a confirmed *BRCA* (1 or 2) mutation.
Methods A Markov model was developed to estimate the costs and benefits [i.e., quality-adjusted life years (QALYs), and life years gained (LYG)] associated with prophylactic bilateral mastectomy (BM), prophylactic bilateral salpingo-oophorectomy (BSO), BM plus BSO, BM plus BSO at age 40, and intensified surveillance. Relevant input data was obtained from a large German database including 5902 women with BRCA 1 or 2, and from the literature. The analysis was performed from the German Statutory Health Insurance (SHI) perspective. In order to assess the robustness of the results, deterministic and probabilistic sensitivity analyses were performed.
Results With costs of €29,434 and a gain in QALYs of 17.7 (LYG 19.9), BM plus BSO at age 30 was less expensive and more effective than the other strategies, followed by BM plus BSO at age 40. Women who were offered the surveillance strategy had the highest costs at the lowest gain in QALYs/LYS. In the probabilistic sensitivity analysis, the probability of cost-saving was 57% for BM plus BSO. At a WTP of 10,000 € per QALY, the probability of the intervention being cost-effective was 80%.
Conclusions From the SHI perspective, undergoing BM plus immediate BSO should be recommended to *BRCA 1*

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).

Authors S. Stock and K. Rhiem are contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s10198-017-0887-5) contains supplementary material, which is available to authorized users.

✉ Dirk Müller
dirk.mueller@uk-koeln.de

Marion Danner
marion.danner@uk-koeln.de

Kerstin Rhiem
kerstin.rhiem@uk-koeln.de

Björn Stollenwerk
bjoern.stollenwerk@helmholtz-muenchen.de

Christoph Engel
christoph.engel@imise.uni-leipzig.de

Linda Rasche
linda.rasche@uk-koeln.de

Lisa Borsi
borsilisa@yahoo.de

Rita Schmutzler
rita.schmutzler@uk-koeln.de

Stephanie Stock
stephanie.stock@uk-koeln.de

[1] Institute for Health Economics and Clinical Epidemiology, The University Hospital of Cologne (AöR), Gleueler Straße 176–178, 50935 Cologne, Germany

[2] Center for Hereditary Breast and Ovarian Cancer, The University Hospital of Cologne (AöR), Kerpener Straße 34, 50931 Cologne, Germany

[3] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München-German Research Center for Environmental Health, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany

Published online: 05 April 2017

or *2* mutation carriers due to its favorable comparative cost-effectiveness.

Keywords Cost-effectiveness · Economic modeling · Breast cancer · Risk-reducing surgery · BRCA

Introduction

Breast cancer is the leading cause of disability-adjusted life years (DALYs) in women worldwide. One in every 18 women develops breast cancer between birth and age 79 [1]. In Germany, breast cancer is the most prevalent malignant disease in women with about 70,000 incident cases per year; about 5–10% of these women carry an increased familial cancer risk and a deleterious *BRCA* (BReast CAncer gene 1 or 2) mutation [2]. Women with a *BRCA1* or *BRCA2* mutation face an elevated lifetime risk not only for breast and ovarian cancer but also for a second primary breast cancer—most often in the contralateral breast [3].

The socioeconomic burden caused by breast cancer and its treatment is substantial [4, 5]. In particular, the care of women with distant metastases, including palliative care, is costly. A recent incidence-based cost-of-illness study in metastatic breast cancer showed that treatment-related costs (e.g., medical treatment, toxicity management, and follow-up) contributed 44% to the overall costs of metastatic breast cancer, followed by palliative/best supportive care (31%), and productivity losses (21%) [6]. While targeted drug treatments such as trastuzumab or bevacizumab are available for both metastatic breast and ovarian cancers are available, they provide limited marginal health gains at a very high cost [7, 8].

Due to the socioeconomic burden, strategies to prevent breast and ovarian cancer are recommended in many countries and are gaining in popularity, particularly for women at increased risk [9, 10]. Since 1996, the "German Consortium for Hereditary Breast and Ovarian Cancer" (hereinafter referred to as the "consortium"), a collaboration between 15 German university clinics (supported by German Cancer Aid), collects genotype- and phenotype data on women at increased familiar risk of breast or ovarian cancers. If a deleterious *BRCA* gene mutation is identified, carriers are provided with in-depth information on their absolute individual risks in definite periods by means of non-directive counseling, and offered risk-adjusted preventive options. These vary in terms of efficacy, impact on health-related quality of life, and economic implications. The strategies include intensified surveillance, prophylactic bilateral salpingo-oophorectomy (PBSO), and bilateral mastectomy (PBM). Among carriers of a *BRCA1/2* mutation, PBM decreases breast cancer incidence and mortality, while BSO decreases breast and ovarian cancer incidence and mortality as well as all-cause mortality [11]. However, chemoprevention (e.g., using tamoxifen), which has also proven to be effective in women with a *BRCA* mutation [12], is not approved in Europe and, therefore not a viable option.

The decision for or against one of these risk-reducing strategies is highly preference-sensitive and involves weighing the clinical efficacy of interventions (potential morbidity and mortality reductions) against their implications for overall (and especially long-term) quality of life. Decisions strongly depend on a woman's individual characteristics such as her familial and personal circumstances (e.g., whether or not she is still of child-bearing age), her individual risk attitude, and her level of anxiety. Regardless, decision-makers at the health insurance level are primarily interested in the cost-effectiveness of available treatment strategies. Risk-reducing surgery considerably decreases cancer risk but, in addition to procedural costs, may be associated with a number of follow-up interventions, including pain management and the treatment of long-term surgery-induced comorbidities [11].

Previous modeling studies that have addressed the cost-effectiveness of preventive measures for women at high risk of breast cancer suggest that BSO alone or BSO plus BM are the most cost-effective strategies for *BRCA* mutation carriers [13–15]. However, these studies were conducted in patient populations from the United States, United Kingdom, and Norway, whose health care systems differ from the German one, particularly in terms of clinical pathways for women with breast cancer (e.g., treatment patterns, resource consumption, and cost structure). To date, no study has evaluated the clinical and economic consequences of surgical and non-surgical preventive strategies in German women at high risk of breast and ovarian cancer. The data from the "German Consortium for Hereditary Breast and Ovarian Cancer" now also provides the opportunity to assess the cost-effectiveness of preventive treatment options in the German healthcare system.

This economic modeling study aimed to compare different preventive interventions in a cohort of 30-year-old women with confirmed *BRCA* (1 or 2) mutations in terms of both, effect (life years gained, quality-adjusted life years) and cost. The preventive interventions included in the study were BM, BSO, BM plus BSO, BM plus BSO at age 40, and intensified surveillance.

[4] Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Härtelstraße 16–18, 04107 Leipzig, Germany

[5] Department of Controlling, The University Hospital of Cologne (AöR), Kerpener Straße 62, 50937 Cologne, Germany

Methods

Model overview

A Markov model (© TreeAge ProSuite 2010) was developed to estimate the costs and benefits [i.e., quality-adjusted life years (QALYs), and life years gained (LYG)] associated with different preventive interventions in a cohort of 30-year-old women with a *BRCA* gene mutation but without a history of neither breast nor ovarian cancer. Since the German consortium aims to identify high-risk women and initiate preventive treatment as early as possible, we chose a cohort of 30-year-old women for our analyses. The preventive strategies used for the comparison were BM, BSO, BM plus BSO, BSO at age 40, and intensified surveillance. Intensified screening includes half-yearly palpation and ultrasound, yearly mammography, and breast magnetic resonance imaging. BM plus delayed BSO at age 40 was included as a strategy in the model since women often decide to postpone BSO due to still being at childbearing age. A 'no treatment'-strategy was not included since almost all women in the consortium chose at least intensified surveillance.

The analysis was performed from the German Statutory Health Insurance (SHI) perspective, with costs and benefits discounted at a rate of 3% [16, 17]. To reflect the long-term clinical and monetary consequences of breast/ovarian cancer and the high survival rates of early diagnosed and treated breast cancer patients, the model had a 1-year cycle length and a duration of 75 cycles (i.e., until age 105 or death). Annual cycles were chosen because more than one diagnosis of breast or ovarian cancer per year is unlikely; in contrast to other more aggressive cancers as, such as leukemia.

Women in our 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) (Fig. 1). The breast cancer state included both ipsilateral and contralateral breast cancers in case of a second incidence. Women with breast cancer who did not die in the next cycle and did not develop a recurrent/contralateral/metastatic breast or ovarian cancer moved to a post cancer state with gradually increasing utility, and follow-up treatment costs up to year 5. Using a tunnel state, women were kept in the post breast cancer state for five cycles. From the sixth year on, women stayed in the post-breast-cancer state unless another cancer event occurred. No further treatment costs were attributed to this state, and women experienced constant increases in utility. Women with recurrent breast cancer or local/regional spread (i.e., any non-metastatic cancers) 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 moved to the state 'death' state, but could not return to the 'well' or 'breast cancer' states, since metastatic breast cancer is associated with ongoing high mortality and a low chance of complete remission [18, 19]. Women with ovarian cancer died or moved to the post-ovarian-cancer state (again using a tunnel state for five cycles). A state for recurrent or metastatic ovarian cancer was not included due to a lack of stage-specific data and the expected high mortality rate of ovarian cancer [18]. A transition from ovarian cancer to breast cancer was therefore not included.

Data sources

In order to appropriately reflect the clinical situation of German women, German data was used as far as possible. Predominantly, the relevant input data was obtained from the German consortium including high-risk women (recorded between 1996 and 2012), who were offered preventive treatment based on initial genetic testing [20]. Consortium data was used to calculate the incidence of breast cancer and proportions required to estimate resource consumption. Due to the relatively short follow-up of 3.2 years (which does not allow enable us to keep full track of a woman's disease) and the partial incompleteness of the consortium data (e.g., incomplete information about cancer subtypes of women with breast cancer, no cost data) the model was also based on published data and, in some respects, on expert opinion. As such, several systematic literature searches were performed in PubMed to identify complementary input data (i.e., incidence of ovarian cancer following breast cancer, clinical efficacy of surgical treatment options, utilities, and costs) (Table 1). More information on search strategies, inclusion criteria, and quality assurance can be found in the Online Appendix [21].

Probabilities

The incidence of early breast cancer was obtained from 5902 high-risk women who tested positive for *BRCA 1* ($n = 1327$) or *2* ($n = 784$) [20]. Standard errors were derived from a Poisson distribution. Data on recurrent ipsilateral or contralateral breast cancer, distant metastasis, ovarian cancer with and without preceding breast cancer, and death from both cancer types was taken from the literature. The probability of moving from 'breast cancer' to 'death' takes into account the impact of breast cancer and treatment-related comorbidities on mortality [22]. For high-risk women in the 'well' state, mortality was assumed

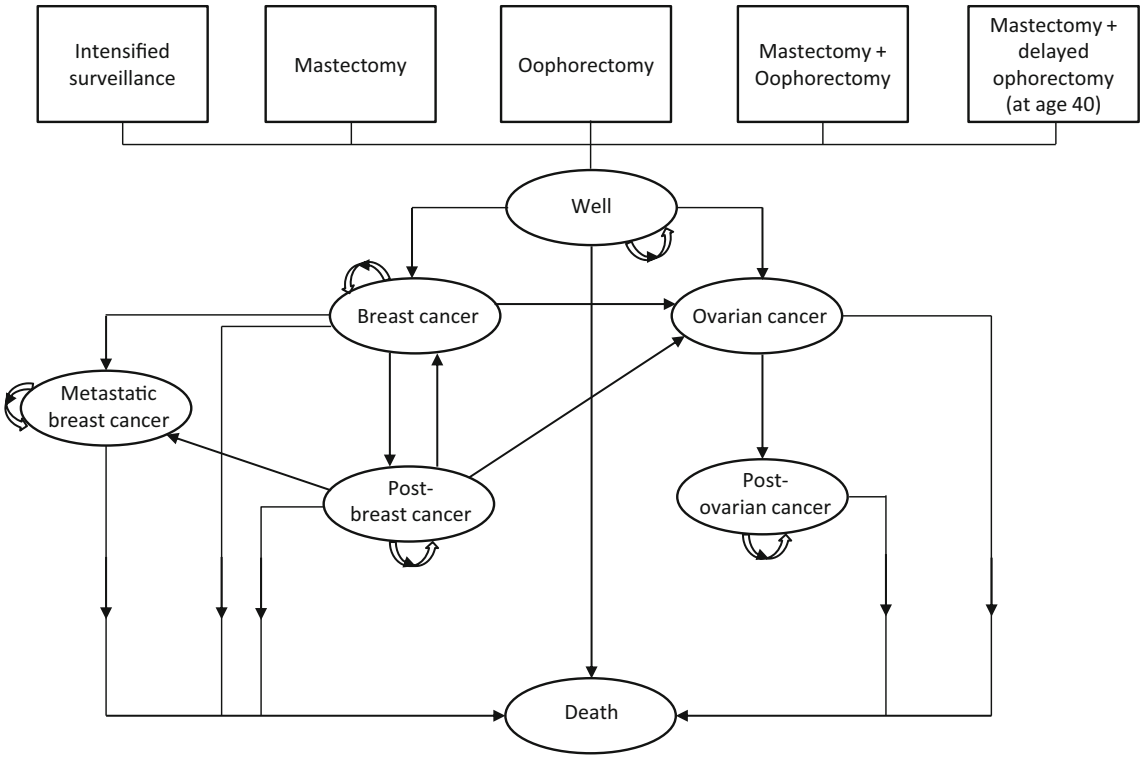

Fig. 1 Model overview using a tunnel state, women were kept in the post-breast cancer states for five cycles. From year 6, no further treatment costs and increments in utility incurred and women remained in this state unless a further event occurred

to be that of the normal population. Cancer-specific death was assumed to occur only in the 'metastatic breast cancer' and 'ovarian cancer' states [19]. Age-specific background mortality from German women has been accounted for all cancer and post cancer states.

Efficacy

In the absence of randomized-controlled trials (RCTs) data on the efficacy of surgical treatment options (i.e., relative cancer risk reductions) were taken from four cohort studies: three prospective and one retrospective. Treatment options included preventive and therapeutic BM or BSO as well as combined preventive BSO/BM and were based on studies including only women with *BRCA1/2* mutations [23–25]. For women without BM or BM/BSO, it was assumed that—in case of breast cancer—they would receive both a therapeutic and a contralateral prophylactic mastectomy [26].

Utility data

Utility was assumed to decrease as a result of breast or ovarian cancer, and also following prophylactic surgery. Reported utilities varied depending on which women were asked (e.g., women with or without high-risk status) and the method used (direct or indirect). In order to ensure a consistent set of utilities, preference values were obtained from studies including both patients/mutation carriers and healthy women. Where utilities for different subgroups were provided, these were combined [27, 28]. 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 [26].

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 [29]. Utilities in case of ovarian cancer and end-stage ovarian cancer were taken from a single study using the time trade-off (TTO) method [30]. 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 [27]. For both, metastatic breast cancer and end-stage ovarian cancer, a permanent decrease in utility was assumed.

For all states, utilities were age-adjusted. The multiplicative method was used to combine age-specific utility values in the 'well' state with utilities in all other states [31].

Table 1 Input data

Variable	Value	SE	Source
Probabilities			
From "Well" (high risk)			
BC	30–34: 0.0321	0.0064	[20]
	35–49: 0.0274	0.0060	
	≥ 50: 0.0285	0.0061	
OC	0.0095	0.0029	[24]
Death	Age- and gender-specific mortality from the general population		[32]
BC–BC (contralateral or ipsilateral recurrence	30–39: 0.0625	0.0163	[25, 33]
	40–49: 0.0542	0.0131	
	50–59: 0.0408	0.0162	
	60–69: 0.0534	0.0222	
	≥70: 0.0474	0.0324	
BC–death	30–39: 0.0003	0.0003	[22, 32]
	40–49: 0.0006	0.0002	
	50–59: 0.0018	0.0003	
	60–69: 0.0039	0.0005	
	70–79: 0.0074	0.0008	
	80–89: 0.0284	0.0026	
	90–99: 0.1391	0.0077	
	≥100: 0.4039	0.0234	
BC–metastatic BC	0.0267	0.0055	[34]
OC–recurrent OC	0.3070		[35]
BC–OC	0.0146	0.0050	[24]
Metastatic BC–death	30–49: 0.2161	0.0460	[19]
	50–69: 0.2187	0.0462	
	≥70: 0.3130	0.0518	
OC–death	30–44: 0.0602	0.0150	[18]
	45–54: 0.1030	0.0154	
	55–64: 0.1420	0.0153	
	65–74: 0.1800	0.0140	
	≥75: 0.2400	0.0164	
Relative risk (surgery versus no surgery)			
BC			
Mastectomy	0.08	0.05–0.11	[23]
Oophorectomy	0.47	0.29–0.77	[36]
Mastectomy + oophorectomy	0.05	0.01–0.2	[23]
OC			
Oophorectomy	0.28	0.26–0.30	[24]
Oophorectomy in case of BC	0.14	0.12–0.16	[24]
Contralateral BC			
Mastectomy	0.05	0.03–0.07	[26]
Oophorectomy	0.59	0.55–0.63	[25]
Health-related quality of life[a]			
Well, at age 30	0.89 (0.02))		[28]
Annual decrease due to age in the state 'well'	0.00029		[37]
Prophylactic mastectomy, oophorectomy, or both	0.850 (0.24)		[27]
	0.830 (0.24)		
	0.780 (0.25)		

Table 1 continued

Variable	Value	SE	Source
Annual increase (years 2 to 5)			
After mastectomy	0.014 (0.006)		[28][b]
After oophorectomy	0.018 (0.007)		
After both	0.028 (0.011)		
BC	0.679 (0.031)		[29]
Metastatic BC	0.629 (0.045)		[29]
OC	0.490 (0.360)		[30]
OC, end stage	0.160 (0.250)		
Annual increase after BC in year 2–5	0.028 (0.01)		[27][c]
Annual increase after OC in year 2–5	0.054 (0.02)		[27][c]

BC breast cancer, *OC* ovarian cancer, *SE* standard error

[a] To combine age-specific utility-values in the 'well'-state with utilities in all other states, the multiplicative method was used [31]

[b] Assumed annual increase to regain the utility of (healthy) women with mutations as described by Grann [28]; standard deviation was assumed to be 40%

[c] Assumed annual increase to reach the utility of a post-cancer state as described in vignettes by Grann [27]

Cost data

In line with the recommendations of the consortium, all high-risk women without surgery and women undergoing BSO alone received continued intensified breast cancer surveillance at a lump sum cost of €560 [20]. In contrast, women undergoing BM (with or without BSO) were assumed to incur only half of these costs since magnetic resonance imaging is excluded from surveillance in these cases.

Breast cancer drug costs were estimated for specific cancer type subgroups. Based on studies suggesting a larger-than-average proportion of triple negative breast cancers in *BRCA* 1 carriers [38], 60% of women were assumed to be triple negative 10% HER2neu+ and 30% hormone-receptor positive (HR+) [39, 40]. The latter subgroup was assumed to be made up primarily of *BRCA* 2 mutation carriers. While the overall proportions of women with non-metastatic breast cancer receiving adjuvant radiotherapy, chemotherapy, and endocrine therapy were taken from the consortium database, those for women with metastatic breast cancer were obtained from the literature. Since the type of therapy differs markedly across hormone-receptor subgroups, these differences were taken into account, e.g., chemotherapy was assumed to be provided more often to women with triple-negative breast cancer than to those with HER2neu and HR+ cancers [10, 41, 42] (Table 2). The chemotherapeutic regimens most frequently prescribed in Germany were assumed to be equally distributed among women (see Table 2). In addition to this, targeted therapy was offered to women with HER2neu or metastatic breast cancers [10]. In order to include non-response, it was assumed that two-thirds of women suffering from metastatic breast cancer did not respond sufficiently or at all to their first-line chemotherapeutic treatment regimen and needed at least one additional treatment regimen. The costs for chemotherapeutic treatment were increased accordingly [43].

The estimates of prophylactic and therapeutic surgical costs were based on actuarial data from the University Hospital of Cologne. The average costs of prophylactic/therapeutic BM and BSO were calculated based on data from 2012 to 2014. According to guideline recommendations, it was assumed that all women with 'breast cancer' receive either a mastectomy or breast-conserving surgery [10]. Data on the costs of treatment for advanced and non-advanced ovarian cancer included drug costs for platinum-sensitive and platinum-resistant carcinoma. It was assumed that one-third of ovarian cancers was not advanced and received carboplatin/paclitaxel alone [44]. In advanced ovarian cancers, 20% of women were assumed to be platinum-resistant (i.e., recurrence within the first 6 months [45]).

The costs of palliative care were calculated for all women with metastatic breast cancer, while for women with ovarian cancer these end-stage costs were applied to the proportion of women who died in the ovarian cancer state [46]. All data on costs are presented in Table 2.

Model validation and sensitivity analyses

In order to assess how the input parameters affected the cost-effectiveness ratio, we performed both deterministic and probabilistic sensitivity analyses. In the deterministic sensitivity analysis, we varied all the parameters that were considered to be uncertain, i.e., cancer incidence, mortality,

Tab. 2 Cost data

Variable	Value in € (SD)[d]	Proportion (SE)	Source
Diagnosis and monitoring			
Ongoing high-risk screening/monitoring	560 (224)	1.00	[20]
Surgical options[a]			
Prophylactic mastectomy	8317 (3327)	0.44 (0.06)	[20, 47]
Prophylactic oophorectomy	2854 (1142)	0.02 (0.01)	
Prophylactic mastectomy + oophorectomy	11,171 (4468)		
Prophylactic oophorectomy in case of BC	2854 (1142)		
Prophylactic mastectomy in case of OC	4783 (1913)		
Therapeutic mastectomy	6556 (2622)	0.44 (0.06)	[20, 47]
Breast-conserving surgery	4318 (1727)	0.56 (0.06)	[20, 47]
Therapeutic oophorectomy	2854 (1142)	0.77 (0.04)	[20, 47]
Medication BC[b,c,d]			
Chemotherapy BC (year 1, proportion in hormone receptor subgroups)	6371 (2548)	All subgroups: 0.70 (overall proportion receiving chemotherapy)	[10, 20, 40–42, 48]
Triple— (0.60)	26,537 (10,615)	0.42 (0.11)	
Her2neu (0.10)	6371 (2548)	0.07 (0.02)	
HR + (0.30)	19,488 (7795)	0.21 (0.05)	
Chemotherapy metastatic BC	48,775 (19,510)	T-: 0.85, HER2neu: 0.75, HR+: 0.40 (subgroup-specific proportion receiving chemotherapy)	
Triple— (0.60)	12,201 (4880)	0.51 (0.13)	
Her2neu (0.10)		0.08 (0.02)	
HR + (0.30)		0.12 (0.03)	
Endocrine therapy (Her2neu/HR)	1120 (448)/320 (128)/1120 (448)	0.42 (0.11)	[10, 20, 42, 48]
BC, year 1/year 2–5		0.28 (0.07)	
Metastatic BC			
Neutropenic sepsis	5782 (2313)	0.15 (0.04) of women receiving chemotherapy	[47, assumption based on 9]
Neulasta (pegfilgrastim)	9852 (3941)	0.50 (0.13) of women receiving chemotherapy	[48, assumption based on 9]
Antiemetics	495 (198)	All women receiving chemotherapy	[10, 48]
Bisphosphonates	421 (168)	All women with metastatic BC	[10, 48]
Other treatment BC			
Adjuvant radiotherapy	1791 (716)	0.60 (0.06)	[20, 49]
Local surgeries	8381 (3328)	0.05 (0.01) of women with metastatic BC	[47, 50]
Psychological treatment in case of cancer diagnosis	1231 (492)	0.36 (0.06)	[20, 49]
(EBM, consortium)			
Lymphatic drainage/physiotherapy (BC)	1480 (592)	0.25 (0.06)	[10, 51, 52]
Medication OC[a]			
Not advanced	10,387 (4155)	0.33 (0.08)	[44, 48]
Advanced	30,080 (12,032)	0.67 (0.17)	
Recurrence (in advanced Ca)	5408 (2163)	0.20 (0.05)	[44, 45, 48]
Platin-resistant	30,080 (12,032)	0.80 (0.20)	
Platin-sensitive			

Tab. 2 continued

Variable	Value in € (SD)[d]	Proportion (SE)	Source
Palliative care			
End of life treatment in metastatic BC or OC	11,145 (4458)	All women with end stage OC or metastatic BC	[46]

BC breast cancer, *OC* ovarian cancer, *HR* hormone receptor, *SE* standard error

[a] Estimates were based on data from the University Hospital of Cologne (year 2012–2014)

[b] Calculated (assumed an equal share of prescription) for three chemotherapy regimes that were frequently prescribed: 5-fluorouracil/epirubicin/cyclophosphamide (FEC), taxane/anthracycline/cyclophosphamide (TAK), 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. In metastatic women, costs of chemotherapy were calculated in relation to the subgroups [42]

[d] Standard deviations of all costs and proportions of medication intake were assumed to be 4

utility assumptions, efficacy of surgical options, and the discount rate. In addition, the impact of including unrelated health care expenditures was assessed [53].

In order to assess how a simultaneous change of several variables affected the cost-effectiveness ratio, a probabilistic sensitivity analysis was conducted based on a Monte Carlo simulation with 10,000 iterations. Relying on the model input data listed in Tables 1 and 2 (except for mortality and the discount rate), we assumed the cost data to be gamma-distributed, probabilities and proportions beta-distributed [54], and relative risks log-normally-distributed. Given that the interpretation of negative cost-effectiveness ratios is ambiguous, these were transformed into cost-effectiveness acceptability curves for different willingness-to-pay (WTP) values (€0 to €100,000) [55].

In order to test potential heterogeneity bias resulting from using one 'ovarian cancer' state with women at different stages of their disease, a structural model validation was conducted. In this analysis, ovarian cancer was split into 'ovarian cancer' (<stage 4) and 'recurrent ovarian cancer' (stage 4). Similarly to the 'metastatic breast cancer' state, women in the 'recurrent ovarian cancer' state could either stay there or move to the state 'death'. The probability of dying was higher in the recurrent cancer state than in the ovarian cancer state [18] (see Table 1). The probability of moving from the 'ovarian cancer' to the 'recurrent ovarian cancer' state was based on de Winter [35] (Table 1). Furthermore, the cost for recurrent cancer was now separately attributed to this new health state (Table 2).

In order to further validate the basic input data sources and assumptions and their impact on the model results, we used incidence data on early breast and ovarian cancer from Mavaddat et al. [25] instead of data from the consortium, since this is the most recent comparable data set in *BRCA* carriers. In order to assess further uncertainty resulting from utility assumptions, we used utility estimates obtained from the preference ratings of an unmixed population (i.e., either only healthy women or only women with increased risk/cancer). In addition to this, basic assumptions were scrutinized, and the technical accuracy of the model was checked for input data entry and potential programming errors.

For external validation, we assessed the extent to which other models for breast cancer prevention came to different conclusions, and explained the potential sources of these differences (cross validation). In order to assess the impact of poorer long-term quality of life due to ongoing surgery-related physical or psychological harm, the steady utility increase following the year of surgery was assumed to take 25 instead of 5 years [56].

Results

Results of base-case analysis

With total costs of €29,434, the provision of BM plus BSO at age 30 for women with *BRCA 1* or *2* was less expensive than all other strategies. In addition to this, the strategy achieved the highest gain in QALYs (17.7) or additional life-years (19.9) compared to the other strategies. As much, BM plus immediate BSO dominated all other strategies. While the strategies including BM plus BSO (immediate or delayed) were the favorite options, women choosing the surveillance strategy had the highest costs at the lowest gain in QALYs/LYG (Table 3).

Results of sensitivity analyses

The results were robust in both deterministic and probabilistic sensitivity analyses. In the deterministic analysis, BM plus BSO at age 30 almost always dominated the other strategies. Only in case of a lower incidence of ovarian cancer or both breast and ovarian cancer did the delayed provision of oophorectomy (at age 40) result in lower costs,

Table 3 Results of the base-case analysis

Strategy	Costs (€)	Δ costs (€)	QALYs	Δ QALYs	LYG	Δ LYG	ICER	
							Cost (€)/QALY	Cost (€)/LYG
Mastectomy + oophorectomy at age 30	29,434		17.66		19.86		(reference)	(reference)
Mastectomy + oophorectomy at age 40	30,810	1375	17.28	−0.38	19.53	0.33	dominated	dominated
Oophorectomy alone	34,802	5368	16.71	−0.94	19.32	0.54	dominated	dominated
Mastectomy alone	37,307	7872	16.27	−1.39	18.49	1.37	dominated	dominated
Surveillance	45,480	16,045	14.96	−2.70	17.65	2.21	dominated	dominated

QALY quality-adjusted life years, *ICER* incremental cost-effectiveness ratio, *LYG* life year gained

which meant it was not dominated by the combined strategy.

Taking utilities from a homogeneous population (i.e., either healthy women or women at increased risk/with cancer) did not affect the results. In contrast, if we assumed that the utility after prophylactic surgery increased to that of a healthy woman within a period of 25 years (instead of 5 years as assumed in the base case), BM plus BSO at age 40 was no longer a dominated strategy. Instead, the incremental cost-effectiveness ratio of BM plus delayed BSO was €6900 compared to BM plus immediate BSO. The variation in other parameters did not substantially affect the results.

Implementing a separate health state for recurrent ovarian cancer as part of the structural sensitivity analyses resulted in lower utility gains and slightly higher costs for all strategies. However, the order of the interventions in terms of QALYs, LYG, costs, and the ICERs did not change. BM plus BSO at age 30 still resulted in the highest gain of QALYs and the lowest costs). Using data on incidence from a different population did not alter the results either. The validation using data from Mavaddat et al. [25] did not alter the results (see Table A4 in the Online Appendix).

Accounting for parameter uncertainty, the probability that BM plus BSO at age 30 is the preferred strategy varies by the willingness to pay. At a willingness to pay of €0, the probability that BM plus BSO at age 30 is the best decision is 57%. For a willingness to pay of €10,000/QALY this probability goes up to 80%. The cost-effectiveness acceptability curve illustrating this relationship can be found in the supplementary appendix (Figure A2).

Discussion

This study suggests that recommendations to undergo prophylactic surgery for *BRCA1/2* mutation carriers with an increased risk of breast or ovarian cancer are highly cost-effective. According to our model, the preferred strategy in women who tested positive for a *BRCA 1* or *2* - mutation is to undergo BM plus BSO at an early age. At the individual level, a woman's decision for or against one of the provided strategies depends to some extent on said strategy's risk-reducing potential. In addition to this, a woman's personal characteristics and her preferences play an important role in whether or not she decides on one or both surgical options instead of intensified breast cancer surveillance. For example, women at childbearing age might prefer to postpone the decision to undergo BSO. In addition to carefully informing women about a non-surgical strategy (e.g., intensified breast cancer surveillance) and its implications, clinicians should also encourage mutation-positive patients to undergo surgery due to a considerably higher gain in QALYs/LYS than observed with surveillance alone.

From a health care payer perspective, undergoing BM plus immediate BSO should be recommended to *BRCA 1* or *2* mutation carriers due to its favorable comparative cost-effectiveness. As a result of annual magnetic resonance imaging, the intensified surveillance strategy implies a costly and recurrent procedure compared to the one-time costs of surgical procedures with lower follow-up costs. Therefore, at the decision-maker's level, the consortium's concept of risk communication favoring surgical removal of breasts and/or ovaries is now reinforced by a strong economic argument.

The model has a number of strengths. Firstly, it includes as much data as possible from a German patient population and setting. Early breast cancer incidence was entirely drawn from the consortium database, as was much of the data on resource consumption in these patients. The consortium prospectively and comprehensively collects breast and ovarian cancer incidence and treatment information for women known to be at increased risk of familial breast and ovarian cancer in Germany. Using this data increased the relevance and representativeness of our analysis for German women. Furthermore, the representativeness of the

analysis was enhanced by using data on mortality in case of metastatic breast and ovarian cancer that was taken from two large German registry studies [18, 39]. Unfortunately, however, data on ovarian cancer incidence could not be drawn reliably from the consortium database—as originally planned due to the relatively short follow-up available at the time of our study and the relatively large proportion of women undergoing BSO.

Secondly, data on resource use and the costs of treatment was, to a large extent, extracted from recent German guidelines and administrative databases. Furthermore, in contrast to previous modeling studies that did not stratify according to the patients' hormone receptor status, we assessed medication costs separately for the subgroups HER2neu, HR+, and triple−. Knowledge of the hormone receptor status is essential when making treatment decisions and the costs vary considerably depending on the drug used for a specific hormone receptor type. As a result, the model was based on a very detailed cost structure that considered subgroup-specific treatment modalities.

Thirdly, the model structure distinguished between early and late i.e., metastatic breast cancer. As a result, the course of the breast cancer was well reflected on both the cost and effect sides of the model (e.g., lower treatment costs and higher utilities in non-metastatic breast cancer versus higher costs and mortality and lower utilities in metastatic disease). In contrast, the model structure did not allow for a transition to recurrent ovarian cancer or breast cancer for women with ovarian cancer (this reflects the fatal course of the ovarian cancer disease [18]). Since the mortality, utility, and cost of ovarian cancer depend on what stage it is in, combining all the stages of ovarian cancer under one health state may result in heterogeneity bias. However, it was not possible to stratify the 'ovarian cancer state' into stage-specific health states due to a lack of applicable data. In order to overcome this situation, a separate state, 'recurrent ovarian cancer', was modeled in a structural sensitivity analysis in addition to ovarian cancer. Based on the available data, we assumed that this state would encompass women suffering recurrent ovarian cancer with higher disease stages, higher costs, and lower utilities compared to the 'ovarian cancer' state. However, the results of these sensitivity analyses suggest only marginal changes in costs and QALYs/LYG. As such, we assume our baseline model structure to be sufficiently valid for predicting the course of the disease.

Finally, in order to reflect the changes in utility caused by surgery, both a decrease in the first year and a gradual increase of utilities in subsequent years were taken into account. Furthermore, lower utility in end-stage ovarian and metastatic breast cancer was also incorporated.

As in most modeling studies, there were several limitations that might have affected our analyses. Although data from the German consortium was used to populate parts of the model, much of the data on resource consumption and costs was missing or not available in sufficient detail to be included. As such, information had to be obtained from alternative data sources (e.g., resource consumption in specific subgroups or metastatic breast cancers/ovarian cancer).

Due to the lack of RCTs that have evaluated the effect of risk-reducing surgeries, data on the efficacy of risk-reducing surgeries were primarily drawn from well-designed cohort studies (either prospective or retrospective). RCTs most likely are not available in this field since the intervention in question is highly preference-sensitive and very few women would agree to be randomly assigned to one of the available surgical options versus no intervention at all.

Because of the overall low rates of events for women included in the German consortium, most of the model's transition probabilities were obtained from published prospective studies that were conducted including non-German women (except incidence of first breast cancer which was taken from the consortium data). Although the representativeness of this data for German women may be questioned, the data on the incidence of first breast cancer in international prospective studies was similar to the consortium data, and calibrating the model against external observed German epidemiological data did not alter the results [24, 25].

Although breast and ovarian cancer risks differ by *BRCA* subtype, this model combined *BRCA 1* and *2* patients. The reason for this was the relatively small absolute number of events in each subgroup (*BRCA 1*: $n = 579$, *BRCA 2*: $n = 331$), which did not allow for a robust estimation of separate breast cancer incidences. A recent observational study has shown that *BRCA* mutations vary not only by type (1 or 2) but also by phenotype and the cluster regions that were associated with an increased risk of breast or ovarian cancer [57]. Provided the occurrence of additional mutation-specific risks can be confirmed in further studies, this data may have implications for cost-effectiveness and future prevention strategies in *BRCA* and other mutation carriers.

A further limitation might be that we assumed women would be willing to receive surgery at a relatively young age (30 years). This contrasts with a prospective study conducted by Chai et al. [58], where only a low number of BRCA carriers chose risk-reducing surgery at that age. However, since the aim in the consortium is to target and treat high-risk women as early as possible, the decision to model a cohort of 30-year-old women that are offered immediate surgery seems justified. Furthermore, preventive

surgery at an increased age for oophorectomy did not substantially alter the results (see A 15 in Table A4).

Our literature search for data on utilities showed heterogeneous results depending on whose preferences were elicited—either those of women at increased risk (due to mutation)/with present breast cancer or those of women from a healthy reference group. For example, women at increased risk of breast/ovarian cancer reported an increase in utility as a result of BSO, whilst women aged 33–50 obtained from a (healthy) reference group reported a substantial decrease [27]. Similarly, there were remarkable differences in the decrease of utilities resulting from suffering newly diagnosed breast/ovarian cancer, i.e., healthy women reported lower utilities than women at high risk or with diagnosed cancer [28, 59]. To ensure consistent utility estimates for the analysis, we used data from either mixed populations [29] or from women at high risk/with cancer [27, 28, 30].

Furthermore, the health utilities applied for the analysis were based on non-German women. Utilities from a recent German study in gynecological oncology [60]—collected directly via visual analogue scale (VAS) and indirectly via EQ-5D—were available, but not considered for this analysis for a number of reasons. Firstly, the usage of VAS as a method for eliciting utilities has been controversial because the method is not founded in utility theory, is not choice-based, and does not take into account uncertainty [61]. Secondly, the indirect utilities derived from a health index converting data from the EQ-5D (using the German tariff by Greiner et al. [62]) showed equal values for most of the valued health states. This was in contrast to the results of other reported studies that were based on SSG or TTO methods. This could be due to either a lack of sensitivity of the EQ-5D to measure utilities in gynecological oncology, or the timing of data collection. In the questionnaire survey performed by Hildebrandt et al. [60], almost half of the participants responded to their current health state within a follow-up appointment in the hospital. As a result, many individuals might be interviewed in a state of recovery where quality of life tends to return to the levels of healthy individuals [63]. Finally, the analysis performed by Hildebrandt et al. does not provide data on a loss of utility in case of prophylactic surgery. Nevertheless, the VAS values reported by Hildebrandt et al. were within the range of values used for the sensitivity analyses, and did not change the order of the preventive options.

Using utilities from women either without increased risk or with high risk/confirmed breast cancer did not alter the results of the analysis. In contrast, the analysis was sensitive to the assumption regarding how long it takes for a woman to regain the utility she had prior to prophylactic surgery. While we originally assumed that it takes a woman 5 years to recover from surgery, we extended this time period to 25 years in order to take into account the potential long-term side effects and comorbidities of both types of surgery. Doing so led to an improvement in the cost-effectiveness of the delayed BM + BSO strategy (i.e., at age 40) compared to the early strategy (i.e., at age 30). This could be explained by the shorter period of time over which the long-term effects of surgery such as chronic pain, psychological distress due to changes in body image/sexuality, or surgery-induced menopause could be experienced. However, although long-term physical and psychological effects have been repeatedly reported [64, 65], a recent study suggests that women who undergo surgery are satisfied with their decision and show increasing quality of life over time [66]. Furthermore, the long-term side effects of surgeries and their treatment, e.g., the treatment of surgery-induced menopause or continued pain management, might increase costs as well as reducing the patients' utility. However, these costs, however, were not taken into account in this model.

In order to compare the results of our study with those of other cost-utility analyses that have evaluated the cost-effectiveness of different strategies for preventing breast or ovarian cancer, two analyses reported similar results despite some methodological differences [13, 14]. In addition to differences in the model structure (e.g., no subgroup for women with metastatic breast cancer), such studies differed from this analysis in their estimates of the costs of treatment for breast and ovarian cancer. While the overall treatment costs of breast cancer in our analysis (€20,000 for first/recurrent and €45,000 for metastatic breast cancer) were between the treatment costs in the analyses of Grann et al. and Anderson et al., treatment costs for ovarian cancer and prophylactic surgeries were below those of the other analyses [13, 14]. Moreover, the previous analyses used preference ratings obtained from women at high risk while in our analysis utilities were obtained from both women at risk and those not at high risk. The latter tended to value preventive measures less favorably [27]. However, all analyses used similar transition probabilities and risk reductions due to prophylactic surgery. As a result, BM alone was dominated in our analysis and in those of Grann and Anderson. In contrast, BSO alone was dominated by BSO plus BM in our analysis but achieved more QALYs in both *BRCA* 1 and 2 carriers in the study performed by Grann (resulting in ICERs of below €5000/QALY compared to the combined surgery) and *BRCA 1* carriers in the study of Anderson et al. resulting in dominance over BSO plus BM (for *BRCA 2* carriers the ICER of BSO plus BM compared to BSO alone was €2000 per QALY).

In summary, this modeling study demonstrates that surgical preventive options for German *BRCA1/2* mutation carriers results in a substantial gain of QALY/life years and

potential of cost savings when compared to no surgical prevention. While the initial costs of prophylactic surgery are considerable, they are outweighed by the subsequent reductions in cancer-related morbidity and mortality.

References

1. Global Burden of Disease Cancer Collaboration: The global burden of cancer 2013. JAMA Oncol **1**(4), 505–527 (2015)
2. Robert-Koch Institut, Zentrum für Krebsregisterdaten: Brustkrebs (Mammakarzinom). http://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Brustkrebs/brustkrebs_node.html (2015). Accessed 28 Apr2016
3. Rhiem, K., Engel, C., Graeser, M., et al.: The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. Breast Cancer Res. **14**(6), R156 (2012). doi:10.1186/bcr3369
4. Luengo-Fernandez, R., Leal, J., Gray, A., et al.: Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol **14**(12), 1165–1174 (2013). doi:10.1016/S1470-2045(13)70442-X
5. Willems, R.A., Bolman, C.A., Mesters, I., et al.: Cancer survivors in the first year after treatment: the prevalence and correlates of unmet needs in different domains. Psycho-oncology (2015). doi:10.1002/pon.3870
6. Sorensen, S.V., Goh, J.W., Pan, F., et al.: Incidence-based cost-of-illness model for metastatic breast cancer in the United States. Int. J. Technol. Assess. Health Care **28**(1), 12–21 (2012). doi:10.1017/S026646231100064X
7. Foster, T.S., Miller, J.D., Boye, M.E., et al.: The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer Treat. Rev. **37**(6), 405–415 (2011). doi:10.1016/j.ctrv.2010.12.008
8. Cohn, D.E., Kim, K.H., Resnick, K.E., et al.: At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. J Clin Oncol **29**(10), 1247–1251 (2011). doi:10.1200/JCO.2010.32.1075
9. Familial Breast Cancer: Classification and Care of People at Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer. National Institute for Health and Clinical Excellence: Guidance. Cardiff (UK) (2013)
10. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032–045OL
11. Nelson, H.D., Pappas, M., Zakher, B., et al.: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann. Intern. Med. **160**(4), 255–266 (2014). doi:10.7326/M13-1684
12. Phillips, K.A., Milne, R.L., Rookus, M.A., et al.: Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J. Clin. Oncol. **31**(25), 3091–3099 (2013). doi:10.1200/JCO.2012.47.8313
13. Grann, V.R., Patel, P.R., Jacobson, J.S., et al.: Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res. Treat. **125**(3), 837–847 (2011). doi:10.1007/s10549-010-1043-4
14. Anderson, K., Jacobson, J.S., Heitjan, D.F., et al.: Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann. Intern. Med. **144**(6), 397–406 (2006)
15. Norum, J., Hagen, A.I., Maehle, L., et al.: Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. Eur. J. Cancer **44**(7), 963–971 (2008). doi:10.1016/j.ejca.2008.02.025
16. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: Allgmeine Methoden. Version 4.2 vom 22.04.2015. https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf (2015). Accessed 28 Apr 2016
17. Schad, M., John, J.: Towards a social discount rate for the economic evaluation of health technologies in Germany: an exploratory analysis. Eur. J. Health Econ **13**(2), 127–144 (2012). doi:10.1007/s10198-010-0292-9
18. Chen, T., Jansen, L., Gondos, A., et al.: Survival of ovarian cancer patients in Germany in the early 21st century: a period analysis by age, histology, laterality, and stage. Eur. J. Cancer Prev. **22**(1), 59–67 (2013). doi:10.1097/CEJ.0b013e3283552e28
19. Holleczek, B., Brenner, H.: Trends of population-based breast cancer survival in Germany and the US: decreasing discrepancies, but persistent survival gap of elderly patients in Germany. BMC Cancer **12**, 317 (2012). doi:10.1186/1471-2407-12-317
20. German Consortium for Hereditary Breast and Ovarian Cancer. http://www.krebshilfe.de/wir-helfen/adressen/familiaerer-krebs/brustkrebszentren.html (2016). Accessed 28 Apr 2016
21. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. Chapter 13: Including non-randomized studies. http://handbook.cochrane.org/chapter_13/13_including_non_randomized_studies.htm (2011). Accessed 31 Jan 2017
22. Land, L.H., Dalton, S.O.: Jensen, et al.: impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990–2008. Breast Cancer Res. Treat. **131**(3), 1013–1020 (2012). doi:10.1007/s10549-011-1819-1
23. Rebbeck, T.R., Lynch, H.T., Neuhausen, S.L., et al.: Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N. Engl. J. Med. **346**(21), 1616–1622 (2002). doi:10.1056/NEJMoa012158
24. Domchek, S.M., Friebel, T.M., Singer, C.F., et al.: Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA **304**(9), 967–975 (2010). doi:10.1001/jama.2010.1237
25. Mavaddat, N., Peock, S., Frost, D., et al.: Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J. Natl. Cancer Inst. **105**(11), 812–822 (2013). doi:10.1093/jnci/djt095
26. Boughey, J.C., Hoskin, T.L., Degnim, A.C., et al.: Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann. Surg. Oncol. **17**(10), 2702–2709 (2010). doi:10.1245/s10434-010-1136-7
27. Grann, V.R., Jacobson, J.S., Sundararajan, V., et al.: The quality of life associated with prophylactic treatments for women with BRCA1/2 mutations. Cancer J Sci Am **5**(5), 283–292 (1999)
28. Grann, V.R., Patel, P., Bharthuar, A., et al.: Breast cancer-related preferences among women with and without BRCA mutations. Breast Cancer Res. Treat. **119**(1), 177–184 (2010). doi:10.1007/s10549-009-0373-6
29. Peasgood, T., Ward, S.E., Brazier, J.: Health-state utility values in breast cancer. Expert Rev Pharmacoecon Outcomes Res **10**(5), 553–566 (2010). doi:10.1586/erp.10.65
30. Havrilesky, L.J., Broadwater, G., Davis, D.M., et al.: Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecol. Oncol. **113**(2), 216–220 (2009). doi:10.1016/j.ygyno.2008.12.026

31. Ara, R., Wailoo, A.: Using health state utility values in models exploring the cost-effectiveness of health technologies. Value Health **15**(6), 971–974 (2012). doi:10.1016/j.jval.2012.05.003
32. Federal Statistical Office of Germany: Life expectancy 2015. https://www.destatis.de/EN/FactsFigures/SocietyState/Population/Deaths/Deaths.html (2015). Accessed 28 Apr 2016
33. Metcalfe, K., Lynch, H.T., Ghadirian, P., et al.: Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res. Treat. **127**(1), 287–296 (2011). doi:10.1007/s10549-010-1336-7
34. Litiere, S., Werutsky, G., Fentiman, I.S., et al.: Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol. **13**(4), 412–419 (2012). doi:10.1016/S1470-2045(12)70042-6
35. Winter, W.E., Maxwell, G.L., Tian, C., Gynecologic Oncology Group Study, et al.: Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. J. Clin. Oncol. **25**(24), 3621–3627 (2007)
36. Rebbeck, T.R., Friebel, T., Lynch, H.T., et al.: Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J. Clin. Oncol. **22**(6), 1055–1062 (2004). doi:10.1200/JCO.2004.04.188
37. Sullivan, P.W., Lawrence, W.F., Ghushchyan, V.: A national catalog of preference-based scores for chronic conditions in the United States. Med. Care **43**(7), 736–749 (2005)
38. Dawood, S.: Triple-negative breast cancer: epidemiology and management options. Drugs **70**(17), 2247–2258 (2010). doi:10.2165/11538150-000000000-00000
39. Holleczek, B., Jansen, L., Brenner, H.: Breast cancer survival in Germany: a population-based high resolution study from Saarland. PLoS One **8**(7), e70680 (2013). doi:10.1371/journal.pone.0070680
40. Hess, K.R., Esteva, F.J.: Effect of HER2 status on distant recurrence in early stage breast cancer. Breast Cancer Res. Treat. **137**(2), 449–455 (2013). doi:10.1007/s10549-012-2366-0
41. Inwald, E.C., Ortmann, O., Zeman, F., et al.: Guideline concordant therapy prolongs survival in HER2-positive breast cancer patients: results from a large population-based cohort of a cancer registry. Biomed. Res. Int. **2014**, 137304 (2014). doi:10.1155/2014/137304
42. DeKoven, M., Bonthapally, V., Jiao, X., et al.: Treatment pattern by hormone receptors and HER2 status in patients with metastatic breast cancer in the UK, Germany, France, Spain and Italy (EU-5): results from a physician survey. J Comp Eff Res **1**(5), 453–463 (2012). doi:10.2217/cer.12.43
43. Dufresne, A., Pivot, X., Tournigand, C., et al.: Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. Breast Cancer Res. Treat. **107**(2), 275–279 (2008). doi:10.1007/s10549-007-9550-7
44. Martin, L.P., Schilder, R.J.: Management of recurrent ovarian carcinoma: current status and future directions. Semin. Oncol. **36**(2), 112–125 (2009). doi:10.1053/j.seminoncol.2008.12.003
45. Modesitt, S.C., Jazaeri, A.A.: Recurrent epithelial ovarian cancer: pharmacotherapy and novel therapeutics. Expert Opin. Pharmacother. **8**(14), 2293–2305 (2007). doi:10.1517/14656566.8.14.2293
46. Lux, M.P., Reichelt, C., Wallwiener, D., et al.: Results of the Zometa cost-utility model for the German healthcare system based on the results of the ABCSG-12 study. Onkologie **33**(7), 360–368 (2010). doi:10.1159/000315699
47. Universitätsklinikum Münster DRG Research Group Medizinisches Management: Webgrouper. http://drg.uni-muenster.de/index.php?option=com_webgrouper&view=webgrouper&Itemid=26 (2015). Accessed 28 Apr 2016
48. Rote Liste® Service GmbH: Rote Liste. http://www.rote-liste.de/ (2015). Accessed 28 Apr 2016
49. Kassenärztliche Bundesvereinigung: Uniform value scale. http://www.kbv.de/html/ebm.php (2015). Accessed 28 Apr 2016
50. Arican, A., Bozkurt, T., Bozcuk, H., et al.: A cross-sectional survey of the diagnosis and management of bone metastasis in breast cancer patients in Turkey. Support. Care Cancer **22**(10), 2629–2634 (2014). doi:10.1007/s00520-014-2253-9
51. Verband der Ersatzkassen: Rahmenverträge und Vergütungslisten bei Heilmitteln.. http://www.vdek.com/vertragspartner/heilmittel/rahmenvertrag.html (2015). Accessed 28 Apr 2016
52. IntelliMed GmbH.:Catalog of therapeutic products. http://www.heilmittelkatalog.de/heilmittelkatalog-online.html (2014). Accessed 28 Apr 2016
53. Statistisches Bundesamt. GENESIS-Online Datenbank. https://www-genesis.destatis.de/genesis/online;jsessionid=131E6809880313E767FC8E952532F25D.tomcat_GO_1_3?operation=previous&levelindex=2&levelid=1479294919749&step=2 (2016). Accessed 31 Jan 2017
54. Fryback, D.G., Chinnis Jr., J.O., Ulvila, J.W.: Bayesian cost-effectiveness analysis. An example using the GUSTO trial. Int. J. Technol. Assess. Health Care **17**(1), 83–97 (2001)
55. Stinnett, A.A., Mullahy, J.: Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med. Decis. Making **18**(2 Suppl), S68–S80 (1998)
56. Geiger, A.M., Nekhlyudov, L., Herrinton, L.J., et al.: Quality of life after bilateral prophylactic mastectomy. Ann. Surg. Oncol. **14**(2), 686–694 (2007). doi:10.1245/s10434-006-9206-6
57. Rebbeck, T.R., Mitra, N., Wan, F., et al.: Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA **313**(13), 1347–1361 (2015). doi:10.1001/jama.2014.5985
58. Chai, X., Friebel, T.M., Singer, C.F., et al.: Use of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers. Breast Cancer Res. Treat. **148**(2), 397–406 (2014). doi:10.1007/s10549-014-3134-0
59. Cappelli, M., Surh, L., Humphreys, L., et al.: Measuring women's preferences for breast cancer treatments and BRCA1/BRCA2 testing. Qual. Life Res. **10**(7), 595–607 (2001)
60. Hildebrandt, T., Thiel, F.C., Fasching, P.A., et al.: Health utilities in gynecological oncology and mastology in Germany. Anticancer Res. **34**(2), 829–835 (2014)
61. Parkin, D., Devlin, N.: Is there a case for using visual analogue scale valuations in cost-utility analysis? Health Econ. **15**(7), 653–664 (2006). doi:10.1002/hec.1086
62. Greiner, W., Claes, C., Busschbach, J.J., von der Schulenburg, J.M.: Validating the EQ-5D with time trade off for the German population. Eur. J. Health Econ. **6**(2), 124–130 (2005)
63. Chan, Y.M., Ngan, H.Y., Li, B.Y., et al.: A longitudinal study on quality of life after gynecologic cancer treatment. Gynecol. Oncol. **83**(1), 10–19 (2001). doi:10.1006/gyno.2001.6345
64. den Heijer, M., Seynaeve, C., Timman, R., et al.: Body image and psychological distress after prophylactic mastectomy and breast reconstruction in genetically predisposed women: a prospective long-term follow-up study. Eur. J. Cancer **48**(9), 1263–1268 (2012). doi:10.1016/j.ejca.2011.10.020
65. den Heijer, M., Seynaeve, C., Vanheusden, K., et al.: Long-term psychological distress in women at risk for hereditary breast cancer adhering to regular surveillance: a risk profile. Psycho-Oncology **22**(3), 598–604 (2013). doi:10.1002/pon.3039
66. Hooker, G.W., King, L., Vanhusen, L., et al.: Long-term satisfaction and quality of life following risk reducing surgery in BRCA1/2 mutation carriers. Hered Cancer Clin Pract **12**(1), 9 (2014). doi:10.1186/1897-4287-12-9