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Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in *BRCA1* mutation carriers: A cost-effectiveness analysis ☆

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ARTICLE INFO

Article history:
Received 21 September 2007
Received in revised form
18 February 2008
Accepted 21 February 2008
Available online 24 March 2008

Keywords:
BRCA
Breast cancer
Ovarian cancer
Cost
Life years gained

ABSTRACT

Women with germline *BRCA1* mutation have a significant risk of breast and/or ovarian cancer. Prophylactic bilateral mastectomy (PBM) and prophylactic bilateral salpingo-oophorectomy (PBSO) prevent cancer in mutation carriers.

The cost-effectiveness of PBSO (age of 35 years) with or without PBM five years earlier was compared to a no intervention setting employing a marginal cost analysis. National data on cancer incidence, mortality rates and costs were implemented together with observed Norwegian *BRCA1* data in a Markov model and PBSO was assumed to reduce the risk of ovarian cancer by 90%. A 3% discount rate was used.

The additional health care cost per mutation carrier undergoing PBSO and PBM was €15,784, and 6.4 discounted life years gained (LYG) was indicated (PBSO alone with 100% acceptance 3.1 LYG). The additional cost per LYG was €1973 (PBSO alone €1749/LYG). Including all resource use, the figure was a cost of €496 and €1284 per LYG, respectively.

PBSO with or without PBM in *BRCA1* mutation carriers is cost-effective. A testing of all incident breast cancers to identify mutation carrying families should be explored.

1. Introduction

Breast cancer is the most common cancer amongst women in the western world and frequently clusters in families.[1,2] In Norway (population 4.7 million), the annual incidence in 2005 of breast and ovarian cancer was 2798 and 420 cases, respectively. The breast cancer susceptibility gene (*BRCA1*) was located by Hall and coworkers[3] and described four years

☆ *Financial information*: The study was supported by a research grant from the Sigurd K. Thoresen Foundation.

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doi:10.1016/j.ejca.2008.02.025

later by Miki and associates.[4] Various *BRCA1* mutations (founder mutations) have been described in most populations examined. In Norway, several families with *BRCA1* mutations have been identified and investigated, mostly through an index patient suffering from breast cancer.[5] Today tests for the frequent mutations may detect about two out of three mutation carriers.[6]

Women with germline *BRCA1* mutation may have up to 85% and 65% cumulative lifetime risk of breast and ovarian cancer, respectively.[5] Prophylactic bilateral salpingo-oophorectomy (PBSO) may prevent ovarian and fallopian tube cancer and reduce the breast cancer risk.[7] Today family history is used to select patients for mutation testing though it has both a low sensitivity and specificity.[6,8,9] We have measured 'sensitivity for positive family history' to be 23% and 33% in incident breast and ovarian cancer cases, respectively.[6] Uptake of testing (97% and 80%) and diffusion of the information within the family are important factors in this setting. The study initiated a debate on whether or not all breast and/or ovarian cancer patients should be offered testing for frequent *BRCA* mutations. In this study, we have explored the health economics of PBSO with or without prophylactic bilateral mastectomy (PBM) compared to no intervention. No intervention was chosen as comparator due to the fact that many women today are unknown mutation carriers. We have also investigated a suggested testing of all incident breast and ovarian cancer cases to access families that should be offered counselling and subsequent interventions.

2. Materials and methods

In the cost-effectiveness analysis, we focused on *BRCA1* mutation carriers and employed a Markov model. Being aware of an intervention consisting of PBSO with or without PBM may influence on the quality of life as fertility, body image, sexual problems and psychosocial well being may be affected, a cost-utility analysis should be the first choice in this setting. However, we did not reveal solid data on the quality of life over time, making such a study possible. The BRCA1 mutation carriers were selected due to the fact that we have less Norwegian data on BRCA2 mutation carriers and consequently a great number of uncertain variables have to be implemented in the analysis. An intervention (PBSO with or without PBM) was compared to no intervention. A no intervention setting is not recommendable, but is frequently the case as many mutation carriers are still unknown because the family based history approach has a low sensitivity.[6] The effect of secondary prevention (early diagnosis and treatment) with respect to survival is of limited value in *BRCA1*-associated breast or ovarian cancer and was not considered for the model. According to the Norwegian experience, almost all patients contracting cancer die of their disease and adjuvant therapy/chemotherapy does not influence the course to any extent.[5]

We implemented four Markov states as illustrated in Fig. 1. State A represented a healthy *BRCA1* mutation carrier, state B included patients with a diagnosed ovarian cancer, state C involves the patients who developed a breast cancer and state D when they die. Arrows show how women progress through the model over the cycles, which were taken to be 1 year. A

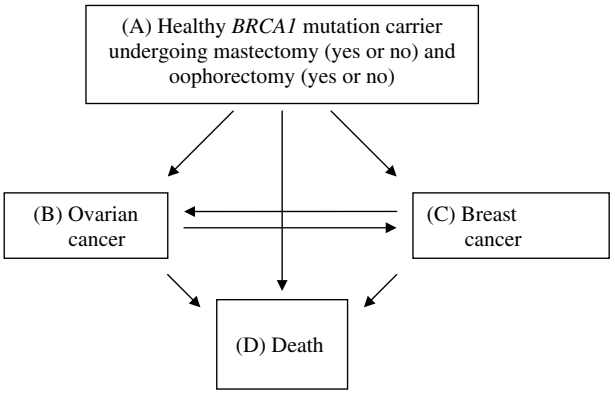

Fig. 1 – The Markov model.

one year cycle was selected as such a cycle was in concert with the Norwegian data we implemented.[5] The model had a time perspective of 70 years (from 30 to 100 years of age). The transition probabilities describe the rate at which patients develop cancer/die. These are used to estimate the expected amount of time spent in each living health state for the groups and to produce an estimate of the expected life years gained for each group. Ovarian cancer was calculated to constitute none of the cancers amongst women aged 30–34 years, one-third amongst those aged 35–43 years, half of those aged 44–51 years, 70% in the age interval 52–59 years and finally two-thirds of cases amongst 60–70-year-old women.[5] The remaining share comprised breast cancer. When women passed the age of 70 years, we did not implement any raised risk of breast or ovarian cancer. Retesting the model, we calculated the lifetime risk of breast and ovarian cancer at age 70 years to be 58% and 58%, respectively (at 50 years the figures were 30% and 17%, respectively). Whereas these figures may look high in an international setting, they are in accordance with the previous finding in Norway.[5]

The annual death rate in breast and ovarian cancer was calculated to be 11.2% and 5.4%, respectively.[10–12] Death rates are generally dependent on the stage of disease and treatment received. This is different amongst breast and ovarian cancer patients carrying a *BRCA1* mutation. In practice they all have a poor prognosis.[10,11] Furthermore, the annual death rate amongst healthy mutation carrying women was calculated according to Statistics Norway.

2.1. *Treatment and comparator*

A model-based cost-effectiveness analysis was done. We employed a marginal cost assessment method and implemented the additional cost to the society of PBSO and PBM. The expected survival amongst *BRCA1* mutation carriers was based on studies from the Section of Cancer Genetics at the Rikshospitalet-Radiumhospitalet Medical Centre. The group undergoing recommended PBSO (at the age of 35 years) with or without PBM five years earlier was compared with no prophylactic approach. The time of intervention was selected based on Norwegian guidelines and clinical data.[5] In the PBSO alone setting, we implemented our data showing that 70% of mutation carriers choose PBSO and added an acceptance figure of 100%. The model is illustrated in Fig. 2.

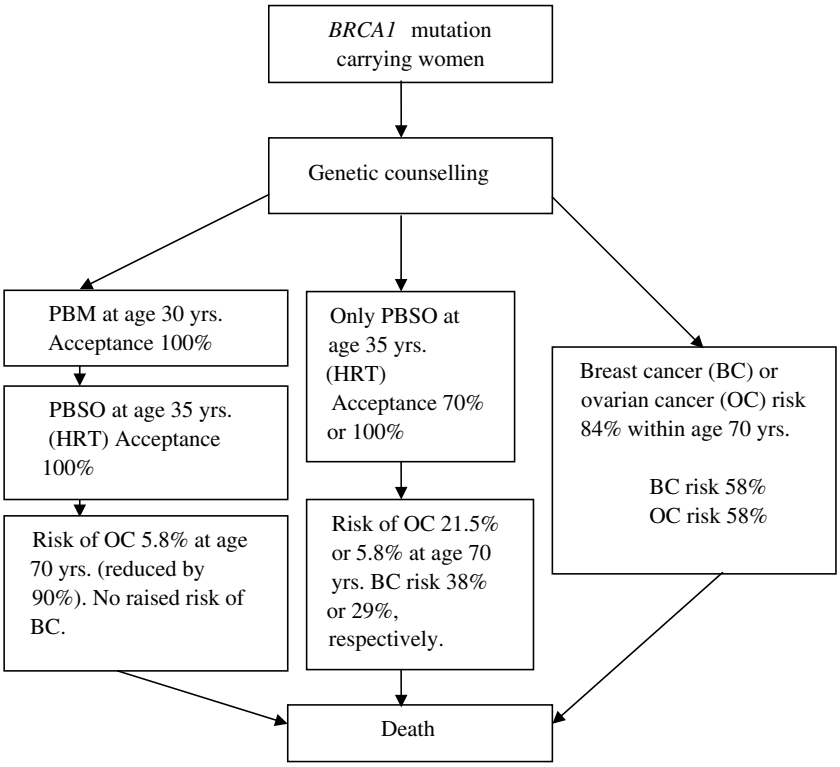

Fig. 2 – The figure illustrates two intervention alternatives and the comparator group. (BC = breast cancer, OC = ovarian cancer. PBM = prophylactic bilateral mastectomy, PBSO = prophylactic bilateral salpingo-oophorectomy) HRT = hormonal replacement therapy.

A calculation of the cost of offering the incident cancer cases, our rapid test for the 10 most common *BRCA1* mutations was added. We assumed a complete acceptance based on past experience.[6] Demonstrated mutation carriers are then offered genetic counselling, and through them relatives are invited to predictive testing and the option of PBSO with or without PBM for those having a mutation demonstrated. Our experience is that all patients participate and within a short time most (81.4%) female relatives (>30 years) have undergone predictive testing.[13]

3. Effectiveness

PBM at the age of 30 years was calculated (assuming all women in the PBM + PBSO arm undergo the surgical procedure) to reduce the risk of breast cancer to that of the Norwegian female population (8%). The remaining risk was kept because there may still be some mammary gland tissue left following surgery. We are aware of figures indicating the actual risk being 2% or less, but to avoid possible underestimation in the long run (70 years), the figures of the general population was employed.[14,15] PBSO at the age of 35 years is known to improve the prognosis of breast cancer.[10] Due to the beneficial effect of PBSO, we assumed incident breast cancers would have a similar prognosis to those in the general population. It has been calculated that PBSO reduces the risk of ovarian cancer by 90%.[10] Based on this figure, ovarian cancer was predicted to affect 2% and 5.8% of women at age 50 years and 70 years, respectively.

PBSO alone was modelled to reduce absolute breast cancer risk by 50% in *BRCA1* carriers.[12] A 70% and 100% acceptance of the recommended surgical procedure was implemented causing a life time risk of 38% (58% – (58% × 0.7 × 0.5)) and 29% (58% – (58% × 1.0 × 0.5)). Furthermore, this brought the risk of ovarian cancer down to 21.5% (58% – (58% × 0.7 × 0.9)) and 5.8% (58% – (58% × 1.0 × 0.9)). In the model, all patients contracting breast or ovarian cancer were calculated dying of their disease according to our prior study.[5]

3.1. *Costs (C)*

All costs were calculated in Norwegian unit costs and converted to Euros (€) at the rate of 1€ = 8.16 NOK as of 6th March 2007. The costs were calculated according to the national 2007 out-patient tariff and the diagnosis related groups (DRG) system for 2007.[16,17] The following cost items were identified in the intervention group:

3.1.1. *Health care costs (C_1)*

(a) Visit to a breast surgeon (€16.3). (b) Bilateral prophylactic mastectomy (DRG 502, €6843 – raised by 25% to reflect bilateral surgery = €8554). (c) Visit to a gynaecologist (€16.3). (d) Salpingo-oophorectomy (DRG 359 = €5530.2). (e) Hormonal replacement therapy consisting of sequential treatment with oestradiol (various doses) and norestisteronacetate (cost (Trisekvens®) €84.1 × 20 years (age 35–55 years) = €1682).[18]

3.1.2. *Patient/family related costs (C_2)*

According to today's practice, all Norwegian women having a *BRCA* mutation disclosed or a known familial risk of breast/ovarian cancer are offered genetic counselling. Thus, the

activity discussed does not in itself include additional resources for genetic counselling, and genetic counselling of relatives was not included as a cost.

Patients and relatives have to cover a minor amount (code 201b = €32.5) when visiting the gynaecologist and breast surgeon.[16] Norwegian hospitals have to cover patient related transportation costs. This is internationally calculated as patient/family related costs and therefore presented here. The cost of travelling was reflected by the national tariff per kilometre (€0.37) and a distance both ways of 80 km (qualified guess by the authors).

3.1.3. *Costs in other sectors (C_3)*

The indirect costs in this setting are production losses. The employer's annual labour cost (including income, pension and social costs) were used as a measure of the production value. The 2004 mean figure was €41,958/year (Statistics Norway). The 2007 figure (€47,664/year) was calculated by raising the costs by 13.6% according to the raise in wages in Norway in the time period 2004–2007. We calculated a careful estimate of half of mutation carriers being in the workforce.

3.1.4. *Cost of testing all breast and ovarian cancer patients*

The cost of testing all breast cancer patients for common mutations in the *BRCA* genes was calculated employing the annual incidence of breast and ovarian cancer in Norway (2798 + 420 = 3218 cases) in 2005 and multiplying with the present cost per woman screened (€125.9 – based on an offer given to the Rikshospitalet-Radiumhospitalet Medical Centre).[19] The total cost was €405,146.

3.2. *Savings (S)*

The economic savings in this setting is related to breast and ovarian cancers avoided and occur as women progress through the Markov model.

3.2.1. *Health care savings (S_1)*

(a) Breast cancer: In this survey, we assumed the absolute risk of breast cancer reduced by 50% due to the PBM + PBSO intervention. Most of this risk reduction is due to PBM, but we know PBSO also influences on the risk of breast cancer. The risk amongst the *BRCA1* mutation carriers was 58% and we calculated this intervention reaching the level of the Norwegian population (8%). The corresponding figure of PBSO (70% accepting) was a reduction from 58% to 38% ($0.7 \times 0.5 \times 58\%$ = 20% reduction). When all women underwent the intervention, a 29% reduction was achieved.

The undiscounted savings per breast cancer case avoided were: Diagnosis €44.3, mammogram €38.6, surgery (DRG 258) €4177.7, adjuvant chemotherapy (ACT) FEC regimen (90% dose intensity) €2340.7, most cancers are infiltrative, high grade and oestrogen receptor negative.[11,16,20] Based on this information, we assumed 75% undergoing adjuvant FEC-therapy (adjuvant hormonal therapy (AHT)), 25% candidates and 66% undergoing 5 years of AHT (tamoxifen – 2 years, anastrozole 3 years) €946.1, radiotherapy (€50.5/field × 4 fields × 25 fractions × 30% N+) €1515.[18] As both women in the intervention and no intervention group have to undergo annual MRI, this cost is equal in all groups and it was not included in the analysis. There may be savings in the intervention group as women do not undergo MRI examinations following PBM, but we had no solid data on costs in this setting. Furthermore, there are reasons to believe these savings will be balanced by raised costs due to a possible prolonged follow up as overall survival is improved. Both factors were excluded due to lack of solid data.

(b) The health care savings related to avoided ovarian cancer due to PBM and PBSO was calculated as the value of reducing the absolute life time (at age 70) risk of ovarian cancer by 52.2% from 58% to 5.8% (90% reduction). PBSO alone was calculated causing a 36.5% reduction (52.2% × 0.7). The savings per cancer prevented was calculated: Diagnosis €28 and €16.3, surgery (DRG 357) €10,424.3. There will be initial savings related to less frequent follow-ups in the intervention group, but they will undergo a prolonged survival and thus a prolonged follow-up. Savings related to follow-up was therefore not implemented.

3.2.2. *Patient/family related savings (S_2)*

These savings were: Travelling saved €61.1 in the context of diagnosis and treatment for breast and/or ovarian cancer. Patients' shares avoided per breast cancer diagnosed €32.5 and mammography €24.5 (50% candidates).[16] Patients' costs were related to diagnosis in terms of clinical examination (€32.5) and CT-scans (€24.5) for the detection of ovarian cancer (52.2% candidates). CT-scan in this setting is internationally often employed in clinical studies, but in this study we focused on Norwegian standard care.

3.2.3. *Savings in other sectors (S_3)*

These were production gains. The intervention avoided production loss (€47,664 × 0.5 × 0.83 × 0.5 = €7417.7) during ACT for 6 months amongst 83% of women.[20] Furthermore, the PBM + PBSO intervention prolonged life expectancy by 25

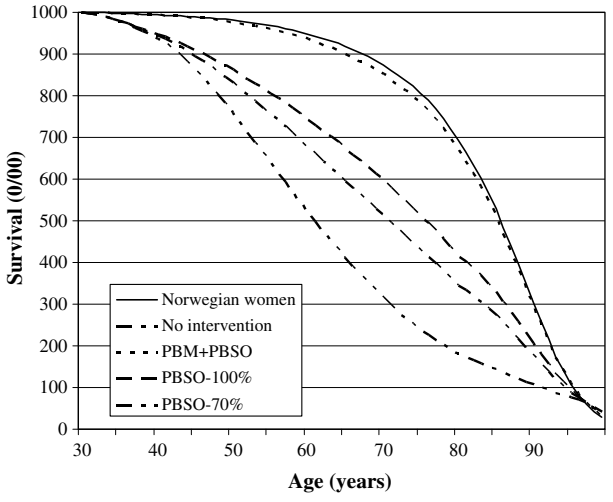

Fig. 3 – The figure visualises the expected survival figures of Norwegian women aged 30 years, the corresponding expected figures of *BRCA1* mutation carrying women undergoing prophylactic bilateral mastectomy (PBM) (age of 30 years) and prophylactic bilateral salpingo-oophorectomy (PBSO) (age of 35 years), the same women undergoing PBSO alone (70% and 100% acceptance) and finally no intervention at all.

years. Based on this, we assumed that half of the women stayed in the workforce for seven more years (from age 55 to 62 years). The saving was then calculated €47,664 × 0.5 × 7 = €166,824 (discounted €73,042). In the PBSO alone setting, only two thirds of this effect (€111,104 (discounted €48,646)) was implemented based on less survival gain (16 years) in this group.

3.3. *Statistics, authorisation and discount rate*

The Microsoft Office Excel 2003 was employed for the health economic calculations. Costs and benefits occurring in the future were discounted employing a 3% discount rate.

4. Results

Based on the model, the intervention gained 6.4 discounted life years (19.0 undiscounted life years) per mutation carrying woman undergoing PBM and PBSO at the age of 30 years and 35 years, respectively. The corresponding figures in PBSO alone (all participate and 70% participate) settings were 3.1 years (9.5 undiscounted years) and 2.2 years (6.7 undiscounted years), respectively. The survival gain is illustrated in Fig. 3 by the area between the no intervention alternative and the various interventions. The median survival was improved by 25 years (from 60 to 85 years), 16 years (from 60 to 76 years) and 8 years (from 60 to 68 years), respectively.

The total undiscounted cost (savings exclusive) per patient treated was €4949–19,855, depending on the type of intervention (PBSO with or without PBM) and whether production loss and travelling were taken into account. Including savings, the corresponding figures were in the range of a cost of €4534–52,861 saved. The cost-effectiveness analysis (CEA) indicated the figure per life year ranging from a cost of €340 until €2784 saved (Table 2). When all resources were implemented,

Table 1 – The table shows costs and savings (undiscounted) of prophylactic bilateral salpingo-oophorectomy (PBSO) plus prophylactic bilateral mastectomy (PBM), PBSO alone (70% and 100% acceptance) and none intervention at all

Costs (C)	PBM/PBSO (€)	PBSO-70% (€)	PBSO-100% (€)	No intervention
Health care costs (C_1)				
Visit to gynaecologist (code B02)	16	11	16	0
PBSO (DRG 359)	5519	3790	5414	0
Hormonal replacement therapy (20 years):	1679	1153	1647	0
Visit to breast surgeon (code B02)	16	0	0	0
Subcutaneous mastectomy (DRG 502)	8,554	0	0	0
C_1*sum*	15,784	4954	7077	0
Patient/family related costs (C_2)				
Visit gynaecologist (patient's share)	32	22	32	0
Travelling (80 km × 3.05/8.166)	19	12	18	0
Visit breast surgeon (patient's share)	33	0	0	0
Travelling (80 km × 3.05/8.166)	19	0	0	0
C_2*sum*	102	35	50	0
Costs in other sectors (C_3)				
Prod. loss (PBM), €47,664 × 0.5/12	1986	0	0	0
Prod. loss (PBSO), €47,664 × 0.5/12	1982	1361.0	1944.3	0
C_3*sum*	3968	1361	1,944	0
Savings (S)				
Health care savings (S_1)				
Breast cancer diagnosis	13	3	4	0
Mammogram	12	2	4	0
Surgery (DRG 258, mastectomy)	1247	266	380	0
Hormonal therapy (25%, 5 years 66%)	282	60	86	0
Chemotherapy (FEC, 75% therapy)	699	149	213	0
Radiotherapy (€50.5/field × 4 × 25fr × 10%)	452	97	138	0
Ovarian ca. diagnosis	13	9	13	0
Surgery (DRG 357) (58%)	2949	2099	2.9980	
S_1*sum*	5667	2685	3836	0
Patient/family related savings (S2)				
Travelling: Breast ca. diagnosis/therapy	18	4	5	0
Ovarian ca. diagnosis/therapy	17	12	17	0
Pt's shares: Breast ca. diagnosis	11	2	3	0
Mammogram	7	2	2	0
Ovarian ca. diagnosis	9	7	9	0
S_2*sum*	62	26	37	0
Savings in other sectors (S_3)				
Prod. gain (55–62 yrs, 50% workforce)	62,559	17,517	25,024	0
Prod. gain, avoided FEC (75%):	4428	1323	1890	0
S_3*sum*	66,987	18,840	26,914	0

Table 2 – The table shows cost-effectiveness (C/E) ratios depending on key costing assumptions

	C/E					
	PBSO (70%)		PBSO (100%)		PBSO + PBM	
	0% d.r.	3% d.r.	0% d.r.	3% d.r.	0% d.r.	3% d.r.
Health care costs only (C_1):	1061	2526	743	1838	831	2248
Net health care resources (C_1–S_1):	486	2499	340	1749	533	1973
Health care costs + travelling ($C_1 + C_2$):	1069	2646	748	1852	837	2263
Total costs ($C_1 + C_2 + C_3$):	1360	3409	952	2386	1046	2838
Net costs ($C_1 + C_2 + C_3 - S_1 + S_2$)	779	3279	545	2295	744	2559
All resource use ($C_1 + C_2 + C_3 - S_1 + S_2 + S_3$)	−1595	1834	−2279	1284	−2784	496

Effectiveness (E) was calculated as life years gained (LYG). 0% and 3% discount rate (d.r.) were employed. When minus, savings per life year gained is disclosed. PBSO = prophylactic bilateral salpingo-oophorectomy, PBM = prophylactic bilateral mastectomy. LYG = life years gained, d.r. = discount rate. Percent (70% and 100%) is the number of persons accepting and undergoing the suggested intervention. E: PBSO + PBM = 19.0 LYG, (3% d.r. = 6.4 LYG), PBSO (100%) = 9.5 LYG (3% d.r. = 3.1 LYG), PBSO (70%) = 6.7 LYG (3% d.r. = 2.2 LYG) For the explanation of C_1, C_2, C_3, S_1, S_2 and S_3, see Table 1.

resources were saved in all undiscounted settings. In the other situations, the cost per life year saved was negligible. This indicates that the up-front cost of investigation and prophylactic therapy is well compensated for by later savings. This is due to a significant reduction in the risk of breast and ovarian cancer, prolonged survival and production gain.

The main weakness of this model is how to access women carrying a *BRCA1* mutation before the age of 30 years. One way to improve this situation is to test all patients with breast and/or ovarian cancer in Norway (2005 annual incidence was 2798 and 420 cases/year) for the 10 most common mutations in the *BRCA1* gene.[19] The cost of this intervention is €125.9 per woman tested and the annual cost is €405,146. Employing the highest cost-effectiveness figure from Table 2 (€2838/LYG) and the national cut-off limit of €52,045/LYG (NOK 425,000), the testing has to induce between one and two new *BRCA1* mutation carrying relatives annually who undertake PBM and PBSO to make it cost-effective [(€2838 × 6.4 + €405,146)/6.4 = €66,142] (see Table 2). If the relative decides to undergo PBSO alone, the cut-off is [(€2386 × 3.1 × 2 + €405,146)/3.1 × 2 = €66,900] between two and three new mutation carriers annually. We conclude that the two interventions amongst *BRCA1* mutation carriers would be cost-effective as would a national testing programme to detect new mutation carriers.

In a sensitivity analysis (Fig. 4), discount rate, life-time risk of breast and/or ovarian cancer, production gain and acceptance of suggested intervention are the main factors having influence on the result. Within reasonable variations, the figures are far from any suggested cut-off limits (in Norway N.O.K. 425,000 = €52,000) regarding cost per LYG. Employing the maximum cost per patient of €19,855 (Table 2, C1 + C2 + C3), a life year gain of only 4.6 months will make the intervention cost-effective. In Fig. 5, the influence on life years gained of acceptance of PBSO alone or PBM + PBSO is illustrated. Implementing the suggested Norwegian cut-off level, only 6.1% and 7.8% of women have to accept the suggested interventions to make it cost-effective. (€496 × 6.43 × 100/52000 = 6.1 and €1284 × 3.1 × 100/52000 = 7.8).

Delaying the time of intervention by 5 and 10 years (PBM at 35/40 years and PBSO at 40/45 years) caused loss of life years. The life years gained (LYG) was reduced by 2.3 (discounted, 0.6) and 5.3 years (discounted, 1.7), respectively.

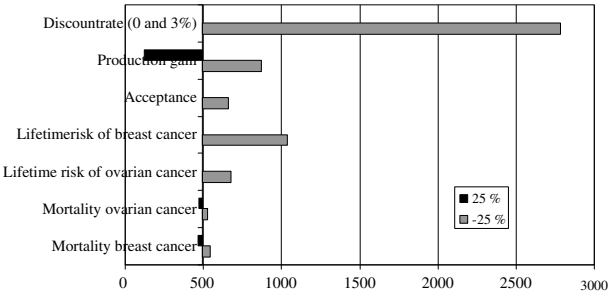

Fig. 4 – A sensitivity analysis. Various factors' influence on the result was focused. They were all varied by ±25% in a univariate sensitivity analysis. Concerning mortality: The annual death rate[5] of *BRCA1*-associated breast cancer was varied by ±25%. The prophylactic bilateral salpingo oophorectomy (PBSO) and prophylactic bilateral mastectomy (PBM) setting was employed as the base scenario (0 = €496, see Table 2).

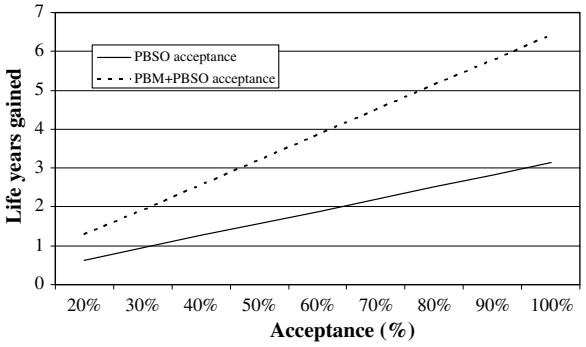

Fig. 5 – The figure illustrates how life years gained (LYG) varies with the acceptance (%) of the suggested prophylactic interventions amongst women. PBSO = prophylactic bilateral salpingo-oophorectomy, PBM = prophylactic bilateral mastectomy.

5. Discussion

In this study, we have documented an intervention consisting of either PBSO alone or in combination with PBM cost-effective

and the figures are superior to any cost-effectiveness analysis we have performed in various settings.[20–24] The combined intervention is indicated as saving twice as many life years as today's 'practice' of PBSO alone (all participating). The intervention improved the median survival figure from 60 to 85 years. This figure is close to the expected median survival of 86 years amongst 30-year-old Norwegian women in general. Thus, PBSO is an effective means of preventing ovarian cancer in high risk women, but there is still a residual risk for peritoneal cancer having a minor influence on overall survival.

The women's age at intervention is of great importance. In a study by Finch and colleagues,[25] the cumulative risk of peritoneal cancer was 4.3% at 20 years after oophorectomy. These figures compare favourable with the Norwegian figures (5.8% after 35 years) employed in our model. Whereas our modelled intervention was done whilst women were young and fertile, Laki and colleagues performed PBSO at the median age of 49 years.[7] After a median follow up of 30 months, 4 occult cancers (4.9%) were detected. Our suggested age at intervention (35 years) may clearly influence women's fertility, but will save life years.

The cost-effectiveness of preventive strategies for women with *BRCA1/2* mutations has been focused by several investigators.[26–31] Schrag and colleagues reported prophylactic mastectomy the most life saving intervention (0.6–2.1 years).[30] The corresponding figure of PBSO was 0.2–1.8 years. The magnitude of gain is least for women with low penetrance mutations. Grann and associates concluded prophylactic oophorectomy improving survival for a 30 years old woman by 0.4–2.6 years, mastectomy by 2.8–3.4 years and the combination by 3.3–6 years.[29] The latter is not far from our figure of 6.4 LYG. In a second publication, Grann and colleagues claimed both surgeries could prolong survival by 4.9 years.[27] Schrag and colleagues reported in another survey that 30-year-old women who carry *BRCA* mutations gain from 2.9 to 5.3 years of life expectancy from prophylactic mastectomy and 0.3–1.7 years from prophylactic oophorectomy.[31] Whereas these survival gain figures are concluded deemed cost-effective, they are lower than ours. The major differences are that the Norwegian mutation carriers have high penetrance mutations and we employed the survival figures from our prospective study.[5] In the reported studies, investigators assumed that *BRCA* mutation carrying women who developed cancer would have the same probability of death as women with cancer in the general population. This is clearly not the fact in Norway.

Current Norwegian practice so far has been to advocate PBSO, but not PBM. This has been reported as being acceptable to mutation carriers. This is not so for PBM. Until the disturbing confirmation of the poor prognosis of early detected *BRCA1*-associated breast cancer emerged, it has not been routinely discussed with *BRCA* mutation carriers in Norway. Faced with reality, the Norwegian breast cancer group (NBCG) now advocates that the clinical geneticists should discuss PBM whenever a female has a *BRCA1* mutation demonstrated. For this reason, we have based calculations on the combined effect of PBM + PBSO. Our knowledge concerning patient acceptance of suggested interventions is limited to PBSO, for which reason we have calculated cost-effectiveness for that separately. However, as long as the expenses (if any) are very low when all resources are focused, the matter of acceptance is less important to the health care system, but should be of interest to the women being rescued from an early death.

An annual national testing programme for any of the 10 most common *BRCA* mutations and implementing all new breast and ovarian cancer cases was cost-effective if two 'new' relatives carrying the mutation were detected and underwent a prophylactic intervention. This is achievable. A study at the University Hospital of Trondheim revealed 2% of consecutive breast cancer patients being new mutation carriers in previously unidentified kindreds.[26] These women and their family members were offered genetic counselling and subsequent testing and recommended intervention when *BRCA1* mutation was detected. In a similar series of incident ovarian cancer cases at Stavanger University Hospital in Norway, 20% of all patients represented mutation carriers.

As mentioned in Section 1, the family history based approach is insufficient because of low sensitivity (⩽33%). This has also been shown recently by Weitzel and co-workers.[32] It could be argued that the criteria (www.legeforeningen.no/asset/34023/1/34023_1.pdf) we employ should be changed to improve cost-effectiveness. However, we believe testing for locally frequent mutations will be a better way forward. Such a test will demonstrate about two out of three mutation carriers in our geographic area, including all with the mutations tested for. In contrast to family history where the vast majority of patients identified have no demonstrable mutation, there will be no false positives when testing for frequent local mutations. This may have several implications: Available resources will be shifted from considering families with a low probability to have an inherited mutation to care for families with a demonstrated mutation. The fact that the risk of breast cancer can be influenced not only by *BRCA1/2* mutations, but also by modifier genes has to be kept in mind when a shift is performed.[33] As the most severely affected families have now been investigated, more and more clinical genetic work is focused on families with a less 'strong' family history, implying lower cost-effectiveness of the resources invested, and an unnecessary degree of anxiety in many families. Most of the high risk families identified by testing women with cancer would never be found through the family history method. Because total population screening is both forbidden by law and obviously less cost-efficient, the majority of the families to be found by offering diagnostic testing to incident cases, cannot be found by any other method.

Do we have any alterative to PBSO with or without PBM? A number of arguments not discussed here, now question the effect of ameliorated early diagnosis of *BRCA1*-associated breast cancer by annual MRI instead of annual mammography. We have demonstrated that MRI diagnoses tumours at an earlier stage and reduced breast cancer mortality may be achieved, but nobody has documented any survival gain.[34,35] Furthermore, a request for MRI in this setting may of capacity reasons make it unrealistic that these women will get access to annual MRI examinations. We have no assumed effect of MRI to implement in the calculation and this factor was consequently omitted. The concept of promoting PBM without knowing whether or not it is necessary is outside oncological standards for suggesting treatment. We therefore distinguish between the results of PBSO alone (our best estimate of current preventive modalities) and our calculations on PBM in

addition. The latter is presented for the current debate on the way forward. However, many life years may be lost whilst the debate is ongoing and time is spent waiting for prospective data with sufficient follow up.

Testing of all incident cases with breast or ovarian cancer will identify many mutation carriers, most of them unidentifiable with the family history method. We see no alternative strategy within current ethical and legal standards to identify these patients, and thereby offering their relatives predictive testing and enable the mutation carriers to choose preventive modalities.

A quick test for all 60 *BRCA* mutations disclosed in Norway so far is close to being available at a cost of €250. A full *BRCA1* mutation search may be achieved at a cost of about €1000. Whereas such a test is cost-effective in Norway, health care authorities in countries with a diversity of ethnic population may have to implement a large number of 'common' mutations in their testing program and consequently have to deal with higher costs. The differences in outcome of the two Norwegian approaches will be that testing for locally known mutations only will have reduced sensitivity. Though much better than targeting only the top 10 mutations, full gene sequencing will produce results of unknown significance. Both methods will be cost-efficient, but we would recommend expansion of the test panel for known mutations, and argue against employing methods which generate large numbers of results of uncertain significance.

Some of our assumptions employed to arrive at our conclusions may be debated. One such item is the prognosis of breast cancer amongst *BRCA1* mutation carriers. According to our data, the prognosis of breast cancer amongst mutation carriers in Norway is poor with almost no effect of early diagnosis or adjuvant chemo/radiotherapy.[5] The prognosis of *BRCA* associated breast cancer vary between countries and populations and this fact has to be kept in mind when health authorities consider implementing test programs. Just recently an Israeli study disclosed figures with equal prognosis for *BRCA1/2* mutation carriers as breast cancer in general.[36] This was a retrospective study focusing an Israeli population with a different mutation of the gene compared to the Norwegian experience. This result indicates that the cost-effectiveness of our suggested intervention may be less effective in an Ashkenazi Jewish population.

In conclusion, the intervention consisting of PBSO with or without PBM in Norwegian *BRCA1* mutation carriers is cost-effective. Diagnostic testing to all incident breast and/or ovarian cancer cases can be recommended on a health economic basis.

Conflict of interest statement

None declared.

Acknowledgement

A research grant from the Sigurd K. Thoresen Foundation was greatly appreciated and that made this project manageable within a limited time period.

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