Breast Cancer Res Treat (2018) 167:263–267
https://doi.org/10.1007/s10549-017-4476-1

EPIDEMIOLOGY

The expected benefit of preventive mastectomy on breast cancer incidence and mortality in *BRCA* mutation carriers, by age at mastectomy

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Received: 17 August 2017 / Accepted: 19 August 2017 / Published online: 15 September 2017

Abstract
Purpose Preventive breast surgery is offered to unaffected *BRCA* mutation carriers to prevent breast cancer incidence and mortality. The clinical benefit of preventive mastectomy can be measured in several ways, including extension of life expectancy (mean years of life gained) and by estimating the probability of surviving until age 80. We sought to estimate the expected benefit of a preventive mastectomy at various ages, using these indices of mortality, by simulating hypothetical cohorts of women.
Methods The age-specific annual risks of developing breast cancer were used to estimate the actuarial risk of developing breast cancer by age 80 for women with a BRCA1 or BRCA2 mutation. The probability of developing breast cancer before age 80 was then modified to include competing causes of death, including from ovarian cancer. The mortality rate from breast cancer after a diagnosis of breast cancer was set at 2% annually for the first 10 years and then 1% annually for years ten to twenty. The incidence rate and mortality rate from ovarian cancer were based on published literature. We assumed that preventive mastectomy was associated with complete protection against subsequent breast cancer. A series of simulations was conducted to evaluate the reduction in the probability of death (from all causes) until age 80, according to the age at mastectomy.
Results The actuarial risk of developing breast cancer until age 80 was estimated to be 70.8%. The actual risk (incorporating competing risks) was 64.0%. The probability of being alive at age 80 by having a mastectomy at age 25 increased by 8.7% (from 42.7 to 51.3%). The estimated benefit declined with age at mastectomy; for surgery done at age 50 the improvement in survival to age 80 was much more modest (2.8% at age 80, from 42.7 to 45.5%).
Conclusions Among *BRCA* mutation carriers, the mortality benefit of preventive mastectomy at age 25 is substantial, but the expected benefit declines rapidly with increasing age at surgery.

Keywords *BRCA* · Breast cancer · Ovarian cancer · Mastectomy

Introduction

Women with an inherited *BRCA1* or *BRCA2* mutation face a high risk of developing breast cancer and must decide between screening and preventive surgery [1, 2]. The annual risk of *BRCA*-associated breast cancer for women between the ages of 30 and 60 for women with a mutation in either gene is approximately 2.5% and this falls to approximately 2% annually between ages 60 and 80 [2]. The cumulative risk of developing breast cancer to age 70 is approximately 70% for carriers of either mutation, providing the woman does not die of another cause. In Ontario, the provincial health care system offers women with *BRCA* mutations the option of prophylactic bilateral

Electronic supplementary material The online version of this article (doi:10.1007/s10549-017-4476-1) contains supplementary material, which is available to authorized users.

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mastectomy to reduce breast cancer incidence and mortality. The value of preventive breast surgery is greater for women with long life expectancies than for women with short ones. For this reason, preventive mastectomy is rarely offered to women after age 60. The decision to have a preventive mastectomy is a personal one and women have several concerns, some which relate to the experience of surgery and some which relate to the expected reduction in cancer risk and mortality. In order to help facilitate consultations between genetic counsellors and physicians and women with mutations, it is important to accurately estimate the expected benefits of mastectomy. There are several ways of estimating and conveying risk and it is not clear how risk is best communicated. Risk estimates can be offered under different clinical scenarios, for example, a young woman (e.g. age 25) seeks to know if she can delay a mastectomy until later in life and if so, at what cost. Alternatively, a woman who is newly diagnosed with a BRCA mutation and who has no history of breast cancer will wish to know the benefit of having a mastectomy at her current age (or in the future). Our objectives were: (1) to estimate the lifetime probability of developing hereditary breast cancer for healthy carrier women of various ages; (2) to estimate the life expectancy to be gained for women with a *BRCA* mutation carrier if she chooses to have a bilateral mastectomy, now or later, according to her current age and age at mastectomy and; (3) to estimate the probability of being alive at age 80 for women with and without a bilateral mastectomy.

Methods

The age-specific annual incidence rates for breast cancer were taken from Ref. [2]; the annual risks of breast cancer among BRCA1 carriers were estimated to be 0.6% annually from age 21 to 30, to be 2.4% annually from age 31 to 40, to be 2.8% annually from age 41 to 50, to be 2.6% annually from age 51 to 60 to be 2.5% annually from age 61–70 to 60 and to be 1.7% annually from age 71 to age 80. The annual mortality rates from breast cancer were 2% for years one to ten post-diagnosis and 1% for years ten to 20 [3]. The age-specific incidence rates of ovarian cancer for BRCA1 carriers were also taken from Ref. [2]. The annual mortality rate after a diagnosis of ovarian cancer were taken from Ref. [4] and ranged from 4.8% at year 1 to 22.5% at year 4. The mortality rate from ovarian cancer after 10 years from diagnosis was taken to be zero (i.e. all deaths from ovarian cancer occurred within 10 years of diagnosis). For the purpose of the simulation, we also introduce the probability of deaths from other causes (i.e. non-breast, non-ovary) according to the published mortality rates for Canadian women [5]. We considered that after a bilateral mastectomy the risk of a new breast cancer was eliminated. We considered that bilateral mastectomy did not reduce the mortality from pre-existing breast or ovarian cancers. We considered that all women in the cohort had both ovaries intact and were at risk for ovarian cancer. We considered that after a diagnosis of ovarian cancer, women did not have a preventive mastectomy.

We conducted a series of simulations by incorporating the rates described above into a life-table based model. We considered the life history of a woman from age 25 to age 80 and modelled the incidence of breast and ovarian cancer, the mortality from breast and ovarian cancer (after a diagnosis of breast or ovarian cancer respectively) and the mortality from non-cancer causes. We applied these rates iteratively, on an annual basis, to a hypothetical cohort of 100,000 women, from age 25 to age 80. This gave us an estimate of the lifetime probability of developing breast cancer, of developing ovarian cancer, of dying of breast cancer, of dying of ovarian cancer and of dying of another cause by age 80. Cause of death was recorded as from breast cancer, from ovarian cancer or from another cause.

In the first simulation, we estimated these numbers for a 25-year-old woman who had not had a mastectomy. We then introduced a bilateral mastectomy, which essentially eliminated her risk of new breast cancers entirely, but did not prevent mortality from existing cancers. We estimated the probability of being alive at age 80, with and without a mastectomy done at age 25. We then repeated the analysis a number of times, keeping the period of observation from age 25 to age 80, but varying the age at mastectomy from age 25 to age 65, by five-year interval.

In the second simulation, we repeated the analyses done in the first simulation, but we also varied the age of consultation from age 25 to age 55 by ten-year interval. At the time of consultation the patient had not been diagnosed with breast or ovarian cancer.

Results

The results of these analyses are presented as the answers to a series of clinical questions that might be posed by a patient with a BRCA1 mutation. (results for women with a BRCA2 mutation are presented separately in the Online Appendix).

What are my chances of getting breast cancer before age 80 if I don't get a bilateral mastectomy? What are my chances of dying of breast cancer before age 80 if I don't get a bilateral mastectomy?

These data are based on women who did not have a mastectomy. Further, our model was based on women without an oophorectomy, of whom 24.3% died of ovarian cancer by age 80. Also, in the basic model (no preventive

surgery) 18.4% of the women died of causes other than breast/ovarian cancer before age 80. For this reason, the estimated risk of breast cancer to age 80 (64.0%) was less than the actuarial cumulative incidence of 70.8% (which assumes no other causes of death). The likelihood of being diagnosed with cancer and the cancer incidence and mortality figures are presented in Table 1. These estimates can be considered to be the baseline probabilities for women in the absence of a preventive mastectomy. The life expectancy of all women in the USA is 81.1 years and 70.7% of women can expect to live until age 80.

What are my chances of being alive at age 80 if I don't get a mastectomy? What are my chances of being alive at age 80 if I get a mastectomy now? What are my chances of being alive at age 80 if I wait until I get a mastectomy?

These probabilities can be read from Table 1 and from Figs. 1 and 2. In the absence of a mastectomy, the chances of being alive at age 80 are 42.7% for a 25-year-old woman, 43.6% for a 35-year-old woman, 46.5% for a 45-year-old woman and 52.6% for a 55-year-old. The increase in the probability of being alive at age 80 was 8.7% for a 25-year-old who had a mastectomy at age 25. For women who had a mastectomy later on, the reduction in the overall mortality figure diminished with age—the increase in the probability of being alive at age 80 was 8.1% for a 35-year-old who had a mastectomy at age 35, was 7.0% for a 45-year-old who had a mastectomy at age 45 and was 5.0% for a 55-year-old who had a mastectomy at age 55.

What are the expected benefits of a preventive mastectomy in terms of years of life gained?

In this analysis, we consider years of life gained prior to age 80. A 25-year-old woman can expect to gain 3.3 years of life by a mastectomy at age 25, but this drops to just below 1.5 years of life gained if she postpones the surgery until age 40. The benefit was 2.6 years gained for a 35-year-old who had a mastectomy at age 35, was 1.5 years gained for a 45-year-old who had a mastectomy at age 45 and 0.7 years gained for a 55-year-old who had a mastectomy at age 55.

What is the chance that if I die before age 80, the cause of death will be breast cancer?

We expect that in the absence of preventive mastectomy or oophorectomy, 42.7% of BRCA1 carrier women will live until age 80, compared to 70.7% of women in the general population. Overall, in a cohort of 25-year-old women who do not have a mastectomy or salpingo-oophorectomy, it is expected that 25.6% of deaths (before age 80) will be from breast cancer, 42.3% will be from ovarian cancer and 32.1% will be from other causes (Table 2). In our model, a 25-year-old woman who has a mastectomy pre-empts the possibility of dying of breast cancer and the distribution of causes of death (before age 80) were 56.6% for ovarian cancer and 43.4% for other causes. If a 25-year-old defers the mastectomy, the probability that a death before age 80 will be from breast cancer is 6.4% if she intends to wait until age 35, is 15.2% if she intends to wait until age 45 and is 21.3% if she intends to wait until age 55 (Table 2).

The analysis was repeated using incidence figures for BRCA2 carriers. These results are presented in the Online Appendix 1

Discussion

In this simulated analysis, we found that the expected benefit of preventive mastectomy, in terms of prolonging life expectancy and increasing survival, diminishes substantially for women who delay surgery. For example, a woman who had preventive surgery at age 25 could expect to add 3.3 years to her life, but at age 55 the expected benefit decreases to 0.7 years of life added. Based on the data presented in Table 1, a 55-year-old woman with a BRCA1 mutation who undergoes a bilateral mastectomy

Table 1 Probability of breast cancer and of death from breast cancer to age 80 for women without preventive mastectomy

Current age	Incidence of breast cancer to age 80 (%)	Mortality from breast cancer to age 80 (%)	Death before age 80 (all causes) (%)	Alive at age 80 (all causes) (%)
25	64.0	14.7	57.4	42.7
30	62.6	14.2	57.0	43.0
35	59.7	13.4	56.4	43.6
40	54.9	12.0	55.7	44.3
45	49.6	10.3	53.5	46.5
50	42.8	8.9	50.8	49.2
55	36.8	6.8	47.4	52.6

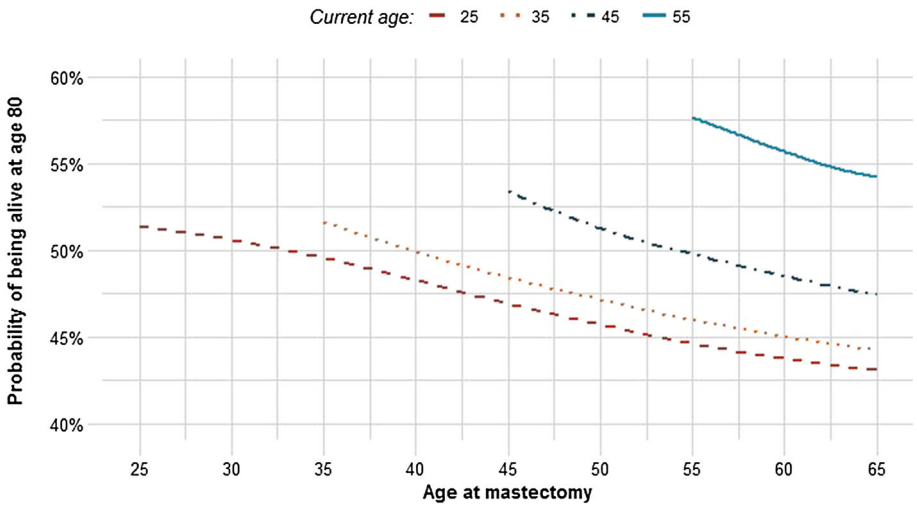

Fig. 1 Probability of being alive at age 80 in BRCA1 carriers, according to current age and age at mastectomy

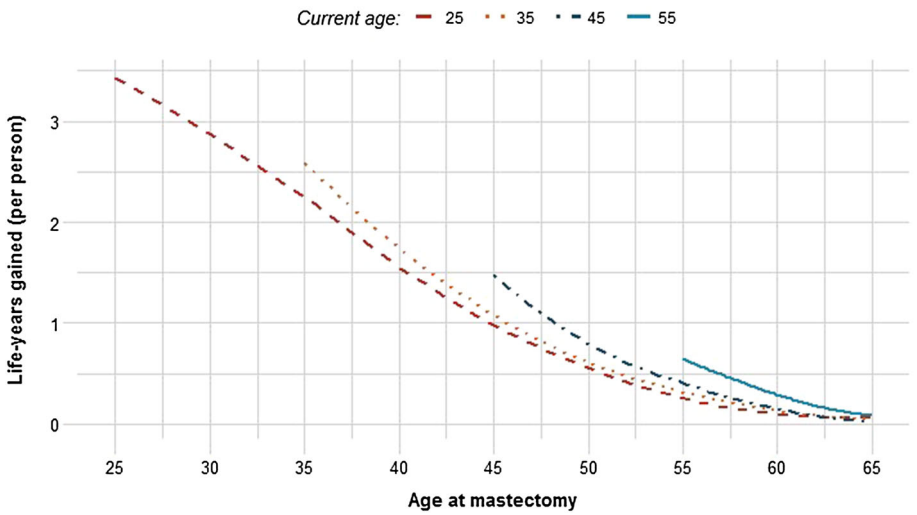

Fig. 2 Expected life-years gained in BRCA1 carriers, to age 80, by current age and age at mastectomy

Table 2 Proportions of all deaths by various causes, according to age at mastectomy, for a 25 year old woman. Deaths before age 80

Age at mastectomy (years)	Death from breast cancer (%)	Death from ovarian cancer (%)	Death from other causes (%)
No mastectomy	25.6	42.3	32.1
25	0	56.6	43.4
30	1.5	55.6	42.9
35	6.4	52.9	40.6
40	10.8	50.8	38.4
45	15.2	47.9	36.9
50	18.4	46.4	35.1
55	21.3	44.5	34.2
60	23.2	43.2	33.5
65	24.5	42.9	32.6

Deaths before age 80

will reduce her chance of developing breast cancer (to age 80) by 36.8% and her chance of dying of breast cancer before age 80 by 6.8%. As physicians, on statistical grounds alone we cannot justify routinely recommending preventive mastectomy to 55-year-old carriers of BRCA1 or BRCA2 mutations, but we acknowledge that the

perceived benefit of mastectomy for women extends beyond reducing mortality and is driven to a large extent by cancer worry and seeking peace of mind.

In this study, we simulated cohorts of women under several assumptions. The risks of breast and ovarian cancer are derived from a large cohort study and are based on 269 incident cases of breast cancer and on 85 incident cases of ovarian/fallopian cancer in BRCA1 carriers and there is necessarily some random error in these estimates. The main results are presented for BRCA1 carriers. The data for BRCA2 carriers are more sparse and are based on 85 cases of breast cancer and 24 cases of ovarian cancer.

For simplicity, we simulated cohorts of women with intact ovaries. The benefit for women without ovaries intact is expected to be slightly different, because of the reduction in ovarian cancer deaths will be reflected in an increase in the number of breast cancer deaths (by expanding the number of at risk women); however, there is uncertainty about the benefit of oophorectomy on reducing risk from breast cancer and on mortality from breast cancer post-diagnosis and we are unwilling to generate a model which includes women post-oophorectomy at this time. It is not our intention here to model the effect of oophorectomy on mortality but based on previous studies we recommend preventive salpingo-oophorectomy to all BRCA1 and BRCA2 carriers [6].

We assume that preventive mastectomy is fully protective although there have been examples of breast cancer developing post-mastectomy. We assume that women did not pursue mastectomy after ovarian cancer but there are exceptions. This study is based on historical risks of cancer incidence and cancer mortality and these rates might be less among current cohorts of women who are under surveillance with MRI.

We include a novel statistic which is the percentage of deaths to age 80 which can be avoided by mastectomy—this is somewhat akin to relative versus absolute risk—and puts mastectomy in a better light than an absolute reduction in terms of crude mortality. We estimate that in the absence of a mastectomy the proportion of all deaths before age 80 would be 25.6% from breast cancer and that all of these would be prevented by a mastectomy at age 25.

It is our impression from talking to patients and their counsellors that current age is not used to a great extent in counselling regarding the pros and cons of mastectomy; we often see women in their late 50 s and into their sixties who react to the news of a positive test by pursuing preventive surgery mastectomy. It is also possible that they value cancer prevention to a greater degree than a reduction in mortality. For example, a 50-year-old woman with a mastectomy faces a reduction in risk to age 80 of 42.8%, but a reduction in mortality of 8.3%. At age 60 the numbers fall to 19.2 and 2.9%, respectively. We recognise that the decision to undergo preventive mastectomy is a complex one and is made on a personal level and is based on many factors. Nevertheless we provide here a framework based on a numerical analysis that will be a useful adjunct to patients and counsellors when discussion preventive options with high-risk women.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the author.

Informed consent Informed consent was obtained from all individual participants included in the study.

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