Breast Cancer Research and Treatment (2019) 174:769–774
https://doi.org/10.1007/s10549-018-05076-w

EPIDEMIOLOGY

# Age-specific risks of incident, contralateral and ipsilateral breast cancer among 1776 Polish *BRCA1* mutation carriers

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Received: 21 November 2018 / Accepted: 27 November 2018 / Published online: 5 January 2019


## Abstract

**Purpose** Women with an inherited germline *BRCA1* mutation have a high lifetime risk of developing breast cancer. We have previously shown that, among *BRCA* mutation carriers, incidence rates of breast cancer vary by country of residence.

**Methods** In the current study, we prospectively calculated the cumulative and annual incidence rates of incident breast cancer, contralateral breast cancer and ipsilateral breast cancer recurrence among *BRCA1* mutation carriers in Poland. Study subjects comprised a cohort of 1776 Polish women with a *BRCA1* mutation who had no prior diagnosis of breast or ovarian cancer at the time of enrollment, the women were followed with a biennial follow-up by questionnaire. Women were followed for an average of 6.1 years (range 0.0–18.2) and 191 new breast cancer cases were diagnosed.

**Results** The cumulative incidence of breast cancer to age 70 was 52%. The annual risk of breast cancer was estimated at 1.78%; the maximum annual risk was observed between the ages of 30 and 65. Among the 941 women with a prior diagnosis of breast cancer, 106 women developed a contralateral breast cancer. The 20-year cumulative incidence of contralateral breast cancer was 31% and the annual rate of contralateral breast cancer was 1.96%. There were 11 recurrences among the 215 women with breast cancer (ipsilateral breast cancers). The cumulative incidence at 20 years was 17% and the annual rate of an ipsilateral recurrence was 1.03%.

**Conclusion** Our findings confirm the high annual rates of early-onset incident, contralateral and recurrent breast cancer among Polish *BRCA1* mutation carriers. These risk estimates are important in the context of the clinical management of unaffected women as well as in the treatment of newly diagnosed primary breast cancers and can also be used as the basis for the planning of prevention trials.

**Keywords** *BRCA1* · Breast cancer · Poland

## Introduction

Women with an inherited germline *BRCA1* mutation face a high lifetime risk of breast cancer. It is important to estimate the risk with accuracy to help guide decisions regarding the start of screening and the age of preventive surgery. To date, penetrance estimates have been based on studies of women with mixed ethnicities. In a recent prospective analysis of 3886 *BRCA1* mutation carriers, Kuchenbaecker and colleagues reported breast cancer incidence rates by 10-year age groups [1]. Their collaborative study combined several population-based studies.

The risk of breast cancer may vary from country to country, due to allelic variation at the *BRCA1* locus, other genetic factors and non-genetic risk factors. We have previously reported on the penetrance estimates for *BRCA1* mutation carriers from several different countries, including Norway, Poland and North America [2, 3]. Populations with founder mutations are interesting to study, given that the majority of *BRCA*-associated cancers can be attributed to a small number of mutations. In Poland, three founder mutations in

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*BRCA1* are responsible for the majority of hereditary breast cancers and this panel facilitates inexpensive and comprehensive genetic testing at the population level [4–6]. In Poland preventive mastectomy is infrequent and screening with MRI is the preferred method of management.

In 2012, we first reported breast cancer risk estimates for female *BRCA1* mutation carriers in Poland in our longitudinal study of *BRCA1* and *BRCA2* mutation carriers. We have updated this analysis and have now extended the number of subjects from 863 to 1776. We have estimated the annual rates of a first primary breast cancer, of a contralateral breast and of ipsilateral (recurrent) breast cancer among those with and without a personal history of breast cancer.

## Materials and methods

### Study population and data collection

Eligible study subjects were identified from a longitudinal study of *BRCA1* mutation carriers which was initiated in 1995. For the current analysis, we only included women residing in Poland. All women received genetic counselling. Each study subject completed a baseline research questionnaire at the individual centre at the time of a clinic appointment, at their home at a later date or at the time of recruitment into the research study. The questionnaire requests detailed information on family history and personal history of cancer, reproductive and medical histories (including preventive surgery) as well as medication and exogenous hormone use. Follow-up questionnaires are completed every 2 years to update exposure information and to capture incident disease. These are either mailed to each participant to complete and return, or administered over the phone by a genetic counsellor or research assistant. Information on incident breast and contralateral breast cancer was collected from the follow-up questionnaires. Information on an ipsilateral breast cancer (recurrence) is collected in a similar manner. Pathology reports are requested for all women who report incident cancers. Information regarding tumour receptor status, grade, stage, nodal status and distant metastases is abstracted from pathology report and/or medical record review.

### Subjects available for analysis

For the analysis of incident breast cancer, women were eligible for inclusion if they were between the ages of 25 and 70, had no diagnosis of breast cancer prior to completion of the baseline questionnaire, had both breasts intact (no preventive bilateral mastectomy) and if they had completed at least one follow-up questionnaire. A total of 1776 *BRCA1* mutation carriers were identified. For the contralateral breast cancer analysis, we only included women who reported a unilateral breast cancer at baseline. Women were excluded if they had a bilateral mastectomy prior to completion of the baseline questionnaire, or if they had bilateral breast cancer, resulting in 941 eligible subjects. For the ipsilateral breast cancer analysis, we excluded women if they had bilateral breast cancer at baseline or a mastectomy (preventive or for treatment of their first breast cancer) resulting in 215 eligible subjects.

### Statistical analysis

We estimated the annual rate of developing an incident breast cancer over the follow-up period. We followed women from the date of completion of the baseline questionnaire until the: (1) date of diagnosis of the first breast cancer, (2) date of bilateral mastectomy, (3) date of death or (4) date of completion of last follow-up questionnaire. The annual rate (%) was estimated as the ratio of the number of incident breast cancers to the total number of person-years in each year of follow-up. We used the age-specific annual incidence rates to estimate the lifetime risk of breast cancer for a theoretical cohort of *BRCA1* mutation carriers.

A similar statistical approach was used for estimating the annual rates of contralateral and ipsilateral breast cancer. For contralateral breast cancer, we included women who did not have bilateral mastectomy. For ipsilateral breast cancer, we included only women who were treated with breast-conserving surgery (with or without radiotherapy). The data were presented from the date of diagnosis of the first breast cancer and censored at the date of diagnosis of the contralateral or ipsilateral recurrence, respectively. For ipsilateral breast cancer, we subdivided the cohort into women with did and who did not receive radiotherapy.

All analyses were performed using the SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC, USA). All *P* values were based on two-sided tests and were considered statistically significant if $P \leq 0.05$.

## Results

In the cohort, was a total of 4418 women; of these 941 had breast cancer in one breast and 1776 had never had breast cancer at study entry. Of those who had breast cancer, 741 (79%) were treated with mastectomy and 199 (21%) were treated with breast-conserving surgery. Of those who had breast-conserving surgery, 162 (81%) had radiotherapy and 37 (19%) did not have radiotherapy. One hundred and seventy women (85%) received chemotherapy and 41 women (21%) received tamoxifen.

There were 1776 unaffected *BRCA1* mutation carriers included in the study of incident breast cancer. The mean age at study entry was 41.8 years (range 24.0–70.6) and

**Table 1** Annual incidence rate of breast cancer among Polish *BRCA1* mutation carriers, by 5-year age intervals

| Age category | Person-years | Lost to follow-up (*n*) | Incident cancers (*n*) | Annual rate, % (95% CI) |
|---|---|---|---|---|
| 25–<30 | 882.18 | 52 | 6 | 0.68% (0.14–1.22%) |
| 30–<35 | 1589.15 | 207 | 20 | 1.26% (0.71–1.81%) |
| 35–<40 | 1657.12 | 258 | 41 | 2.47% (1.73–3.22%) |
| 40–<45 | 1459.07 | 260 | 26 | 1.78% (1.10–2.46%) |
| 45–<50 | 1495.87 | 247 | 31 | 2.07% (1.35–2.79%) |
| 50–<55 | 1462.67 | 246 | 31 | 2.12% (1.38–2.86%) |
| 55–<60 | 1019.77 | 235 | 21 | 2.06% (1.19–2.93%) |
| 60–<65 | 606.56 | 139 | 10 | 1.65% (0.63–2.66%) |
| 65–<70 | 342.46 | 84 | 3 | 0.88% (0–1.87%) |
| 70–<75 | 142.77 | 32 | 2 | 1.40% (0–3.32%) |
| Overall | 10,758.79 | 1776 | 191 | 1.78% (1.53–2.02%) |

*CI* confidence interval

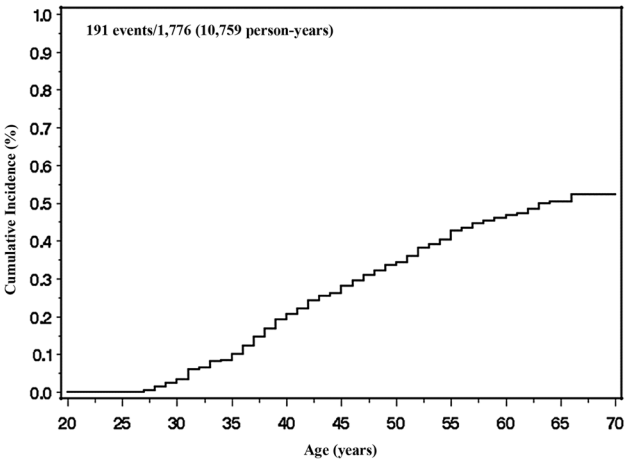


**Fig. 1** Cumulative incidence of breast cancer among Polish *BRCA1* mutation carriers

the average follow-up was 6.1 years (range 0.1–18 years). There were 191 new breast cancer cases diagnosed in the cohort (Table 1). The mean age at diagnosis was 45.7 years (range 27.4–71.6). The overall average annual risk of breast cancer was estimated at 1.78%. The age-specific annual risks (by 5-year age intervals) are presented in Table 1. The annual risk started to increase by age 30 (1.26%) and the peak incidence rate was observed among women aged 35 to 40 (2.47%). The risk remained high between 40 and 65 (range 1.65–2.06%). Using these annual risks we estimate the cumulative incidence of a primary breast cancer to age 70 to be 52% (Fig. 1).

Among the 941 women with a prior diagnosis of breast cancer at the time of enrolment and no contralateral breast cancer, 106 women developed a contralateral breast cancer (Table 2). The mean age at diagnosis of the first breast cancer was 45.6 years (range 23.4–81.7) and the mean age at

**Table 2** Annual incidence rate of contralateral breast cancer among Polish *BRCA1* mutation carriers, by 5-year age intervals

| Age category | Person-years | Lost to follow-up (*n*) | Incident cancers (*n*) | Annual rate % (95% CI) |
|---|---|---|---|---|
| 25–<30 | 18.28 | 0 | 0 | 0.00% |
| 30–<35 | 90.74 | 18 | 2 | 2.20% (0–5.21%) |
| 35–<40 | 220.14 | 38 | 8 | 3.63% (1.16–6.11%) |
| 40–<45 | 437.92 | 66 | 17 | 3.88% (2.07–5.69%) |
| 45–<50 | 744 | 104 | 12 | 1.61% (0.71–2.52%) |
| 50–<55 | 1124.3 | 162 | 23 | 2.05% (1.22–2.87%) |
| 55–<60 | 1116.7 | 185 | 20 | 1.79% (1.01–2.57%) |
| 60–<65 | 792.82 | 169 | 16 | 2.02% (1.04–3.00%) |
| 65–<70 | 416.97 | 99 | 4 | 0.96% (0.02–1.89%) |
| 70–<75 | 224.8 | 53 | 2 | 0.89% (0–2.12%) |
| 75–<80 | 135.89 | 19 | 2 | 1.47% (0–3.49%) |
| Overall | 5409.49 | 941 | 106 | 1.96% (1.59–2.33%) |

diagnosis of the contralateral breast cancer was 51.6 years (range 30.5–78.1). The average annual risk was estimated at 1.96%. The rate of contralateral breast cancer was highest between ages 35 and 45 (annual risk 3.6–3.9%). The risk remained high until age 65 (range 1.61–2.02%) and declined thereafter. The cumulative incidence of contralateral breast cancer in the 20 years following the first diagnosis was 31% (Fig. 2).

Among the 215 women eligible for inclusion in the analysis of ipsilateral breast cancer (e.g. no mastectomy), 11 developed an ipsilateral recurrence after a mean follow-up of 5.95 years (range 1.5–13.1) following the first diagnosis. The mean age at diagnosis of the first breast cancer was 44.9 years (range 26.2–81.7) and the mean age of the ipsilateral recurrence was 53.2 years (range 41.8–72.4). The average annual risk was 1.03% and the cumulative incidence to 20 years following the first diagnosis was 17% (Fig. 3). The cumulative incidence was 14% among the 174 women who received and was 34% for the women who did not receive radiotherapy ($P = 0.0004$) (Fig. 4).

## Discussion

In this prospective study of 1776 Polish *BRCA1* mutation carriers, the average annual risk of a primary incident breast cancer between ages 25 and 75 was 1.8%. This risk was (slightly) less than the risk for contralateral breast cancer (2.0%)—which is perhaps surprising given that women in the first category were at risk for first cancer in two breasts and for contralateral cancer in only one breast. We conclude from this and from a previous study [7], that an initial diagnosis of a breast cancer among a woman with an inherited *BRCA1* mutation is associated with a significant increased risk of developing cancer in the other breast. In a matched case-control study of 3920 *BRCA1* or *BRCA2* mutation carriers, we previously reported that a history of a breast cancer diagnosis in the right breast was a significant and independent predictor for beyond the *BRCA* mutation itself to predispose a woman to developing a second breast cancer [7]. This could be due to treatment effects or because there are other predisposing factors. In the latter case, those women who develop one breast cancer are a group enriched for the predisposing factors and remain at substantial risk for a second cancer. The risks reported here are similar to those in our earlier report of Polish women which was based on a much smaller number of women ($n = 863$) and a shorter follow-up (3438 person-years) [2]. In this previous study, we reported an annual breast cancer incidence rate of 1.7%.

Recently, Kuchenbaecker *et al*., estimated age-specific incidence rates and cumulative risks of *BRCA1*-associated

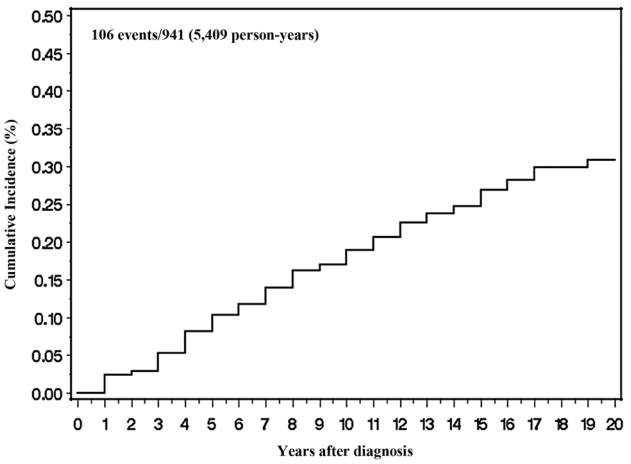


**Fig. 2** Cumulative incidence of contralateral breast cancer among Polish *BRCA1* mutation carriers with a prior breast cancer diagnosis

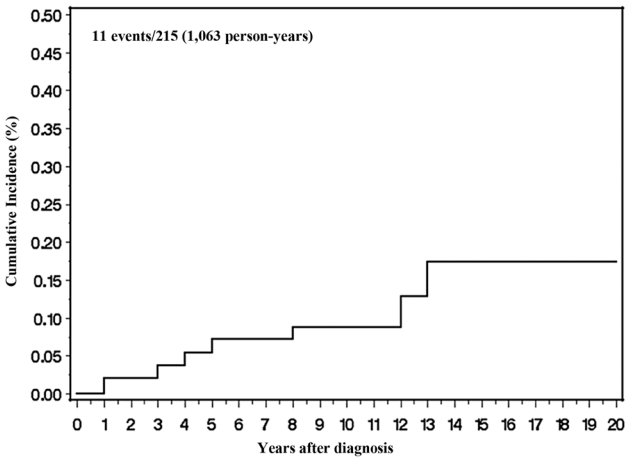


**Fig. 3** Cumulative incidence of ipsilateral breast cancer among Polish *BRCA1* mutation carriers with a prior breast cancer diagnosis

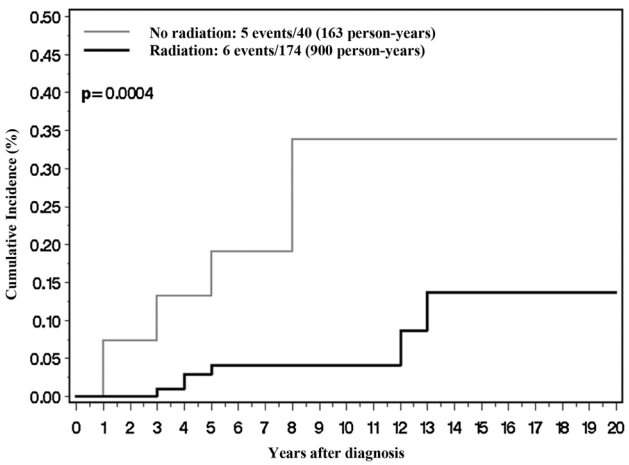


**Fig. 4** Cumulative incidence of ipsilateral breast cancer among Polish *BRCA1* mutation carriers with a prior breast cancer diagnosis, by radiotherapy treatment

breast cancer among 2276 mutation carriers; both the annual rates and cumulative incidence were slightly higher compared to our findings [1]. Overall, the annual rate of breast cancer was 2.18% and incidence rates peaked between ages 31–40 (2.35%) and remained stable until age 61–70 (2.5%), while in our current analysis, risk started to increase substantially by age 35 (average annual rate of 2.47%) and remained high (range 1.65–2.06%) until age 65. We reported an annual incidence rate of 1.78%. The cumulative incidence of breast cancer to age 70 was 52% in our study compared to 66% in the Kuchenbaecker et al. paper. The slightly lower risk estimates may be attributed to chance or differing study populations. We included women of Polish decent that were mostly carriers of one of three founder mutations in *BRCA1* and many were predominantly identified via population-based genetic testing [8], while in the Kuchenbaecker study, study participants included women from three consortia of *BRCA* mutation carriers across North America (Canada, United States), Europe (United Kingdom, Netherlands, France), Australia and New Zealand, and were mostly identified through clinical genetics centres and they were more likely to have a family history of disease.

Among women with primary breast cancer, we found that the average annual rate of developing a contralateral breast cancer was 1.96%; the risk was highest between ages 35 and 45 (3.6–3.9%) and then started to decline after age 65. In the Kuchenbaecker analysis of contralateral breast cancer which included 1305 women with a *BRCA1* mutation, the incidence rates for contralateral breast cancer were reported by age at first breast cancer diagnosis and ranged between 2.3% and 2.8%. They reported a cumulative incidence of 40% for contralateral breast cancer 20 years following the first breast cancer diagnosis compared to 31% in our report. Given the elevated risk of contralateral breast cancer (31% at 20 years) in Poland and elsewhere, *BRCA1* mutation carriers should be given the option of bilateral mastectomy at the time of diagnosis of the first cancer. A study of 390 *BRCA* mutation carriers showed that contralateral mastectomy for the treatment of a first breast cancer was associated with a significant reduction in breast cancer mortality (hazard ratio 0.52, 95% CI 0.29–0.93) [9].

The ipsilateral rates we reported are in line with an earlier report by Metcalfe et al. [10]. Among 396 women with stage I or stage II breast cancer who resided in North America, the annual risk of ipsilateral breast cancer was 1.0% per year in the current study, compared to 1.2% per year in the earlier study. A key difference between the two reports is that we included all cases of ipsilateral breast cancer and did not limit to early-stage disease. Apart from surgery (i.e. mastectomy vs. breast-conserving surgery), chemotherapy, radiotherapy and oophorectomy have also all been associated with a significant reduction in the risk of recurrence [10–12]. In the current study, women who received radiotherapy for the treatment of their first breast cancer experienced a substantial lower risk of developing a recurrence (34% vs. 14%). In an earlier study of 353 *BRCA* mutation carriers, Pierce and colleagues reported a 20-year cumulative incidence rate of 30% for an ipsilateral recurrence which is higher than our current report of 17%; and they found no difference in local recurrence rates between women who did and did not receive radiation [11].

There are several strengths associated with this study including a large number of established *BRCA1* mutation carriers with a relatively long follow-up period. Follow-up was similar for all patients. Potential limitations include that we did not stratify our analysis by mutation type although the majority of the women included in this analysis were likely carriers of one of the three Polish *BRCA1* founder mutations. Furthermore, we did not take into account potential confounders such as family history, reproductive exposures or exogenous hormone use.

In summary, Polish *BRCA1* mutation carriers face high annual risks of incident breast cancer between the ages of 35 and 65. The elevated rates of contralateral breast cancer indicates that mastectomy at the time of the primary breast cancer diagnosis be considered. Bilateral mastectomy is currently rare in Poland among breast cancer patients with *BRCA1* mutations. Metcalfe et al., has recently reported that rates of preventive mastectomy were low in Poland (4.5% of unaffected carriers) compared to women North America (38–50%). Given that mutation carriers from Poland opt for imaging aimed at early detection rather than preventive mastectomy, clinicians should enforce the guidelines requiring yearly MRI and mammography (and/or ultrasound).

**Acknowledgements** We would like to acknowledge the study staff, students, and volunteers including Shana Kim, Farah Shoukat, Ellen MacDougall, Zoella Pasta, Nida Mian, Jennifer Ng, Sarah Chin, Hamida Begum, Harmeet Chaudhary, Asrafi Azmi, Shahana Nargis, Clotilde Ngwa, Mai Abdelhadi, Saiveena Penikalapati, Laavanya Somasundaram, and Hannah Horvath who helped with the data collection and data entry.

**Funding** Joanne Kotsopoulos is a recipient of a Tier II Canada Research Chair. Steven A. Narod is the recipient of a Tier I Canada Research Chair. This study was supported by a Canadian Cancer Society Research Institute grant (703058) and the Peter Gilgan Foundation.

## Compliance with ethical standards

**Conflict of interest** All authors declare 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.

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

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