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### **► To cite this version:**

Dorina M. Kolk, Geertruida H. Bock, Beike K. Leegte, Michael Schaapveld, Marian J. E. Mourits, et al.. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in and families: high cancer incidence at older age. *Breast Cancer Research and Treatment*, 2010, 124 (3), pp.643-651. <10.1007/s10549-010-0805-3>. <hal-00534550>

**HAL Id: hal-00534550**

**<https://hal.science/hal-00534550v1>**

Submitted on 10 Nov 2010

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**Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in *BRCA1* and *BRCA2* families: high cancer incidence at older age**

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## **ABSTRACT**

### **Purpose**

Accurate estimations of lifetime risks of breast and ovarian cancer are crucial for counselling women from *BRCA1/2* families. We therefore determined breast and ovarian cancer penetrance in *BRCA1/2* mutation families in the northern Netherlands and compared them with the incidence of cancers in the general population in this region.

### **Patients and methods**

We identified 1188 female mutation carriers and first-degree female relatives in 185 families with a pathogenic *BRCA1* or *BRCA2* mutation. The occurrence of breast cancer, contralateral breast cancer, and ovarian cancer was recorded.

### **Results**

The cumulative incidence of breast cancer by age 70 was 71.4% (95%CI 67.2-82.4%) in *BRCA1* and 87.5% (82.4-92.6%) in *BRCA2* mutation carriers. For ovarian cancer at age 70, it was 58.9% (53.5-64.3%) in *BRCA1* and 34.5% (25.0-44.0%) in *BRCA2* mutation carriers. For breast cancer we saw a rise of 24.2% in the cumulative incidence in the seventh decade for *BRCA2* mutation carriers versus 6.3% for *BRCA1*. For ovarian cancer the rise in the seventh decade was 17.3% for *BRCA1* mutation carriers and 15.1% for *BRCA2*. The 10-year risk for contralateral breast cancer was 34.2% (29.4-39.0%) in *BRCA1* families and 29.2% (22.9-35.5%) in *BRCA2*.

### **Conclusion**

We show that the incidence of breast and ovarian cancer in *BRCA2* mutation carriers and of ovarian cancer in *BRCA1* mutation carriers is still high after 60 years. This may justify intensive breast screening as well as oophorectomy even after age 60. The risk of contralateral breast cancer rises approximately 3% per year, which may affect preventive choices.

## INTRODUCTION

Molecular testing for germline mutations in the *BRCA1* and *BRCA2* genes has become widespread in the last decade. Pathogenic mutations confer high risks of breast and ovarian cancer, especially at young age. Accurate estimation of the breast and ovarian cancer risk is crucial in counselling these families, since mutation carriers and family members have to make decisions on mutation testing, breast and ovarian screening, and prophylactic surgery. Intensive screening of breasts and ovaries is recommended to mutation carriers and first-degree female relatives [1-2]. In the Netherlands, breast screening is started at the age of 25 years with annual MRI, with annual mammography added from age 30. From 60 to 75 years the national breast cancer surveillance protocol is applied, with mammography every 2 years. Annual ovarian cancer screening is started at age 35. However, since ovarian cancer screening is not effective[3], women are advised to undergo a prophylactic bilateral salpingo oophorectomy (pBSO) after child-bearing age [4-5]. Mutation carriers may also opt for prophylactic mastectomy to reduce their risk. Risk assessment and counselling is based on published penetrance estimates of breast and ovarian cancer, which show varying results worldwide. Estimates of penetrance up to age 70 vary between 45-85% for breast cancer and between 10-65% for ovarian cancer, depending on type of population and way of ascertainment [6-11]. The risk of a contralateral breast cancer has been studied mostly in relatively small series. A 10-year actuarial risk between 26-37.6% for contralateral breast cancer [12-17], and a cumulative risk between 52-65% up to age 70 have been reported [8,18]. A recent study reported a 25-year risk of 62.9% for *BRCA1* mutation carriers who were younger than 40 years of age at first breast cancer [19]. In clinical genetic practice in the Netherlands the following risk figures are used: for a female *BRCA1* or *BRCA2* mutation carrier, the breast cancer risk by age 70 is 60-80% [6,8,10,11], the ovarian cancer risk is 30-60% for a *BRCA1* mutation carrier [6,11] and 5-20% for a *BRCA2* mutation carrier [6,10,11]. The risk of contralateral breast cancer is given as a

maximum of 60% [8,14,18]. The latter risk may be significantly lower if the first breast cancer was treated with tamoxifen or if premenopausal pBSO has been performed [14,20].

Estimates of breast cancer risks for *BRCA1* and *BRCA2* mutation carriers from population-based studies are generally lower (26-65%)[6,7,21-24] than the earlier reported risks from specifically ascertained multiple-case families [8,10]. However, because women attending genetic counselling services are usually members of such high-risk families, the cancer risks used in counselling these women should be appropriate to their familial cancer load and background population.

The aim of our study was to determine the penetrance of (contralateral) breast cancer and ovarian cancer in *BRCA1* and *BRCA2* mutation families in the northern Netherlands and to compare these data with the general female population in this region.

## PATIENTS AND METHODS

Since 1997, families with breast and ovarian cancer have been tested for *BRCA* mutations in the northern region of the Netherlands, which covers around 2.1 million people. Women are referred to the clinical genetics department of the University Medical Center Groningen where, after counselling and with informed consent, screening for *BRCA1* and *BRCA2* mutations is carried out, if the family history meets one of the following criteria: one breast cancer case <35 years of age; two breast cancer cases in first-degree relatives with one case <50 years of age;  $\geq 3$  first-degree relatives with breast cancer in two successive generations; the occurrence of breast and ovarian cancer in first-degree relatives; the occurrence of a male breast cancer. This study was approved by the institutional review board.

Women harboring a *BRCA* mutation and their first-degree female relatives, born between 1910 and 1987 and  $\geq 18$  years at last moment of contact, were included in the study. Mothers of mutation carriers whose mutation came from the paternal family were excluded. For each family the first person in whom a mutation was identified was designated as the index case. In most families the index is the person most likely to harbor a *BRCA* mutation, based on mainly the youngest age at diagnosis or the presence of bilateral breast cancer. In some *BRCA2* families the index case was a male with breast cancer. In the index cases comprehensive *BRCA1* and *BRCA2* analysis was performed simultaneously. Once a family-specific mutation was identified, predictive testing was offered to family members.

Because the index cases were likely to be biased towards younger diagnosis and bilaterality and thus affect penetrance estimates, we performed the statistical analysis both with and without the index cases.

Comprehensive mutation scanning of the *BRCA1* and *BRCA2* gene included denaturing gradient gel electrophoresis, the protein truncation test, direct sequencing and multiplex ligation-dependent probe amplification, as described elsewhere [25].

Data of all the individuals were entered into an SPSS database. Information on the familial gene mutation and individual mutation status (i.e. carrier, obligate carrier, not tested or proven non-carrier); dates of birth and death or last moment of contact; diagnoses of (contralateral) breast cancer (ductal carcinoma in situ was recorded as breast cancer) and ovarian cancer; prophylactic mastectomy (n=85) and pBSO (n=210) were collected. The cancers were confirmed by hospital or pathology records or else through a first degree family member. A woman was considered an obligate carrier (n=53) if a child as well as a parent or a sibling carried a *BRCA* mutation. In the analyses they were considered as mutation carriers.

Age related penetrances of breast and ovarian cancer were calculated for the mutation carriers, the not-tested women, and the proven non-carriers. This approach was chosen since we hypothesized that women affected with cancer might be more inclined to have mutation testing than non-affected women, which would lead to an overestimation of cancer penetrance in the carrier group and an underestimation in the other groups. So the two other groups function as control groups for the mutation carrier group.

For the penetrance calculation of contralateral breast cancer, the mutation carriers and not-tested women were pooled, assuming that women with bilateral breast cancer in the not-tested group (n=19) were extremely likely to be mutation carriers.

## **Statistical analysis**

The Student's t-test for independent samples was used to calculate differences between ages at diagnosis of (contralateral) breast and ovarian cancer.

The cumulative incidence of (contralateral) breast cancer and ovarian cancer was estimated using Kaplan-Meier survival analyses. For the (contralateral) breast cancer curves, women were censored at the age of prophylactic mastectomy and last follow-up or death. They were also censored at the age of pBSO (if under age 50), which is known to reduce breast

cancer risk(4). For the ovarian cancer curves, censoring was applied at pBSO, last follow-up or death.

The risk of breast and ovarian cancer was quantified using standardized incidence ratios (SIR), in which observed numbers of cancer in the *BRCA1/2* populations are compared to age- and period-specific breast and ovarian cancer incidence rates in the general population.

Incidence rates were obtained from the Dutch Cancer registries (3-year averages). From 1989 onwards we used incidence rates from the Comprehensive Cancer Center Northeast registry, which covers the referral area of the Clinical Genetics Department of the University Medical Center Groningen. Because their cancer incidence data were incomplete before 1989, data from the Comprehensive Cancer Center South registry were used for the period 1978-1989, assuming that regional differences in the incidence of breast and ovarian cancer within the Netherlands in the pre-breast screening era were negligible. Cancer risks were estimated including index cases and risks were estimated separately for mutation carriers, not-tested women, and proven non-carriers. The 95% confidence interval for the SIR was determined assuming a Poisson distribution for the observed cancer numbers. All *P* values are two-sided and the statistical significance level was set at  $P < 0.05$ .



## RESULTS

We identified 185 families with a pathogenic *BRCA1* or *BRCA2* mutation, 111 *BRCA1* and 74 *BRCA2* families. The total group comprised 1188 women (755 *BRCA1*; 433 *BRCA2*), with 94 index cases in the *BRCA1* families and 58 index cases for *BRCA2*. The numbers of mutation carriers, not-tested women, and proven non-carriers are summarized in table 1, where an overview of the number of cancer cases for each *BRCA* gene is given.

### Breast cancer

#### *Cumulative incidences*

The cumulative incidence of breast cancer by age 70, including the index cases, was 71.4% (95%CI 67.2-75.6%) in *BRCA1* and 87.5% (95%CI 82.4-92.6%) in *BRCA2* mutation carriers (figure 1A). In the *BRCA2* mutation carriers, the cumulative incidence at 60 years was 63.3%, showing a steep rise of 24.2% in the seventh decade (table 2).

The cumulative incidence by age 70 excluding the indexes was 60.0% (95%CI 54.5-65.5%) for *BRCA1* mutation carriers and 78.3% (95%CI 68.9-87.7%) for *BRCA2*.

In the not-tested women the cumulative breast cancer incidence at age 70 was 35.1% (95%CI 31.1-39.1%) in *BRCA1* and 34.7% (95%CI 29.8-39.6%) in *BRCA2* families.

The proven non-carriers had a cumulative incidence at 70 of 8.6% (95% CI 4.8-12.4%) in *BRCA1* and 16.1% (95% CI 8.6-23.6%) in *BRCA2* families.

#### *Age at diagnosis of breast cancer*

The mean age at diagnosis of breast cancer in mutation carriers and not-tested women in the *BRCA1* group was 42.5 years (SD 10.4 years, range 19.3-79.1 years). The mean age at breast cancer diagnosis in proven non-carriers was similar (mean 43.9 years, SD 5.6, range 38.4-50.2 years). Breast cancer occurred at older age in the *BRCA2* group (mean 46.8 years

SD 10.4 years, range 29.3-74.8 years,  $p<0.001$ ). The mean age at diagnosis of the proven non-carriers with breast cancer was 52.5 years (range 50.4-56.1 years).

## Ovarian cancer

### *Cumulative incidences*

The cumulative incidence of ovarian cancer by age 70, including the index cases, was 58.9% (95%CI 53.5-64.3%) in *BRCA1* and 34.5% (95%CI 25.0-44.0%) in *BRCA2* mutation carriers (figure 1B). In the *BRCA1* mutation carriers, the cumulative incidence rose steeply from 3.3% at the age of 40 years to 20.9% at age 50, with a rise of still 17.3% in the 7<sup>th</sup> decade (table 2). In the *BRCA2* carriers the cumulative incidence was 1.9% at 40 years of age and 6.6% at 50 years of age, with a rise of 15.1% in the 7<sup>th</sup> decade.

The cumulative incidence of ovarian cancer by age 70, excluding indexes was 51.7% (95%CI 44.9-58.5%) for *BRCA1* and 13.3% (95%CI 7.4-19.2%) for *BRCA2* mutation carriers.

In the not-tested women, the cumulative incidence at age 70 was 28.7% (95%CI 24.6-32.8%) for *BRCA1* and 12.8% (95%CI 8.3-17.3%) for *BRCA2*. For both the *BRCA1* and *BRCA2* families, the proven non-carriers showed a cumulative incidence of 0% at age 70.

### *Age at diagnosis of ovarian cancer*

Ovarian cancer was diagnosed at an older age than breast cancer in both the *BRCA1* (mean 50.1 years, SD 9.1 years, range 33.1-87.5 years,  $p<0.001$ ) and the *BRCA2* cohort (mean 57.5 years, SD 12.5 years, range 28.4-78.4 years,  $p<0.001$ ). The age at ovarian cancer diagnosis was significantly younger in *BRCA1* than in *BRCA2* mutation carriers ( $p=0.001$ ).

## **Standardized Incidence Ratios (SIR) of breast and ovarian cancer**

The observed numbers of breast and ovarian cancer cases in the *BRCA* populations were compared with the expected numbers in the general female population (table 3). The observed number of cancers was significantly increased for both breast and ovarian cancer in the *BRCA1* and *BRCA2* mutation carriers and in the not-tested women.

The SIR for *BRCA1* mutation carriers is highest at a young age and gradually decreases with age. For *BRCA2* mutation carriers, the SIR is highest in the fourth as well as the seventh decade. For ovarian cancer SIR is highest between 50 and 60 years for *BRCA1* and between 60 and 70 years for *BRCA2* mutation carriers (table 4).

## **Contralateral breast cancer**

Contralateral breast cancer was observed in 67 women, 43 (of which 6 synchronous) in the *BRCA1* families and 24 (of which 6 synchronous) in the *BRCA2* families. The mean interval between the first and second breast cancer was 4.2 years (SD 4.2 years, range 0.0-20.0 years) for *BRCA1* and 4.3 years (SD 4.6 years, range 0.0-18.6 years,  $p=0.89$ ) for the *BRCA2* group.

The mean age at diagnosis of the contralateral (i.e. second) breast cancer for *BRCA1* was 43.8 years (SD 8.4,  $n=43$ ) versus 51.9 years (SD 9.9,  $n=24$ ,  $p=0.01$ ) in the *BRCA2* group.

The 10-year risk of a contralateral breast cancer was 34.2% (95%CI 29.4-39.0%) in *BRCA1* and 29.2% (95%CI 22.9-35.5%) in *BRCA2* families (fig 2).

## DISCUSSION

For *BRCA1* mutation carriers this study shows a cumulative incidence of breast cancer at 70 years of 71.4% including index patients, and of 60% excluding indexes. This is similar to the meta-analysis by Antoniou et al. and the study by King et al., who observed a cumulative risk of 65% (95%CI 51-75%) and 69% (SD 5%) at 70 years [6,11]. Both studies excluded index cases. The *BRCA2* breast cancer incidences at 70 in our study (87.5% including index cases, 78.3% excluding index cases) are at the higher end of the range of incidences published to date: 84% (95%CI 43-95%, including indexes) [10], 45% (95%CI 33-54%, excluding indexes) [6], 74% (excluding indexes, SD 8%) [11] and 75% (including indexes, 95%CI 71.7-78.3%) [9], all at age 70.

In our *BRCA2* families the age at diagnosis of breast (mean 46.8 years) and ovarian cancer (mean 57.5 years) was higher than in the *BRCA1* families (43.7 and 50.8 years, respectively), which confirms previous reports [6,10]. These ages at diagnosis are considerably younger than in our regional general population (breast cancer 61.9 years, SD 14.3 and ovarian cancer 65.5 years, SD 13.7) [26]. Referral criteria for mutation analysis are heavily weighted towards young age at cancer diagnosis. *BRCA2* families are therefore more likely to be missed, because they may fail to meet the age-related criteria for referral. If these *BRCA2* mutation families would have a lower cancer penetrance, the true cumulative incidence would be lower than presented here. Moreover, the higher incidence of breast cancer in *BRCA2* versus *BRCA1* might be related to the competing risk of mortality from ovarian cancer in *BRCA1* families.

The ovarian cancer incidence at 70 for *BRCA1* (58.9% including index cases; 51.7% excluding index cases) and *BRCA2* (34.5% including index cases; 13.3% excluding index cases) also appear to be at the high end of the spectrum as compared to other studies [6,8,10,11].

If women affected by cancer are more inclined to choose for mutation testing than non-affected women, this would lead to overestimation of cancer penetrance in mutation carriers and underestimation in the not-tested group. In the *BRCA1* group the cumulative incidence at 70 in the not-tested group is half the incidence of the proven mutation carriers (breast cancer: 35.1% versus 71.4%; ovarian cancer: 28.7 versus 58.9%). However, the *increase* of breast cancer incidence *above* the population level of 8.6% at 70 [27] is approximately 26% versus 63%, which might indeed indicate skewing towards testing in affected women. In the *BRCA2* group the same phenomenon was seen.

We chose to present the data with and without the index cases, because the index cases were selected on the basis of early diagnosis and bilaterality, which leads to ascertainment bias. Indeed the mean age at diagnosis of breast cancer in the indexes only was lower than in the non-index cases for *BRCA1* (difference 3.4 years,  $p=0.02$ ) and *BRCA2* (difference 6.2 years,  $p=0.01$ ). However, in daily counselling practice, the indexes are members of *BRCA1/2* families and the cancer risks are communicated even before mutation analysis in the index is carried out. We would therefore plead to communicate risk estimations based on calculations including indexes in counselling practice.

In this study women testing negative for the familial mutation showed a breast cancer cumulative incidence of 8.6% for *BRCA1*, with all breast cancers ( $n = 5$ ) occurring before 50 years and a SIR of 2.0 (range 0.7-4.7). For *BRCA2* this was 16.1%, with all breast cancers ( $n=4$ ) occurring after 50 and a SIR of 2.5 (range 0.7-6.3). Although the number of cases was small and there was no statistical significance, the young age at diagnosis, especially in the *BRCA1* group, is intriguing. These results confirm Smith et al.'s study [28], who showed a SIR for breast cancer of 3.2 (95% CI 2.0-4.9) for these proven non-carriers. Whether modifier genes or other study-related factors play a role is still unclear and needs to be explored.

Previous studies on contralateral breast cancer are based on small patient numbers, between 5 and 36 patients [12,13,15,17,29]. A larger study by Metcalfe et al. presented 97 contralateral breast cancers and showed a 10-year risk of 29.5% (32% for *BRCA1* and 24.5% for *BRCA2*) [14]. These data are confirmed by our results, showing a 10-year risk of 34.2% for *BRCA1* and of 29.2% for *BRCA2* families. The 20-year risk of contralateral breast cancer in our study rises to 42.8% in *BRCA1* and 49.8% in *BRCA2* families, but these figures are based on small numbers. Our data were, however confirmed by a recent study that reported a 25-year mean risk for contralateral breast cancer of 47.4% in *BRCA1* and *BRCA2* families [19].

The observed cancer incidence in mutation carriers after the age of 60 appeared to be even higher than we expected. Current intensive breast screening for *BRCA* mutation carriers runs from age 25 till 60 years; between age 60 and 75 women are screened in the national breast cancer surveillance protocol. In the *BRCA2* group, the increase in cumulative incidence was as high as 24.2% in the decade from 60 till 70 years. This suggests that it might be appropriate to consider extension of intensive screening above age 60 for at least *BRCA2* mutation carriers.

Ovarian screening starts at about 35 years, no consensus exists till what age it has to be continued. Since the annual incidence of ovarian cancer is highest between age 60 and 70 in both *BRCA* groups, we would advise to still offer pBSO at least up to age 70. Recent studies have shown that screening of *BRCA* mutation carriers through ultrasound and CA125 determination is not effective to prevent advanced stage ovarian cancer and related death [3,30]. In our population the ovarian cancer incidence at age 40 was 3.3% in *BRCA1* and 1.9% in *BRCA2* mutation carriers, and rose to 20.9% and 6.6% respectively at age 50. Carriers of a *BRCA1* mutation should therefore be offered pBSO from 35-40 years of age. For *BRCA2* mutation carriers, an age threshold for pBSO is more difficult to stipulate. Age related ovarian

cancer incidence might justify postponement until age 40-45, but this will reduce the beneficial effect of premenopausal pBSO on breast cancer risk.

This study presents data on breast and ovarian cancer penetrance in a well-defined group of proven *BRCA1* and *BRCA2* families, selected according to the currently used inclusion criteria for DNA testing in the Netherlands. Our data are therefore particularly applicable to counselling on DNA-testing and preventive options for *BRCA* families in the clinical setting.

### **Acknowledgements**

We thank Rob H.A. Verhoeven and Maaïke van der Aa for providing breast and ovarian cancer incidences in the female population in the Netherlands. We thank Jackie Senior for editorial support.

### **Conflict of interest statement**

The authors declare that they have no conflict of interest and that this paper is based on their own original research.

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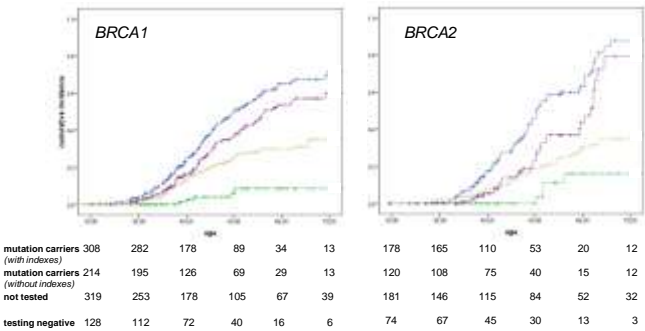
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FIGURE LEGENDS

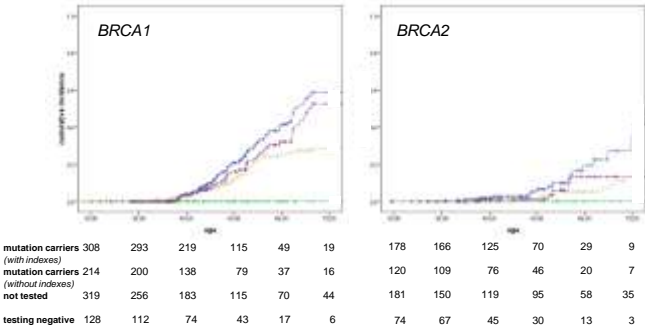
**Fig 1.** Cumulative incidence of breast cancer (A) and ovarian cancer (B) for *BRCA1* and *BRCA2* mutation carriers including (blue) and excluding (purple) indexes, not-tested women (grey) and proven non-carriers (green).

**Fig 2.** Cumulative incidence of contralateral breast cancer for *BRCA1* (n=43: 35 mutation carriers and 8 not-tested women) and *BRCA2* (n=24: 13 mutation carriers and 11 not-tested women).

A Breast cancer



B Ovarian cancer



### Contralateral breast cancer

