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ORIGINAL ARTICLE

BRCA1 gene mutations may explain more than 80% of excess number of ovarian cancer cases after breast cancer – a population based study from the Western Sweden Health Care region

ZAKARIA EINBEIGI[1], CHARLOTTA ENERBÄCK[2], ARNE WALLGREN[1], MARGARETA NORDLING[2] & PER KARLSSON[1]

[1]*Department of Oncology, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden and* [2]*Department of Clinical Genetics, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden*

Abstract

Aim. In a previous cohort study, we showed that there was a significant variation in the frequency of ovarian cancer after having breast cancer in Sweden, with the highest risk occuring in the Western region. The present study aimed to evaulate whether the high prevalence of the founder mutation *BRCA1* 3171ins5 may explain the excess number of ovarian cancer. *Method.* Among more than 26 000 women with breast cancer in the Western Swedish Health Care Region, 159 cases were subsequently diagnosed with ovarian cancer, whereas the expected number was 96. Archived tissue material was analysed for six common Scandinavian *BRCA1* and *BRCA2* gene mutations. *Results.* The excess number of cases was 63 (95% CI 47–77), based on person-years at risk and national incidence rates of ovarian cancer. A *BRCA1* gene mutation was detected in 33 cases corresponding to 52% of the excess number. The founder mutation, *BRCA1* 3171ins5, was detected in 44% of the excess number. The identified mutations decreased from 45% in women less than 50 years of age at follow-up to 14% at 60+ years at follow-up. There was no obvious decrease in mutation frequency by excess numbers with age. Age at follow-up and first-degree relatives with breast and/or ovarian cancer were the best predictors of a mutation in this material. *Conclusion.* The founder mutation, *BRCA1* 3171ins5, explains the excess of ovarian cancer after breast cancer in the region. From the relative frequency of the studied mutations found at the cancer genetic counselling clinic, it is estimated that *BRCA1* gene mutations are associated with about 80–85% of the excess cases. This means that a negative screening for these mutations in similar cases may have a predictive value and could strongly reduce the risk of ovarian cancer in relatives.

Multiple cases of breast and ovarian carcinomas in a family are the cardinal indicators of a possible associated *BRCA1* or *BRCA2* gene mutation [1]. We have attempted to define the circumstances under which breast and ovarian carcinoma in the same woman may be used to predict these mutations. We have previously in a Swedish registry study, which included all Swedish women born 1920 or later reported that there was an excess of ovarian cancer following breast cancer in Sweden. (Standardised Incidence Ratio, SIR 1.7) [2]. A two-fold increase in the risk of ovarian cancer after breast cancer was reported in a similar Swedish study in women who were born after 1931 [3]. Both studies showed that the risk decreased with increasing age. This is compatible with a common underlying factor, predominantly of genetic origin, which also appeared to be supported by the finding of breast and ovarian cancer in first-degree relatives in the latter study. Furthermore, our previous Swedish registry study showed a significant variation in the risk between the different health care regions in Sweden, which appeared roughly to correspond to the frequency of ascertained *BRCA1* gene mutations in the different regions [2]. The highest excess of ovarian cancer in breast cancer patients was found in the Western Swedish Health Care Region. Several specific *BRCA1* and *BRCA2* mutation have been described in different poulations [4–6]. A specific *BRCA1* founder mutation (*BRCA1* 3171ins5) has been found to be the dominant mutation at the cancer genetic counselling clinic in the Western Swedish Health Care Region [7,8]. We postulated that the prevalence of this mutation was the reason for the high incidence of ovarian cancer after breast cancer in this region.

Correspondence: Zakaria Einbeigi, Sahlgrenska University Hospital, Department of Oncology, SE-413 45 Göteborg, Sweden. Tel: +46 31 3424381. Fax: +46 31 820114. E-mail: zakaria.einbeigi@oncology.gu.se

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In a population-based follow-up study of all women irrespective of age from Western Sweden, mutation analysis of the western Swedish founder mutation, *BRCA1* 3171ins5, and a selection of other common Scandinavian mutations (*BRCA1* 1135insA, 1201del11, 1806C>T, 2594delC and *BRCA2* 4486delG) was performed on archival paraffin material from all 263 individuals with both breast and ovarian neoplasia, irrespective of histological diagnosis, at least one of which occurred in patients living in the western region [9]. In 45 of 241 (16%) women from whom material could be analysed, a *BRCA1* gene mutation was detected and, in 38 of these cases, the *BRCA1* 3171ins5 mutation was found. In 159 of the 263 individuals a diagnosis of breast cancer preceded the ovarian cancer.

The aim of the present investigation was to study to what extent the *excess* of ovarian cancer in patients with previous breast cancer in the Western Swedish Health Care Region noted in the Swedish registry study could be explained by the mutational pattern of the *BRCA1* gene and especially the western Swedish founder *BRCA1* gene mutation seen in the regional population-based follow-up study from Western Sweden. If the majority of the excess could be explained by BRCA1 gene mutations, this may have a bearing on the interpretation of the future risk of ovarian cancer in a negative mutation analysis of a breast cancer patient.

Material and methods

Cases

The present study was based on all 26 237 breast cancer patients diagnosed in the Western region and reported to the Swedish Cancer Registry between January 1, 1958 and December 31, 1998, with no previous diagnosis of ovarian cancer.

They were followed up in the Cancer Register for epithelial ovarian cancer between January 1, 1972 and December 31, 1998, irrespective of where in Sweden the latter had occurred. The follow-up time, which was censored by death or emigration, totalled 205 180 person-years. In this cohort there were 159 patients with an epithelial ovarian carcinoma. Archived material has been analyzed in the above mentioned study for *BRCA* gene mutations [9].

The present study was based on all 26 237 breast cancer patients diagnosed in the Western Sweden region with no previous diagnosis of ovarian cancer. These patients were reported to the Swedish Cancer Registry between January 1, 1958 and December 31, 1998.

Through record linkage with the Swedish multigeneration register, information on first-degree relatives and their possible cancer diagnoses was added (for a description see [10]). This register contains only information on individuals born after 1931 who were residents of Sweden after 1961. To secure anonymity, the Ethics Committee decided that the genetic analyses were only to be performed on anonymous material. The identity of the individuals was therefore only known to one officer at the Regional Cancer Registry. After all record linkage and the addition of mutation results, the personal identification numbers were removed and the file was returned for statistical analyses.

Mutation analysis and BRCA1/2 gene mutations

The *BRCA1/2* mutations in the present 159 cases were obtained in the previous study [9]. However, as only paraffin-embedded tissue was available, the analyses were restricted to a few common mutations. The following six mutations were searched for; *BRCA1* 3171ins5 which is the most commonly identified mutation in the western Swedish region [11,12], this mutation, a further three mutations of the *BRCA1* gene (1201del 11, 1806 C>T and 2594 delC) [13] and one *BRCA2* gene mutation (4486delG) [14] have been recurrently identified in the neighbouring southern region. *BRCA1* 1135insA is one of three Norwegian founder mutations [15].

For three of the patients, no paraffin tissue was obtained. In addition, due to the poor quality of the extracted DNA, one or more of the *BRCA1/2* analyses were inconclusive in 36 cases. A total of 33 mutations were found. The *BRCA1* gene mutation, 3171ins5, was detected in 28 cases. A further five mutations of the *BRCA1* gene were found in this group: *BRCA1* 1201del11 in two cases and BCRA1 2594delC and *BRCA1* 1806C>T, each in one case. In addition, one case with a truncating mutation, *BRCA1* 1159delT, was detected in the sample amplified for the detection of *BRCA1* 1135insA. No *BRCA2* gene mutation was found. Assuming the same frequency of mutation for failed analyses as for successful ones, it can be estimated that some 3.0 mutations may have been missed, 2.4 of which hypothetically could have been *BRCA1* 3171ins5.

Frequency of the studied BRCA1/2 gene mutations at the Regional Cancer Genetic Counselling Unit at Sahlgrenska Hospital, Göteborg

To estimate the percentage of all *BRCA1*/2 gene mutations in the region covered by the studied mutations, the number of families and individuals with *BRCA1*/2 gene mutations were studied in the files of the counselling unit for the period 1995 to 2008.

Statistical analyses

There were 159 *observed* cases of invasive ovarian cancer following breast cancer. The *expected* numbers

were based on the numbers of person-years at risk and the national incidence rates of invasive epithelial ovarian carcinoma for each five-year age group and every five years of follow-up since 1972. The excess numbers of cases were calculated as observed-expected. The confidence intervals for excess numbers were calculated assuming that observed numbers were Poisson distributed.

Standardised Incidence Ratios (SIR) were defined as the observed numbers of cases divided by the expected numbers of cases and 95% confidence intervals (95% CI) were calculated under the assumption of Poisson distribution among the observed cases.

The percentages of mutation frequency will be given as the number of identified carriers of *BRCA1* gene mutations by the observed and the expected number of cases, without any attempt to adjust for the lack of confirmation of mutational status for some cases. The confidence limits for mutation frequencies were calculated assuming binominal distributions of the observed number of cases.

A comparison of the results from the re-analysis of the regional population-based follow-up study from Western Sweden with the excess of ovarian cancer found in Western Sweden in the Swedish registry study was performed to study to what extent the BRCA mutations could explain the excess.

Results

BRCA1/2 mutations in relation to excess number of cases with ovarian cancer

During the follow-up of 26 237 breast cancer patients in the western region, 159 cases of ovarian cancer occurred and 95.8 were expected. The excess number of cases was therefore 63.2 (95% CI 47.0–76.6) and the SIR was 1.7 (95% CI 1.4–1.9, Tables I, II).

Among these 159 individuals with ovarian cancer, 33 (20.7%, 95% CI 14.7–28.9) had a confirmed *BRCA1* mutation, 28 of which were *BRCA1* 3171ins5. Mutations were therefore detected in 52.2% (95% CI 43.1–70.2) of the excess number of cases.

Age at breast cancer and age at follow-up

Table I shows the material by age when the breast cancer was detected, while Table II shows it by age at follow-up. The observed and expected numbers of ovarian cancer are given, as well as the calculated excess numbers of ovarian cancer and the SIR for each age group. The SIR decreased from 6.0 (95% CI 3.5–9.6) in women with breast cancer before age 40 to 1.1 (95% CI 0.9–1.5) if the breast cancer was detected after age 59. The SIR also decreased during the age at follow-up from 5.9 (95% CI 3.8–8.7) before age 50 to 1.3 (95% CI 1.0–1.6) after 59 years of age.

Table II gives the numbers of cases with identified *BRCA* gene mutations by the age at which the ovarian cancer was detected. The identified mutations are also given as the percentage of the observed and excess cases by age at follow-up. The percentage of mutation carriers decreased from about 45% before 50 years of age at follow-up to around 14% after 59 years of age. However when the mutations were related to the *excess* rather than the observed numbers of ovarian cancer cases, no distinct trend for age at follow-up was seen.

Increasing age when breast cancer was detected ($p=0.01$) and increasing age when ovarian cancer was detected ($p=0.0002$) correlated significantly to

Table I. Observed, expected, excess numbers of ovarian cancer cases following breast cancer, standardised incidence ratios (SIRs), numbers and percentages of identified BRCA1 mutations by age at breast cancer diagnosis.

	Age at breast cancer, years				
	< 40	40–49	50–59	60+	All ages
No. of women	1123	3922	5270	5922	26237
Person-years	11458	42979	49606	101136	205179
No. of ovarian cancer cases					
Observed	15	43	41	60	159
Expected	2.5	16.6	23.9	52.9	95.8
Excess number (95% CI)	12.5 (10.7–13.4)	26.4 (18.8–28.4)	17.1 (7.9–23.1)	7.1 (–8.9–18.6)	63.2 (47.0–76.6)
Rate per 10^5 (95% CI)	109.1 (59.3–181.3)	61.5 (40.9–88.0)	34.5 (20.7–53.6)	7.0 (3.1–13.6)	30.8 (23.1–39.0)
SIRs (95% CI)	6.0 (3.5–9.6)	2.6 (1.9–3.5)	1.7 (1.2–2.3)	1.1 (0.9–1.5)	1.7 (1.4–1.9)
Carriers of BRCA1 mutations (BRCA1 3171ins5)	6 (6)	11 (9)	8(6)	8 (7)	33 (28)
By observed no. (%)	40.0	25.6	19.5	13.3	20.8
By excess no. (%)	48.0	41.7	46.8	112.7	52.2

Table II. Observed, expected, excess numbers of ovarian cancer cases following breast cancer, standardised incidence ratios (SIRs), numbers and percentages of identified BRCA1 mutations by age at follow-up.

	Age at follow-up, years			
	< 50	50–59	60+	All ages
Person-years	20109	37553	147518	205180
No. of ovarian cancer cases				
Observed	22	38	99	159
Rate per 10^5 (95% CI)	109.4 (68.6–165.6)	101.2 (71.6–138.9)	67.1 (54.5–81.7)	77.5 (65.6–90.5)
Expected	3.7	15.0	77.0	95.8
Rate per 10^5 (95% CI)	18.4 (13.0–25.4)	39.9 (33.8–46.9)	52.2 (48.8–56.0)	46.7 (43.8–49.7)
Excess number (95% CI)	18.3 (16.1–19.5)	23.0 (17.0–26.9)	22.0 (3.0–43.5)	63.2 (47.0–76.6)
Rate per 10^5 (95% CI)	91.0 (80.6–97.0)	61.2 (45.3–71.6)	14.9 (2.0–29.5)	30.8 (23.1–39.0)
SIRs (95% CI)	5.9 (3,8–8.7)	2.5 (1.8–3.4)	1.3 (1.0–1.6)	1.7 (1.4–1.9)
Carriers of *BRCA1* mutations (*BRCA1* 3171ins5)	10 (10)	9 (6)	14 (12)	33 (28)
By observed no. (%)	45.4	23.6	14.1	20.7
By excess no. (%)	54.6	39.1	63.6	52.2

a decreasing frequency of *BRCA1* gene mutations. When both age at breast cancer diagnosis and age at ovarian cancer diagnosis were added simultaneously to the regression model, only age at ovarian cancer diagnosis remained significantly correlated to the frequency of *BRCA1* mutations (p=0.009). Age at breast cancer diagnosis and age at ovarian cancer diagnosis were significantly correlated to each other (p<0.0001).

Bilateral breast cancer

In 17 of the observed cases of ovarian cancer, the women had metachronous breast cancer. Seven of these cases had a *BRCA1* gene mutation (42.2%, 95% CI 18.4–67.1). Among 142 women with unilateral breast cancer, 26 mutations were detected (18.3%, 95% CI 12.3–25.7). The correlation between bilateral breast cancer and the detection of a *BRCA1* gene mutation was statistically significant (p=0.03).

First-degree relatives with breast and/or ovarian cancer

Information about first-degree relatives was retrieved for 106 individuals. Thirteen of 20 women with at least one first-degree relative with breast and/or ovarian cancer had *BRCA1* mutations (65%, 95% CI 40.1–84.6). Among the remaining 86 women, 12 mutations were found, (14.0% 95% CI 7.4–23.1%). The difference between these two groups was significant (p<0.0001). In 53 women, no first-degree relative had been recorded and eight of these had a mutation, (15% 95% CI 6.7–27.6).

Frequency of the studied mutations in the clinical setting

In 1995–2008, 138 families (286 individuals) were diagnosed with mutations of the *BRCA1* (n=123, 89%) or *BRCA2* genes (15, 11%) at the Regional Cancer Genetic Counselling Unit. In all, 85 (61.6%, CI95% 52.9–69.7) of the families and 190 of the individuals (66.2%, CI95% 60.4–71.7) had one of the six studied gene mutations. The most commonly found mutation was *BRCA1* 3171ins5, which was found in 62 families (44.9%, CI95% 36.5–53.6) and in 156 cases (54.6%, CI95% 48.6–60.4).

To which extent does BRCA1 3171ins5 account for the excess of ovarian cancer after breast cancer in the Western Swedish Health Care Region compared with the rest of Sweden?

Among 33 women with a proven mutation of *BRCA1*, 28 (85%, CI95% 68.1–94.9) carried the western Swedish founder mutation, *BRCA1* 3171ins5. This mutation was present in 17.6% of all 159 cases with ovarian cancer, corresponding to 44.3% of the excess number.

In the previously mentioned population study of women born in 1920 and later, the SIR was 2.0 (95% CI 1.3–2.9) for the city of Gothenburg and 2.7 (95% CI 2.0–3.5) for the rest of the region [2]. The combined SIR for the total region was 2.4 (95% CI 1.9–3.0). In the present study, there were 12 570 women who were born after 1919 and who were followed up for 97 440 person-years. Among these, 88 cases of ovarian carcinoma occurred, where as 39.9 were

expected (SIR 2.2, 95% CI 1.8–2.7). In that group, 22 *BRCA1* 3171ins5 mutation carriers were detected. If this number was subtracted from the number of observed cases, the SIR would be reduced to 1.7 (95% CI 1.3–2.1) for the region, which is similar to that for the entire Swedish population [2].

Discussion

Ovarian cancer after a breast cancer diagnosis is rare. In the present study 159 ovarian cancers (0.6%) were found in the follow-up of more than 26 000 women with breast cancer. In a Swedish population study of women born after 1920 who have had breast cancer, we found 321 such cases [2]. As 11 231 women were diagnosed with ovarian cancer during the same period only 2.8% of them had had a previous breast cancer. Among 161 consecutive patients with ovarian cancer selected for mutation screening of *BRCA1/2* mutations in the Southern Swedish Health Care Region, only three reported previous breast cancer (1.9%) [16] and, in a similar yet larger study of invasive or borderline ovarian cancer in Ontario, 30 (4.6%) had previous breast cancer [17]. However in familiar breast and ovarian cancer syndrome, these two diseases are common in the same woman [1]. Among the first 16 families diagnosed with the western Swedish founder mutation, *BRCA1* 3171ins5, there were 25 cases of ovarian cancer, nine of whom (36%) also had had breast cancer [11]. Population studies based on material from the Swedish Cancer Registry have shown that breast cancer patients during follow-up run an increased risk of ovarian carcinoma compared with the general population risk [2,3]. The risk is highest for young women and for women with a family history of breast or ovarian cancer, especially if they are less than 50 years of age at their diagnoses. This supports the hypothesis that the increased incidence is largely caused by hereditary factors, such as mutations in the *BRCA1* or *BRCA2* genes, and numerous studies have also confirmed the age-dependency of breast and ovarian cancer risks (For a review see Antoniou et al. 2003 [18]. In our population study, we found that the SIRS varied geographically from 1.0 (95% CI 0.6–1.6) to 2.7 (95% CI 2.0–3.4) between regions. The excess of ovarian cancer after breast cancer was highest in the southern parts of Sweden and especially in the Western Swedish Health Care Region [2]. The clinical experience from the regional cancer genetic counselling units suggests that the excess may coincide with the specific founder mutation in this region. The present study is an attempt to evaluate quantitatively the mutation frequency in the western region in relation to the excess of ovarian cancer after a breast cancer diagnosis.

The present study was based on cases of ovarian carcinoma from a follow-up in the Cancer Register of more than 26 000 breast cancer patients from the Western Swedish Health Care Region. National population risk figures for ovarian cancer applied to this material indicated that 96 cases of ovarian cancer would have been expected during the follow-up, while 159 were actually found, giving an excess number of cases of 63 (about 40%, Tables I, II).

As only paraffin tissue material was available, the mutation analysis was limited to six *BRCA1* and one *BRCA2* mutations [9]. These mutations account for 62% of the families with confirmed *BRCA1*/2 gene mutations at the Regional Cancer Genetic Counselling Unit. We found that 33 women carried a *BRCA1* gene mutation (21% of all cases or 52% of the excess number). There was a similar frequency of verified mutations by excess number over the age groups (Table II). The decreasing frequency by age in the observed cases appears to be due to a dilution by the increasing number of incidentally occurring ovarian cancer cases with increasing age at follow-up. If the distribution of the studied mutations were the same in this material as in the clinical setting, *BRCA1*/2 gene mutations may account for 80–85% of the excess of ovarian cancer cases after breast cancer. These mutations are therefore likely to explain almost all the excess.

The number of mutations was slightly underestimated, as no material was obtained for mutation analysis in three cases and one or more of the studied mutations were inconclusive in 36 cases due to the poor quality of the extracted DNA [9]. However the expected (i.e. *BRCA1* gene mutation negative) number of ovarian cancer cases may be slightly overestimated. The ovarian cancer risk tables were based on all cases of ovarian cancer, also including to an unknown extent cases with the *BRCA1*/2 gene mutation-associated cancer. No study has been made of the frequency of these mutations in ovarian cancer in the western Swedish region. In the vicinity of this region, there are two population-based studies of *BRCA1*/2 mutations in ovarian cancer. In a Norwegian study, two dominant founder mutations, including *BRCA1* 1135insA were analysed and found in 3% of all ovarian cancer cases [15]. In the Southern Swedish Health Care Region, 13 of 161 or 8% of ovarian cancer patients were found to carry deleterious *BRCA1* and *2* gene mutations [16]. Three of the analysed *BRCA1* mutations in our study (*BRCA1* 1201del11, 1806 C>T, 3171ins5) were found in five of the 13 cases. The comparison of ovarian cancer after breast cancer between the Swedish health care regions suggests that the frequency of *BRCA1* and *BRCA2* gene mutations is probably only slightly lower in the southern region

compared with the western Swedish region [2]. To reduce the influence of *BRCA*-gene-associated ovarian cancer in the calculation of the excess numbers, we therefore used national rather than regional ovarian cancer risk tables. Another possible cause of overestimation in the expected number of ovarian cancer cases may be explained by oophorectomies in this population. It is, however, not known how often an oophorectomy was performed as a treatment for breast cancer or for other reasons in this breast cancer cohort.

Bilateral breast cancer, a first-degree relative with breast and/or ovarian cancer, young age at breast cancer diagnosis and young age at follow-up were all significantly correlated to a high frequency of *BRCA1* mutations.

The most common mutation was the western Swedish founder *BRCA1* 3171ins5 which was detected in 28 (85%) of the mutation carriers and in approximately 18% of all observed cases. This corresponds to 44% of the excess cases. In our previous study of the excess of ovarian cancer after breast cancer in the Swedish health care region, the Western Swedish Health Care Region had the highest excess in the country [2]. The present study indicates that the excess of ovarian cancer after breast cancer in the region, above the national mean, could be explained by the number of individuals carrying this founder mutation.

We conclude that ovarian cancer detected after breast cancer is rare. The founder mutation, *BRCA1* 3171ins5, appears to explain the excess of ovarian cancer after breast cancer in the western Swedish region compared with the rest of the country [2]. It can be estimated from our study that *BRCA1* or *BRCA2* gene mutations are associated with approximately 80–85% of the excess cases. This means that a negative screening for mutations in these genes in a woman with both breast and ovarian cancer also has a predictive value and reduces the risk of ovarian cancer in relatives. This appears to be compatible with a recent publication from Ontario indicating no excess of ovarian cancer during the follow-up of non-affected members of *BRCA1*- and *BRCA2*-negative breast or ovarian cancer families [19], which, if this is verified in further studies, increases the predictive value of negative testing for *BRCA1* or *BRCA2* mutations. In the counselling situation the decision whether or not to screen for a mutation, it is important to consider both young age at the second cancer diagnosis and other contributory factors, the most important of which is a family history of confirmed cancers. A known geographical or ethnic origin of the family, such as the western Swedish region where a specific mutation is prevalent, may also be of importance.

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