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# The incidence of leukaemia in women with *BRCA1* and *BRCA2* mutations: an International Prospective Cohort Study

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**Background:** Germline mutations in *BRCA1* and *BRCA2* increase the susceptibility to develop breast and ovarian cancers as well as increase the risk of some other cancers. Primary objective was to estimate the risk of leukaemia in *BRCA1* and *BRCA2* mutation carriers.

**Methods:** We followed 7243 women with a *BRCA1* or a *BRCA2* mutation for incident cases of leukaemia. We used the standardised incidence ratio (SIR) to estimate the relative risk of leukaemia, according to mutation and history of breast cancer.

**Results:** We identified five incident cases of leukaemia (two *BRCA1*, three *BRCA2*). All five women had a prior history of breast cancer and four had received chemotherapy. The mean time from breast cancer diagnosis to the development of leukaemia was 10.2 years (range 3–18 years). The SIR for *BRCA1* carriers was 0.66 (95% CI: 0.11–2.19, $P=0.61$) and the SIR for *BRCA2* carriers was 2.42 (95% CI: 0.61–6.58, $P=0.17$). The SIR was significantly higher than expected for women with a *BRCA2* mutation and breast cancer (SIR = 4.76, 95% CI:1.21–12.96, $P=0.03$), in particular for women who received chemotherapy (SIR = 8.11, 2.06–22.07, $P=0.007$).

**Conclusions:** We observed an increased risk of leukaemia in women with a *BRCA2* mutation who receive chemotherapy for breast cancer.

Germline mutations in the *BRCA1* and the *BRCA2* genes increase the susceptibility for a woman to develop breast and ovarian cancer (Miki *et al*, 1994; Wooster *et al*, 1995). Women with an inherited mutation in the *BRCA1* or the *BRCA2* gene have a life-time risk of ~70% of developing breast cancer (Claus *et al*, 1996; Ford *et al*, 1998; Antoniou *et al*, 2003; Chen and Parmigiani, 2007; Mavaddat *et al*, 2013). Reports from the Breast Cancer Linkage Consortium suggested that women with *BRCA1* and *BRCA2* mutations have elevated risk of cancers other than breast and ovarian cancers (The Breast Cancer Linkage Consortium, 1999; Thompson *et al*, 2002). However, it is not clear to what extent a mutation in *BRCA* genes affects the risk of leukaemia.

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Cytotoxic chemotherapy for breast cancer is known to increase the risk of therapy-related myeloid neoplasms (Swerdlow *et al*, 2008). Chemotherapy-related myeloid neoplasms constitute up to 20% of all acute myeloid leukaemias and myelodysplastic syndromes (Morton *et al*, 2013). The National Surgical Adjuvant Breast and Bowel Project trials suggest that the use of an intense dose cytotoxic chemotherapy (such as adriamycin and cyclophosphamide), and radiation therapy for breast cancer is associated with a higher incidence of acute myeloid leukaemias, and myelodysplastic syndrome (Smith, 2003).

Most women who develop a *BRCA1*- or a *BRCA2*-associated breast cancer are likely to receive chemotherapy and radiation therapy. It is hypothesised that faulty mechanisms, such as altered cellular signalling, enhanced proliferation, diminished apoptosis, and abnormal differentiation increase the risk of chemotherapy-related leukaemias and myelodysplastic syndromes in patients with the *BRCA*-associated breast cancer (Friedenson, 2007). Some case reports have suggested that mutations in *BRCA1* or the *BRCA2* gene might add to the risk of developing leukaemia in patients who receive chemotherapy and radiation therapy for their breast cancer (Fruscalzo *et al*, 2006; Cole and Strair, 2010). However, there are no prospective data on the subject.

We have previously reported on the incidence of pancreatic cancer, endometrial cancer, and colorectal cancer in *BRCA* mutation carriers (Iqbal *et al*, 2012; Segev *et al*, 2013; Phelan *et al*, 2014). Here we report the incidence of leukaemia in a prospective cohort of *BRCA1* and the *BRCA2* mutation carriers, and also estimate the incidence of leukaemia in women with a *BRCA* mutation who were treated with chemotherapy for breast cancer.

## MATERIALS AND METHODS

**Study cohort.** We identified a total of 12 310 women with a *BRCA1* or *BRCA2* mutation through a registry of mutation carriers at the Women's College Research Institute, Toronto. The registry collects data from women who have a known pathogenic *BRCA1* or *BRCA2* mutation at 50 different centres in 11 countries in North America and Europe. The study protocol was approved by Ethics Committees/Human Subjects Review Boards of all participating centres. We obtained informed consent from all women before genetic testing. Mutation detection was confirmed by the direct sequencing of DNA.

Women were eligible for study entry if they were 25–74 years of age, and had a mutation in either the *BRCA1* or the *BRCA2* gene. All *BRCA* carrier women had completed a risk assessment questionnaire at study entry and a follow-up questionnaire every 2 years thereafter. The questionnaires collected information on all new cancers diagnosed including site of cancer and age of diagnosis. At some centres, the questionnaires were completed by telephone interview. The eligible women completed at least one follow-up questionnaire. The diagnosis of leukaemia was confirmed by reference to a pathology report or medical record in all cases.

We excluded women who were $<25$ years ($n=454$; 3.0%) and $>75$ years of age ($n=107$; 0.71%) at baseline, who had no date of birth recorded ($n=5$; 0.03%), who had not completed a follow-up questionnaire ($n=3{,}434$; 22.9%), who were lost to follow-up ($n=986$; 6.6%), and who had a missing date of death ($n=81$; 0.54), leaving 7243 women who were confirmed carriers eligible for study entry. We followed all women from the date of study entry (baseline) until either: 1) the date of completion of the last follow-up questionnaire, 2) diagnosis of leukaemia, and 3) death from any cause. Table 1 describes characteristics of study cohort.

**Incidence and standardised incidence ratios.** We estimated the incidence of leukaemia by dividing the total number of new leukaemia cases by the total person-years of follow-up. The incidence was calculated as rate per 100 000 women per year. We calculated the risk of developing leukaemia in the *BRCA1* and the *BRCA2* mutation carriers relative to general population by calculating standardised incidence ratios (SIR). We calculated the SIRs in the following steps. First, we obtained incidence rates of leukaemia for each participating country using GLOBCAN 2012 (Ferlay *et al*, 2013). The incidence rates were calculated for each 5-year age bins ($<40$, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74). Second, we calculated the number of person-years for each age bin in our carrier database. We then calculated the expected number of leukaemia cases for each age bin by multiplying incidence rate of leukaemia with person-years divided by 100 000. The SIRs were calculated as the ratio of observed cancers to expected cancers. The SIRs were calculated according to the type of *BRCA* mutation (*BRCA1*, *BRCA2*, combined), country of residence (Canada, Italy, Poland, and the United States), age groups ($<50$ years, $\geqslant 50$ years), breast cancer status (yes/no), and chemotherapy (yes/no) for breast cancer.

## RESULTS

After a mean follow-up time of 6.1 years (range 1.0–19.5 years), five women (two *BRCA1*, three *BRCA2*) were diagnosed with

**Table 1. Baseline characteristics of study cohort**

| Characteristic | All women N = 7243 | *BRCA1* N = 5397 | *BRCA2* N = 1790 | Other[a] N = 56 |
|---|---|---|---|---|
| **Age, years** | | | | |
| Mean (min, max) | 47.0 (25–74.9) | 46.2 (25–74.9) | 49.4 (25–74.9) | 48.3 (28–73) |
| **Breast cancer** | | | | |
| Yes | 3200 | 2353 | 813 | 34 |
| No | 4040 | 3042 | 976 | 22 |
| Not known | 3 | 2 | 1 | 0 |
| **Chemotherapy[b]** | | | | |
| Yes | 2346 | 1776 | 540 | 30 |
| No | 788 | 544 | 241 | 3 |
| Not known | 66 | 33 | 32 | 1 |
| **Country** | | | | |
| Canada | 2255 | 1229 | 994 | 32 |
| Italy | 103 | 84 | 19 | 0 |
| USA | 2185 | 1414 | 749 | 22 |
| Poland | 2700 | 2670 | 28 | 2 |

[a]Other category includes women who were confirmed carriers of either *BRCA* mutation, but the type of *BRACA* mutation (*BRCA1* or *BRCA2*) was not known.
[b]Analysis is restricted to women who developed breast cancer ($n=3200$).

leukaemia. Table 2 presents characteristics of incident cases of leukaemia. Three women (one *BRCA1*, two *BRCA2*) were diagnosed with acute myeloid leukaemia and one woman (*BRCA2*) developed chronic lymphocytic leukaemia; one women (*BRCA1*) developed acute leukaemia but the subtype of leukaemia could not be determined. The mean age at diagnosis of leukaemia was 53.4 years. The mean age was 43 years for *BRCA1* mutation carriers and was 60.3 years for *BRCA2* mutation carriers.

All five leukaemia patients had previous history of breast cancer. The mean age at the diagnosis of breast cancer was 43.2 years (*BRCA1* = 34.5 years, *BRCA2* = 49.0 years). Four women (one *BRCA1*, three *BRCA2*) received chemotherapy for their breast cancer. The *BRCA1* mutation carrier who received chemotherapy for breast cancer developed acute myeloid leukaemia 3 years after initial treatment for breast cancer. Of three *BRCA2* mutation carriers, two developed acute myeloid leukaemia after 18 and 10 years, and one patient developed chronic lymphocytic leukaemia 6 years after the treatment for breast cancer.

Overall, five cases of leukaemia were observed *vs* 4.3 cases expected (SIR = 1.16, 95% CI: 0.43–2.58, $P = 0.69$). Among the entire cohort, the incidence of leukaemia was 11.3 per 100 000 women per year. Two incident leukaemia cases were observed among the *BRCA1* carriers *vs* 3.02 cases expected (SIR = 0.66, 95% CI: 0.11–2.19, $P = 0.61$) (Table 3). For *BRCA2* carriers, three leukaemia cases were observed *vs* 1.24 cases expected (SIR = 2.42, 95% CI: 0.61–6.58, $P = 0.17$). Among *BRCA2* mutation carriers the incidence rate of leukaemia was 27.1 per 100 000 women per year. Compared to the general population, the risk of leukaemia was higher for women <50 years (SIR = 2.30, 95% CI: 0.38–7.59, $P = 0.27$); the risk was lower for women 50 years and above (SIR = 0.87, 95% CI: 0.22–2.38, $P = 0.88$). However, the absolute difference in the annual risk of leukaemia was statistically not significant between the two age groups ($P = 0.77$).

Compared to general population, the risk of leukaemia was five-fold higher for women who had a prior *BRCA2*-associated breast cancer (SIR = 4.76, 95% CI: 1.21–12.96, $P = 0.03$), but was not significantly higher for women with *BRCA1*-associated breast cancer (Table 4). Among all women with *BRCA*-associated breast cancer who received chemotherapy, four cases of leukaemia were observed *vs* 1.4 cases expected (SIR = 2.86, 95% CI: 0.91–6.89,

**Table 2. Characteristics of incidence cases of leukaemia in *BRCA* carriers**

| Case no. | Age at breast cancer diagnosis | Treatment of breast cancer | Age at leukaemia diagnosis | Subtype of leukaemia | *BRCA* mutation | Mutation description | Status | Country |
|---|---|---|---|---|---|---|---|---|
| 1 | 35 | No treatment | 49 | Acute leukaemia[a] | *BRCA1* | Exon 11 3913delA | Dead | Italy |
| 2 | 34 | Surgery Chemotherapy | 37 | Acute myeloid leukaemia (M3) | *BRCA1* | Exon 12 Q1395X | Alive | Canada |
| 3 | 52 | Surgery Chemotherapy Tamoxifen | 70 | Acute myeloid leukaemia | *BRCA2* | Exon 11 6024delTA | Dead | Italy |
| 4 | 50 | Surgery Chemotherapy Radiation Tamoxifen Letrozole | 60 | Acute myeloid leukaemia | *BRCA2* | Exon 11 3772delTT | Alive | Canada |
| 5 | 45 | Surgery Chemotherapy Tamoxifen | 51 | Chronic lymphocytic leukaemia | *BRCA2* | IVS24–18C>A | Alive | USA |

Acute myeloid leukaemia, M3 is the acute promyelocytic leukaemia.
[a]The subtype of acute leukaemia is not known for this patient.

**Table 3. Observed and expected number of leukaemia cases in *BRCA1* and *BRCA2* carriers according to country of origin**

| Country | *BRCA* status | *N* | Person-years | Observed cancers | Expected cancers | Incidence (per 100 000 women) | SIR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|---|
| All combined | All | 7243 | 44255.18 | 5 | 4.3 | 11.3 | 1.16 (0.43–2.58) | 0.69 |
| | *BRCA1* | 5397 | 32864.14 | 2 | 3.02 | 6.1 | 0.66 (0.11–2.19) | 0.61 |
| | *BRCA2* | 1790 | 11074.09 | 3 | 1.24 | 27.1 | 2.42 (0.61–6.58) | 0.17 |
| Canada | All | 2255 | 16431.59 | 2 | 2.02 | 12.2 | 0.99 (0.17–3.27) | 0.98 |
| | *BRCA1* | 1229 | 9211.06 | 1 | 1.05 | 10.8 | 0.95 (0.02–5.31) | 0.56 |
| | *BRCA2* | 994 | 7010.24 | 1 | 0.95 | 14.3 | 1.05 (0.05–5.19) | 0.86 |
| Italy | All | 103 | 463.32 | 2 | 0.04 | 431.7 | 50 (8.38–165.2) | 0.0007 |
| | *BRCA1* | 84 | 348.18 | 1 | 0.03 | 287.2 | 33.3 (1.67–164.4) | 0.03 |
| | *BRCA2* | 19 | 115.14 | 1 | 0.01 | 868.5 | 100 (5.0–493.2) | 0.01 |
| USA | All | 2185 | 12343.86 | 1 | 1.30 | 8.1 | 0.77 (0.04–3.79) | 0.9 |
| | *BRCA1* | 1414 | 8379.13 | 0 | 0.87 | 0 | — | — |
| | *BRCA2* | 749 | 3862.16 | 1 | 0.43 | 25.9 | 2.33 (0.12–11.47) | 0.42 |
| Poland | All | 2700 | 15016.41 | 0 | 0.84 | — | — | — |
| | *BRCA1* | 2670 | 14925.77 | 0 | 0.84 | — | — | — |
| | *BRCA2* | 28 | 86.56 | 0 | 0.006 | — | — | — |

Abbreviations: CI, confidence interval; SIR, standardised incidence ratio.

$P = 0.07$). Among women who did not receive chemotherapy, one case of leukaemia was observed *vs* 0.83 cases expected (SIR = 1.20, 95% CI: 0.06–5.94, $P = 0.76$) (Table 4).

The risk of leukaemia was eight-fold higher for women who received chemotherapy for a *BRCA2*-associated breast cancer (SIR = 8.11, 95% CI: 2.06–22.07, $P = 0.007$) (Table 5). For *BRCA1* mutation carriers who received chemotherapy for breast cancer, the risk of leukaemia was similar to the risk in the general population (SIR = 0.97, 95% CI: 0.05–4.79, $P = 1.01$). The absolute risk of leukaemia for women who received chemotherapy for breast cancer was 0.06% (1 of 1776 women) for the *BRCA1* carriers and was 0.55% (3 of 540 women) for the *BRCA2* carriers.

## DISCUSSION

Women who carry a mutation in *BRCA* genes are concerned about their risk of developing cancers other than breast and ovarian cancers. In this prospective study of the *BRCA* mutation carriers, we observed a two-fold increase in the risk of leukaemia among carriers of a *BRCA2* mutation, compared to the risk in general population. The increased risk of leukaemia was statistically significant if a *BRCA2* mutation carrier had breast cancer (SIR = 4.69, $P = 0.03$), and had received chemotherapy (SIR = 8.11, $P = 0.007$).

The risk of leukaemia in the *BRCA1* and the *BRCA2* mutation carriers was first reported in the earlier studies of the Breast Cancer Linkage Consortium (The Breast Cancer Linkage Consortium, 1999; Thompson *et al*, 2002). In their first study, the Breast Cancer Linkage Consortium estimated the risk of leukaemia among the probable carriers of a *BRCA2* mutation, relative to non-carriers, and subjects with an unknown mutation status (The Breast Cancer Linkage Consortium, 1999). The relative risk of leukaemia in probable carriers of the *BRCA2* mutation was 1.12 (95% CI: 0.30–4.25). The risk of leukaemia was relatively lower in the *BRCA1* mutation carriers, compared to non-carriers and untested women (relative risk = 0.88, 95% CI: 0.37–2.14) (Thompson *et al*, 2002). Relative risks reported in studies of the Breast Cancer Linkage Consortium were based on the review of family histories, and diagnosis of leukaemia was based on the information provided by a family member. In comparison, our estimates are based on a prospective follow-up of women with a known *BRCA* mutation status.

Two case reports suggest that carriers of a *BRCA2* mutation who receive treatment for breast cancer might be at a higher risk of developing haematologic malignancies, in particular, leukaemias (Friedenson, 2007; Cole and Strair, 2010). Fruscalzo *et al* (2006) reported of a patient who developed chronic lymphocytic leukaemia 2 years after receiving chemotherapy for the *BRCA2*-associated breast cancer. In another case-series, Cole and Strair (2010) reported on six patients who developed either acute myelogenous leukaemia or myelodysplasia after receiving treatment for breast cancer. Three of six (50%) patients in this case-series had a mutation of one of the *BRCA* genes (*BRCA1* or *BRCA2*), and all of them received adriamycin and cyclophosphamide-based chemotherapy for their breast cancer. Hall *et al* (2006) reported acute myelogenous leukaemia in three Hispanic *BRCA2* carriers who did not receive chemotherapy or radiation therapy for early-stage breast cancers.

The actual risk of leukaemia in our *BRCA* cohort was <1%. One potential reason why the impact of *BRCA* mutations on leukaemia incidence might be less than that for breast and ovarian cancer susceptibility could be that the self-renewal potential of leukaemic cells is dependent on genome stability, which is compromised when there is a *BRCA* mutation (Santos *et al*, 2014).

Our results are based on the prospective follow-up of the largest cohort of women who are confirmed carriers of a *BRCA* mutation, and with two-yearly follow-up of all women.

Our results should be interpreted with caution. Our *BRCA* cohort included only women and therefore we cannot estimate the incidence of leukaemia in male carriers of a *BRCA* mutation. Moreover, the number of incidence cases was relatively small in our study which limits the precision of risk estimates for subgroups. Furthermore, missing follow-up information for nearly 30% women could potentially bias our estimates.

In conclusion, our findings suggest that women with a *BRCA2*-associated breast cancer might be at a higher risk of developing leukaemia; in particular if these women receive chemotherapy for

**Table 4. Observed and expected number of leukaemia in *BRCA* carriers according breast cancer status**

| *BRCA* status | Breast cancer | *N* | Person-years | Observed cancers | Expected cancers | Incidence rate per 100 000 per year | SIR 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|---|
| All | No | 4040 | 24628.12 | 0 | 2.03 | — | — | — |
| | Yes | 3200 | 19617.74 | 5 | 2.26 | 25.5 | 2.21 (0.81–4.90) | 0.11 |
| *BRCA1* | No | 3042 | 18483.11 | 0 | 1.42 | — | — | — |
| | Yes | 2353 | 14376.04 | 2 | 1.60 | 13.9 | 1.25 (0.21–4.13) | 0.69 |
| *BRCA2* | No | 976 | 6027.48 | 0 | 0.60 | — | — | — |
| | Yes | 813 | 5042.28 | 3 | 0.64 | 59.5 | 4.69 (1.19–12.76) | 0.03 |

Abbreviations: CI, confidence interval; SIR, standardised incidence ratio.

**Table 5. Observed and expected number of leukaemia in *BRCA-associated* breast cancer patients according to chemotherapy**

| *BRCA* status | Chemotherapy | *N* | Person-years | Observed cancers | Expected cancers | Incidence rate per 100 000 per year | SIR 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|---|
| All | No | 788 | 5257.98 | 1 | 0.83 | 19.0 | 1.20 (0.06–5.94) | 0.76 |
| | Yes | 2,346 | 14107.09 | 4 | 1.40 | 28.3 | 2.86 (0.91–6.89) | 0.07 |
| *BRCA1* | No | 544 | 3582.22 | 1 | 0.56 | 27.9 | 1.79 (0.09–8.81) | 0.54 |
| | Yes | 1,776 | 10674.21 | 1 | 1.03 | 9.4 | 0.97 (0.02–5.41) | 0.55 |
| *BRCA2* | No | 241 | 1662.88 | 0 | 0.27 | — | — | — |
| | Yes | 540 | 3350.50 | 3 | 0.37 | 89.5 | 8.11 (2.06–22.07) | 0.007 |

Abbreviations: CI, confidence interval; SIR, standardised incidence ratio.

breast cancer. However, given a very low actual risk, we suggest that the risk of leukaemia in the *BRCA* mutation carriers should not influence the choice of chemotherapy to treat their breast cancer.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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