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BRCA1 and BRCA2 families and the risk of skin cancer

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Abstract BRCA1 and BRCA2 mutation carriers have elevated risks of breast and ovarian cancers. The risks for cancers at other sites remain unclear. Melanoma has been associated with BRCA2 mutations in some studies, however, few surveys have included non-melanoma skin cancer. We followed 2729 women with a BRCA1 or BRCA2 mutation for an average of 5.0 years. These women were asked to report new cases of cancer diagnosed in themselves or in their family. The risks of skin cancer were compared for probands with BRCA1 and BRCA2 mutations. Of 1779 women with a BRCA1 mutation, 29 developed skin cancer in the follow-up period (1.6%). Of the 950 women with a BRCA2 mutation, 28 developed skin cancer (3.0%) (OR = 1.83 for BRCA2 versus BRCA1; 95% CI 1.08–3.10; $P = 0.02$). The odds ratio for basal cell carcinoma was higher (OR = 3.8; 95% CI 1.5–9.4; $P = 0.002$). BRCA2 mutation carriers are at increased risk for skin cancer, compared with BRCA1 carriers, in particular for basal cell carcinoma.

Keywords Skin cancer · BRCA1 · BRCA2 · Melanoma · Cohort study

Introduction

Women with a BRCA1 or BRCA2 mutation have an elevated risk of breast and ovarian cancer. Many studies describe the spectrum of other cancers seen in families with mutations in BRCA1 and BRCA2 genes [1–29]; however the range of cancers and the magnitude of the associated risks is not completely clear [30–40]. Cutaneous melanoma has been associated with mutations in the BRCA2 gene [2].

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Whereas a few reports include non-melanoma skin cancer among the many tumours evaluated, the risks of these cancers, which include basal cell carcinoma and the less common cutaneous squamous cell carcinoma, have not been specifically studied in BRCA1 and BRCA2 families [5, 7, 41]. To some extent, this may be due to the general under-reporting (or lack of inclusion) of non-melanoma skin cancers in most cancer registries. We identified pedigrees in which at least one new case of skin cancer (basal cell, melanoma, or 'skin' unspecified) was reported in a follow-up study of families enrolled in a large database of BRCA1 and BRCA2 carriers.

Methods

Pedigrees were selected from a database of BRCA-positive families housed at the Women's College Research Institute, Toronto. Families were referred for genetic counselling and BRCA1/2 genetic testing to participating familial oncology programs in North America, Europe and Israel, between 1995 and 2007. All germline DNA samples from the probands had been previously screened for BRCA1 and BRCA2 mutations using a range of techniques, including the protein truncating test (PTT) DHPLC, DGGE and direct sequencing and were found to carry a germ-line pathogenic BRCA1 or BRCA2 mutation. All patients provided signed informed consent. The protocol was approved by the Research Ethics Board of the Women's College Research Institute at the University of Toronto.

We included 2,729 women for whom a baseline questionnaire and one or more follow-up questionnaires was available (1,779 BRCA1, 950 BRCA2). Women were asked in the baseline questionnaire if they had ever been diagnosed with skin cancer. These women were asked to complete a follow-up questionnaire every 2 years. The women were followed on average for 5.0 years (range 0–13.6 years). In the follow-up questionnaire, the women were asked about new cancer diagnoses.

These 2,729 women represented 1,796 different families; for 1,606 of these families (89%) follow-up information was available for new cancer diagnoses in relatives. In the follow-up questionnaire, women were asked to list all new diagnoses of cancer in family members. Pedigrees were classified as "skin cancer positive" if the proband reported at least one case in a relative with cutaneous basal call skin cancer, melanoma or "skin cancer—not otherwise specified." Pedigrees with no reported case of skin cancer were classified as "skin cancer negative." The study subjects were asked an open-ended question regarding the cancer diagnoses. Subjects typically reported on melanoma, basal cell cancer, 'skin cancer', but rarely squamous cell carcinomas. Therefore, the categories of skin cancer subtypes were based on these reports and not on the conventional histologic categories.

Statistical analysis

The data was analysed in three ways; first, with respect to past diagnoses of skin cancer in the probands; second, with respect to new diagnoses of skin cancer in the probands, and third; with respect to new diagnoses in other family members. For the first two analyses, the proportions of probands with and without skin cancer were compared using the chi-squared statistic. The frequency of skin cancer-positive probands among BRCA1 probands was compared with the frequency among BRCA2 probands. The frequency of skin cancer-positive families among BRCA1 families was compared with that of BRCA2 families. Odds ratios were estimated for each category of skin cancer, based on BRCA2 versus BRCA1 status.

Results

A past history of any skin cancer (i.e. prior to baseline questionnaire) was reported by 4.1% of the BRCA2 carriers and by 3.6% of the BRCA1 carriers. This category includes basal cell carcinoma, 'skin' cancer (not specified) and melanoma (Table 1). After a mean of 5.0 years, 3.0% of the BRCA2 carriers and 1.6% of the BRCA1 carriers reported a new diagnosis of any skin cancer in themselves ($P = 0.02$). The odds ratios for past cancers and for new cancers, for BRCA2 carriers versus BRCA1 carriers, are presented in Table 1. Women with a BRCA2 mutation were approximately four times more likely to develop basal cell carcinoma in the follow-up period than were women with a BRCA1 mutation (OR = 3.8; 95% CI 1.5–9.4; $P = 0.002$).

Table 2 describes the number of probands reporting one or more of basal cell carcinomas, 'skin' cancer and melanoma in their families. Women with a BRCA1 mutation were followed on average for 5.0 years and women with a BRCA2 mutation were followed on average for 4.9 years. Of the 1013 BRCA1-positive probands, none reported a new case of basal cell carcinoma, 10 (1.0%) reported one new 'skin' cancer and 11 (1.1%) reported one new melanoma. Among 593 families with a BRCA2 mutation, 13 probands (2.2%) reported one or more new cases of 'skin' cancer and 3 (0.5%) probands reported one or more new cases with melanoma. Probands from families with a BRCA2 mutation were more likely to have reported at least one new case of 'skin' cancer than were probands from families with a BRCA1 mutation (OR = 2.3; 95% CI 1.0–5.2; $P = 0.05$), but not for melanoma (OR = 0.5; 95% CI 0.1–4.8; $P = 1.7$; $P = 0.23$).

Table 1 Skin cancers reported among women with BRCA1 and BRCA2 mutations

Cancer type	BRCA1 $N = 1779$	BRCA2 $N = 950$	OR (95% CI) P
Basal cell carcinoma			
At baseline	24 (1.35%)	20 (2.11%)	1.57 (0.86–2.86) 0.14
At follow-up	7 (0.39%)	14 (1.47%)	3.79 (1.52–9.41) 0.002
Either	31 (1.74%)	32 (3.37%)	1.97 (1.20–3.24) 0.007
Skin			
At baseline	31 (1.74%)	14 (1.47%)	0.84 (0.45–1.59) 0.60
At follow-up	16 (0.90%)	11 (1.16%)	1.29 (0.60–2.79) 0.52
Either	47 (2.64%)	25 (2.63%)	1.00 (0.61–1.63) 0.99
Melanoma			
At baseline	17 (0.96%)	10 (1.05%)	1.10 (0.50–2.42) 0.81
At follow-up	6 (0.34%)	4 (0.42%)	1.25 (0.35–4.44) 0.73
Either	23 (1.29%)	14 (1.47%)	1.14 (0.58–2.23) 0.70
Any skin			
At baseline	64 (3.6%)	39 (4.1%)	1.15 (0.76–1.72) 0.51
At follow-up	29 (1.63%)	28 (2.95%)	1.83 (1.08–3.10) 0.02
Either	92 (5.2%)	64 (6.7%)	1.32 (0.95–1.84) 0.09

One patient with a basal cell carcinoma at baseline developed another at follow-up.for the odds ratio, BRCA1 carriers for the reference group

Discussion

Cutaneous basal cell carcinoma is the most common cancer in North America, accounting for approximately one-half of all cancers reported. Age-standardized incidence rates for basal cell carcinoma in the United States are estimated to be 407 per 100,000 per year for white males and 212 per 100,000 per year for white women [42]. The age-adjusted incidence rates for melanoma are 29.1 per 100,000 per year for men and 16.0 per 100,000 per year for women [43]. In this report, we describe the occurrences of various categories of skin cancer among probands and relatives of probands with a BRCA1 or BRCA2 mutation. The women were enrolled in a large multi-center cohort study. We found that BRCA2 probands were approximately two times more likely to report any skin cancer in themselves than were probands with BRCA1 mutation in the five years of follow-up. Basal-cell skin cancer was four times more commonly reported among BRCA2 probands than among BRCA1 probands (there were few cases of basal cell carcinoma reported in the relatives of probands, this is likely because they were reported as 'skin' cancers). The frequency of melanoma was similar in BRCA2-positive probands and in BRCA1-positive probands.

The spectrum of cancers in BRCA1 and BRCA2 families has been widely studied [1–29, 40, 41, 44]. Cutaneous melanoma and cancers of the prostate, pancreas and bile duct have been reported to occur more often in families with BRCA2 than BRCA1 mutations [2, 8–10]. Melanoma has been studied in several earlier reports; in particular, ocular melanoma has also been associated with BRCA2 mutations [8, 45]. In 1999, the Breast Cancer Linkage Consortium reported a relative risk of 2.6 for melanoma among BRCA2 carriers, compared to the general population (95% CI: 1.3–5.2) [2]. However, a recent study from Israel failed to find a single carrier of an Ashkenazi founder mutation among 92 patients with melanoma, unselected for family history of cancer [46]. In 2007, Monerrat and colleagues reported on a series of 82 European patients with double primary breast cancer and melanoma, unselected for family history [47]. All subjects were tested for mutations in BRCA1 and BRCA2; one woman carried a BRCA2 mutation and two carried a BRCA1 mutation. In the present study, melanoma was not reported more frequently in BRCA2 carriers than in BRCA1 carriers.

There have been comparatively few studies of non-melanoma skin cancers in BRCA carriers. To our knowledge, ours is the first report which specifically compares the occurrences of non-melanoma skin cancer among BRCA1 and BRCA2 families. We found a statistically significant excess of basal cell carcinomas in BRCA2, versus BRCA1 probands (OR = 2.0; 95% CI 1.2–3.2; $P = 0.007$). We expect that this difference is due to an increased risk of basal cell cancers in BRCA2 carriers, compared to the general population, but it is also possible that this is a consequence of decreased risk among BRCA1 carriers. It is not clear what the basis is for the (presumed) increased risk of skin cancer in BRCA2 carriers, compared to BRCA1 carriers. The most common risk factor for skin cancer is ultraviolet (UV)—induced DNA damage, which is repaired predominantly by nucleotide excision repair. Squamous cell carcinomas of the skin often contain cyclobutane pyrimidine dimers and the removal of these

Table 2 New skin cancers reported among family members of BRCA1 and BRCA2-positive probands

Cancer type	BRCA1 $N = 1{,}013$	BRCA2 $N = 593$	OR (95% CI) P-value
Basal cell carcinoma N (%)	0	0	N/A
Skin cancer N (%)	10 (1.0%)	13 (2.2%)	2.25 (0.98–5.16) 0.05
Melanoma N (%)	11 (1.1%)	3 (0.5%)	0.46 (0.13–1.67) 0.23
Any skin N (%)	21 (2.1%)	15 (2.5%)	1.23 (0.63–2.40) 0.55

OR is based on BRCA1 carriers as reference group

dimers depends in part on an interaction between BRCA1 and P53 [48]. While no similar data currently exist for BRCA2, it would interesting to study this phenomenon in BRCA2-deficient model systems.

In 1999, Johannsson and colleagues [5] described the incidence of all malignancies among 1873 individuals from 29 BRCA1 and 20 BRCA2 families identified in Southern Sweden between 1958 and 1995 and compared the risks to the general population. In male BRCA1 carriers, an increased risk of squamous cell carcinoma of the skin was reported (SMR 6.02; 95% CI 1.96–14.05; $P = 0.002$). They did not find an increased risk for skin cancer among men or women from BRCA2 families. In 2003, the same team calculated cancer risks among a population-based set of 203 early-onset breast cancer patients with known BRCA mutation status [41]. They found no increased risk of non-melanoma skin cancer among first degree relatives of BRCA1 and BRCA2 mutation carriers. However, they reported a standardized incidence ratio of 2.8 (95% CI 1.0–6.1) for non-melanoma skin cancer among the relatives of women with early-onset breast cancer who were BRCA-negative.

There are several strengths of our study. This is a large cohort and the effects were statistically significant. We incorporated three independent measures of risk (past cancers, incident cancers, and familial cancers) and the results of the three analyses were concordant. The follow-up data on probands was not dependent on reporting of cancers by a relative and all probands were confirmed mutation carriers.

There are several limitations as well. We did not have pathologic confirmation on the type of skin cancers and this was based on proband reporting. Cancers in relatives were not verified and the mutation status of the relatives was unknown. In general, studies that rely on the patients reporting of cancers in relatives are vulnerable to misclassification and possibly recall bias. We compare the proportions of families in which at least one case of skin cancer was reported among BRCA1, versus BRCA2 mutations. Recall bias would be expected to occur to a similar extent among families with either mutation. It is possible that the recommendations for surveillance for skin cancer by by skin examination would have occurred to a greater extent in the BRCA2 families, compared to the BRCA1 families, given that conventionally, melanoma has been considered to be part of the BRCA2 cancer spectrum. Ideally, we would compare rates in BRCA carriers with rates in the general population, however, with this research design we were reluctant to compare rates with those collected through cancer registries. Many cancer registries do not record cases of non-melanoma skin cancer and it is therefore difficult to obtain accurate estimates of the underlying rates of skin cancer in the various countries. Therefore, we were limited in comparing incidence in BRCA2 versus BRCA1 carriers ratein. Another limitation of this report is the potential for underestimation of cases of skin cancer in relatives. Basal cell carcinomas were rarely reported in relatives and it is likely that the proband reported these as 'skin cancer'. The majority of skin cancers are not life-threatening, and occur predominantly among older individuals; they may not mention this history to young relatives who seek genetic counseling for familial breast and ovarian cancer.

We did not have information relating to other risk factors for skin cancer, such as exposure to UV-light, occupation, or the presence of pigmented lesions. If environmental exposure to UV light were to differ, on average, between BRCA1 and BRCA2 carriers, this might impact on the difference in skin cancer rates. However, all participating centers provided data on both BRCA1 and BRCA2 carriers, and the geographic distributions of the two genetic subgroups were similar.

In summary, this study suggests that there may be a higher risk of non-melanoma skin cancer in BRCA2, versus BRCA1 carriers. This observation may be due to a higher than expected risk among BRCA2 carriers, or to a lower than expected risk among BRCA1 carriers. The best estimates of the risks of these and other cancers may be determined by long-term follow up of large BRCA1 and BRCA2 cohorts such as ours. We recommend limiting sun exposure as an important preventive measure against all types of skin cancer. Screening by periodic skin examination is also advised. Molecular studies which investigate the possible role of BRCA2 in the repair of UV-induced DNA damage are warranted.

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