LETTER TO JMG

Cancer risks in carriers of the *BRCA1/2* Ashkenazi founder mutations

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Background: The risks for cancers other than breast (BC) or ovarian (OC) cancer in breast cancer gene 1 and 2 (*BRCA1/2*) mutation carriers were elevated in studies of carrier families. However, case-control studies did not confirm this observation.

Objective: To compare the risks for other cancers in *BRCA1/2* mutation carriers and non-carriers, all affected with BC and/or OC. Both groups share risk modifiers of BC/OC, which enabled assessment of the role of *BRCA1/2* mutations.

Methods: 1098 Ashkenazi Jewish women affected with BC and/or OC were ascertained during 1995–2003; molecular testing revealed 229 *BRCA1* and 100 *BRCA2* carriers and 769 non-carriers. COX proportional hazard models were used to evaluate the risk of other cancers. Analyses were conducted including all other cancers or only those diagnosed after BC/OC diagnosis.

Results: The HRs for any other cancer were 2.6 (95% CI 1.7 to 4.2, $p < 0.001$) and 1.8 (95% CI 0.95 to 3.6, $p = 0.07$) in *BRCA1* and *BRCA2* carriers, respectively. The corresponding colon cancer HRs were 3.9 (95% CI 1.3 to 12.1, $p = 0.02$) and 2.3 (95% CI 0.5 to 11.3, $p = 0.3$) in *BRCA1* and *BRCA2* carriers. The HR for lymphoma was 11.9 (95% CI 3.1 to 46.2, $p = 0.001$) in *BRCA2* carriers. Risk estimates for other cancers after the onset of BC/OC were similar.

Conclusion: A 2.5-fold increase in any other cancer and a fourfold risk of colon cancer were found among *BRCA1* carriers. The corresponding HRs in *BRCA2* carriers were non-significant, except for the markedly elevated risk of lymphoma. These results suggest a role for *BRCA1/2* mutations in colorectal cancer risk in a subgroup of BC/OC-affected carriers.

Carriers of mutations in the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes have a substantially elevated lifetime risk of breast cancer (BC) and ovarian cancer (OC). However, the risk of cancers other than breast and ovarian cancers is controversial. Different approaches have been used to elucidate this issue. Studies of associated cancer risks among mutation carriers were conducted in high-risk families, and have suggested an elevated risk of several types of cancers in carrier families.^{1–7} Two large studies reported elevated risk for pancreas and colon cancer (CC) in *BRCA1* carriers; however, these studies were in conflict regarding the risk of other tumour types.^{1–2} Using a similar approach, a study by the Breast Cancer Linkage Consortium (BCLC) reported increased incidence of pancreas, melanoma and prostate cancer among *BRCA2* mutation carriers.⁴ These studies were criticised for selection bias that may overestimate the cancer risks in carriers.^{8,9}

Another approach to address this question is the use of case-control studies estimating the cancer risk by comparing mutation carrier frequency in a series of individuals affected with a specific type of cancer with that of unaffected controls.^{10–12} These studies usually failed to confirm risk elevation for other cancers in *BRCA1/2* carriers.

In this study, we evaluate the cancer risk in *BRCA1/2* carriers identified through oncology or cancer-genetic clinics. The frequencies of other cancers were compared between Ashkenazi *BRCA1/2* carriers of any of the three Ashkenazi founder mutations (185delAG and 5382insC in the *BRCA1* gene and 6174delT in the *BRCA2*) and non-carriers of Ashkenazi. We limited the sample to individuals affected with breast cancer (BC) and/or ovarian cancer (OC), both in the carrier and in the control group. We hypothesised that both groups share common environmental, life style and genetic risk modifiers associated with BC and OC, and this comparison allows estimation of the additional role of *BRCA1/2* carrier status in the risk of other cancers in this subset group.

SUBJECTS AND METHODS

Study population

A total of 1616 females, all of Ashkenazi origin, were tested for the *BRCA1/2* Ashkenazi founder mutations through oncology and cancer-genetic clinics in Hadassah Medical Center (Jerusalem, Israel) during 1995–2003. All participants signed an informed consent approved by the institutional ethics committee. We estimated the contribution of *BRCA1/2* mutations to the risk of additional cancer development by comparing only those affected with breast or ovarian cancer. As the Ashkenazi founder mutations are frequent and easy to test, a large fraction of the Ashkenazi patients with BC and OC were referred for testing; therefore, selection due to diagnosis of any other cancer is probably low and equal among carriers and non-carriers. Of 1616 women tested, we concentrate on 1098 affected with BC ($n = 947$), OC ($n = 109$), or both BC and OC ($n = 42$). In this group, 329 were *BRCA1/2* carriers (185delAG in 172, 5383insC in 36 and 6174delT in 100 individuals, three carried both 185delAG and 6174delT mutations and were omitted from analyses) and 769 did not carry either of these mutations. The frequency of non-founder *BRCA* mutations in the Ashkenazi population is low,¹³ therefore the control group includes only a negligible number of carriers. Table 1 shows the comparison of primary diagnosis (BC and/or OC), age at onset of BC, OC and other cancer, and the average patient years of observation between *BRCA1*, *BRCA2* carriers and non-carriers.

As all individuals were tested while alive and the majority of them were treated in our institution, the accuracy of cancer

Abbreviations: BC, breast cancer; BCLC, Breast Cancer Linkage Consortium; *BRCA1/2*, breast cancer genes 1 and 2; CC, colon cancer; HR, hazard ratio; OC, ovarian cancer; RR, relative risk

Table 1 Clinical characteristics of BC/OC-affected *BRCA1/2* Ashkenazi mutation carriers and non-carriers

	<i>BRCA1</i> (n = 229)	<i>BRCA2</i> (n = 100)	Non-carriers (n = 769)	p Value
Primary diagnosis, n (%)				
BC	155 (67.7)	72 (72.0)	720 (93.7)	<0.001
OC	51 (22.3)	17 (19.0)	39 (5.0)	
BC/OC	23 (10.0)	9 (9.0)	10 (1.3)	
Age at BC onset				
Mean (range)	41.7 (20–81)	45.6 (21–77)	50.8 (26–85)	<0.001
Age at OC onset				
Mean (range)	51.5 (27–71)	58.9 (46–81)	57.1 (26–89)	0.006
Diagnosis of BC at age <50 years n (%)	146/178 (82.0%)	55/81 (67.9%)	381/730 (51%)	<0.001
Age at other cancer onset				
Mean (range)	55.1 (15–77)	49.9 (19–73)	57.6 (14–86)	0.15
Age at diagnosis of other cancer: at the same time as BC/OC	7 (25%)	6 (46.2%)	31* (40.8%)	0.3
After BC/OC	21 (75%)	7 (53.8%)	45 (59.2%)	
Average patient years of observation†	52.8 (27–91)	57.0 (31–90)	59.6 (26–92)	<0.001

BC, breast cancer; OC, ovarian cancer.

Comparison of ages at diagnosis of BC, OC and other cancer.

*Age was missing for other cancer in one individual.

†From birth year to last date of follow-up or death.

diagnoses is very high. In all, 65 of 118 (55%) of all other cancers and 15 of 20 (75%) of CC were operated in Hadassah Medical Center; the rest were confirmed through medical files.

Statistical analyses

Clinical parameters were compared between *BRCA1*, *BRCA2* carriers and non-carriers. We used χ^2 test for primary diagnosis (BC and/or OC), rate of BC diagnosis at age <50 years and timing of diagnosis (before/after BC/OC). Exact p values are reported. Analysis of variance was used for the series of age comparisons (age at onset of BC, OC, CC, all other cancers and patient years of observation from year of birth to last follow-up date or death).

The hazard ratio (HR) for any other cancer was compared between *BRCA1/2* mutation carriers and non-carriers using cox proportional hazard models, with time of onset of other cancers or last follow-up as end point. Average lengths of follow-up were 52.8, 57.0 and 59.6 years in *BRCA1*, *BRCA2* carriers and non-carriers, respectively ($p < 0.001$). To minimise the possible effect of ascertainment bias, treatment effect or surveillance bias HRs were also analysed, including only cancers which were diagnosed after the diagnosis of BC/OC. Separate analyses were conducted for *BRCA1* and *BRCA2* carriers. Specific tumour types with sufficiently high frequency for separate evaluation, or those reported to be associated with *BRCA1/2* carrier status in

previous studies, were also analysed (colorectal, lymphoma and uterine tumours).

RESULTS

Table 1 presents the clinical characteristics of carriers and non-carriers that are potential confounders of other cancer risks. Higher rates of OC diagnosis (with or without BC) were found among *BRCA1* (74/229, 32.3%) and *BRCA2* carriers (28/100, 28%) compared with non-carriers (49/769, 6.3%, $p < 0.001$). Significant differences were observed in the mean age at onset of BC ($p < 0.001$) and OC ($p = 0.006$) and patient years of observation ($p < 0.001$) between the various groups. However, the age at onset of other cancers was similar (55.1, 49.9 and 57.6 in *BRCA1*, *BRCA2* carriers and non-carriers, respectively, $p = 0.2$).

Table 2 presents the rates and related HRs for other cancers in *BRCA1/2* mutation carriers compared with non-carriers. Of 1098 individuals, 118 were diagnosed with additional cancer (11 of them had more than one other cancer, and one individual, a *BRCA2* mutation carrier, had three other tumours). Frequencies of individuals with other cancer diagnoses were 12.2% (28/229), 12.0% (12/100) and 10% (78/769) in *BRCA1*, *BRCA2* carriers and non-carriers, respectively. Although seven

Table 2 Frequency of cancers other than breast and ovarian cancer in female *BRCA1/2* Ashkenazi mutation carriers (all affected with either breast cancer or ovarian cancer), and the corresponding hazard ratio in carriers compared with non-carriers using multivariate Cox proportional hazard models

	<i>BRCA1/2</i> (n = 329) n (%) HR (95% CI), p Value	<i>BRCA1</i> (n = 229) n (%) HR (95% CI), p Value	<i>BRCA2</i> (n = 100) n (%) HR (95% CI), p Value	Non-carrier (n = 769) n (%)
Any other cancer (n = 118)	40 (12.0) 2.4 (1.6 to 3.6), <0.001	28 (12.2) 2.6 (1.7 to 4.2), <0.001	12 (12.0) 1.8 (0.95 to 3.6), 0.07	78 (10.1) 1
Colorectal cancer (n = 20)	8 (2.4) 2.9 (1.04 to 8.2), 0.041	6 (2.6) 3.9 (1.3 to 12.1), 0.018	2 (2.0) 2.31 (0.5 to 11.3), 0.3	12 (1.6) 1
Lymphoma/cancer (n = 11)	5 (1.5) 5.2 (1.4 to 18.4), 0.01	1 (0.4) 0.4 (0.2 to 12.4), 0.7	4 (4.2) 11.9 (3.1 to 46.2), 0.001	6 (0.8) 1
Uterus cancer (n = 10)	5 (1.5) 2.9 (0.7 to 11.1), 0.1	3 (1.3) 2.1 (0.4 to 10.8), 0.3	2 (2.0) 2.2 (0.3 to 14.5), 0.4	7 (0.9) 1

*Individuals with more than one additional other cancers (one *BRCA1* carrier, two *BRCA2* carriers and eight non-carriers) were counted and analysed once in the analyses of risk of any other cancer, but were counted and included in all analyses of all subsets according to diagnosis of each cancer.

Table 3 Frequency of cancers other than breast and ovarian cancers which were diagnosed after BC/OC in female *BRCA1/2* Ashkenazi mutation carriers, and the corresponding hazard ratio in carriers compared with non-carriers using multivariate Cox proportional hazard models

	<i>BRCA1/2</i> (n = 329) n (%) OR (95% CI)	<i>BRCA1</i> (n = 229) n (%) OR (95% CI)	<i>BRCA2</i> (n = 100) n (%) OR (95% CI)	Non-carrier (769) n (%)
Any other cancer (n = 73)	28 (8.8) 3.2 (1.9 to 5.37), p<0.001	21 (9.5) 4.1 (2.3 to 7.1), p<0.001	7 (7.4) 2.0 (0.83 to 4.9), p=0.1	45 (6.6) 1
Colorectal cancer (n = 15)	7 (2.2) 3.2 (0.98 to 10.7), p=0.052	5 (2.3) 4.0 (1.1 to 15.2), p=0.038	2 (2.1) 3.25 (0.61 to 17.4), p=0.1	8 (1.1) 1

of 28 (25%) *BRCA1* carriers were diagnosed with other cancers before or at the same time as BC/OC diagnosis, the corresponding rates were six of 13 (46.1%) and 31 of 76 (40.8%) in *BRCA2* carriers and non-carriers, respectively (p = 0.3, table 1).

A significantly elevated HR of 2.4 (95% CI 1.6 to 3.6, p<0.001) for any other cancer was found in *BRCA1/2* mutation carriers. The corresponding HRs were 2.6 (95% CI 1.7 to 4.2, p<0.001) and 1.8 (95% CI 0.95 to 3.6, p = 0.07) in *BRCA1* and *BRCA2* carriers, respectively (table 2). When only the cancers diagnosed after BC/OC were included, HRs were 4.1 (95% CI 2.3 to 7.1, p<0.001) and 2.0 (95% CI 0.83 to 4.9, p = 0.1) in *BRCA1* and *BRCA2* respectively (table 3).

In separate analyses according to specific tumour type, estimated HRs were significantly elevated for CC among *BRCA1* carriers (3.9, 95% CI 1.3 to 12.1, p = 0.02), whereas in *BRCA2* carriers a non-significant HR of 2.3 (95% CI 0.5 to 11.3, p = 0.3) was found (table 2). The HR for developing CC after the diagnosis of BC/OC was 4.0 (95% CI 1.1 to 15.2, p = 0.04) and 3.3 (95% CI 0.61 to 17.4, p = 0.1) in *BRCA1* and *BRCA2* carriers, respectively. Among patients with CC, three of six *BRCA1* carriers and one of two *BRCA2* carriers were affected with OC. Interestingly, in *BRCA1* carriers affected with CC, ages at onset were approximately 8 years more than the non-carriers, for both BC/OC (61.8 compared with 55.8 years in non-carriers, p = 0.26) and CC (71.0 compared with 62.0 years in non-carriers, p = 0.61). *BRCA2* carriers affected with CC included only two individuals affected approximately 9 years earlier than non-carriers, both with BC/OC and with CC. The risk of lymphoma was markedly increased among *BRCA2* carriers (HR, 11.9, 95% CI 3.1 to 46.2, p = 0.001), but not among *BRCA1* carriers. The estimated HRs for the rest of the tumour types were non-significant.

DISCUSSION

In this study, we evaluate the risk of cancers other than BC and OC, in a subset of *BRCA1/2* mutation carrier females affected with BC and OC. We have found an approximately 2.5-fold increase in risk of any other cancer in *BRCA1/2* mutation carriers, and a threefold increase in CC, which was significant in *BRCA1* but not in *BRCA2* carriers. Additional analyses including only cancers diagnosed after BC/OC diagnosis were conducted to correct for possible treatment, surveillance and ascertainment biases. HRs of 4 were found for the risk of developing any other cancer and CC after BC/OC diagnosis among *BRCA1* carriers; among *BRCA2* carriers, HRs were not significant. In addition, lymphoma risk was highly elevated among *BRCA2* carriers.

Two large studies estimated the risk of other cancers in *BRCA1* mutation carrier families.^{1,2} In these studies, a fraction of the carriers were tested directly, and the probability of being a carrier was calculated for family members who were not tested. Risks were compared with lifetime risk or incidence in

the general population. Both studies found elevated risk of cancers other than BC and OC. In agreement with our results, Thompson *et al*² reported an OR of 2.3 (95% CI 1.93 to 2.75, p = 0.01) for any other cancer in female carriers but not in males. Brose *et al*,¹ on the other hand, found a higher cumulative age-adjusted lifetime risk of diagnosis of any cancer in male carriers of *BRCA1* mutations (26.1%, 95% CI 17.5% to 34.6%) than in carrier women (10.3%, 95% CI 7.2% to 13.3%); however, their analyses were based on 381 females and only 102 males. In *BRCA2* carriers, a relative risk (RR) of 2.45 (95% CI 2.15 to 2.78, p<0.001) for all cancers except BC, OC and non-melanoma skin cancer was found.⁴ It was suggested that the elevated cancer risk found in carrier families, which includes a large fraction of affected individuals, may be overestimated, because of genetic or environmental exposures that are risk factors for other types of tumours in addition to BC and OC, which cluster in these families.^{8,9} Our unique approach of comparison of BC/OC-affected carriers with non-carriers enabled us to evaluate the effect of *BRCA* mutations controlling for these factors.

The strength of our study is the direct testing of all carriers and the high quality of verification of diagnosis of other cancer. In addition, we ascertained all participants in the same way, mainly due to BC or OC diagnosis and the Ashkenazi origin. The high frequency and ease of testing of Ashkenazi founder mutations yielded a series that is less selected on the basis of family history as opposed to previous studies.^{1,2,4,5,7} The ascertainment due to diagnosis of other cancer was probably low and equal in the two groups we compared, in addition, survival bias may have resulted in reduced incidence of other cancers in both groups and underestimation of the risks. The carrier group, especially *BRCA1* mutation carriers, are younger, regarding both age of BC/OC diagnoses and average length of follow-up; however, age at diagnosis of other cancer is similar to that for non-carriers. Therefore, all estimated HRs were analysed from birth to age at onset of other cancers or last follow-up.

CC was the major contributor to the elevated cancer risk we found in our carrier group. In *BRCA1* carriers it was significantly fourfold higher, whereas the HR of 2.3 that was found in *BRCA2* carriers was non-significant. Similar HRs were found when only CCs diagnosed after BC/OC diagnosis were included. Several studies in high-risk carrier families evaluated CC risk. Brose *et al*¹ found a twofold increase in the risk of CC in *BRCA1* carriers; separate analyses by gender were not reported. An older study by the BCLC⁵ reported a fourfold increase in the risk, whereas in a subsequent, much larger study,² a twofold increased risk was found in female, but not in male, carriers. As the incidence of rectal cancer was markedly low, the authors suggested that the elevated risk could be attributable to OC cases misdiagnosed as CC. In *BRCA2* carriers, risk of CC was not elevated.⁴ Recently, two large case-control studies in Ashkenazi patients with CC were reported.^{10,11} Neill *et al*¹⁰ found 2.4% (24/

Key points

- To evaluate the risk for cancers other than breast and ovarian cancers, we compared *BRCA1/2* mutation carriers and non-carriers, all affected with breast and/or ovarian cancer. Both groups share environmental and genetic cancer risk modifiers. Therefore, our unique approach enables us to assess the role of *BRCA1/2* mutations in risk of other cancers in this subset group, which comprise a large proportion of the *BRCA1/2* carrier population.
- *BRCA1* carriers affected with breast and/or ovarian cancer were found to have a 2.5-fold risk for any other cancer, and an approximately fourfold increase in risk for colon cancer.
- Among *BRCA2* carriers, the increased risk for any other cancer and colon cancer did not reach statistical significance; however, lymphoma risk was markedly elevated.

1002) of patients with CC to carry one of the three Ashkenazi founder mutations, compared with 1.9% (19/1038) in the controls, which translated to a non-significant odds ratio of 1.24 (95% CI 0.68 to 2.26). A similar study¹¹ among 586 Ashkenazi patients with CC reported an RR of 0.50 (95% CI 0.22 to 1.14) associated with these mutations.

Common risk modifiers for BC and colorectal cancer, such as diet^{14–16} and exercise,^{17–18} as well as genetic modifiers clustering in high-risk families, may result in elevated CC risk in carrier families, regardless of the *BRCA1/2* carrier status. However, by comparing BC/OC-affected carriers with affected non-carriers who share those factors, we suggest a role, either additive or synergistic, of *BRCA1/2* mutations in occurrence of CC in this subset group. It is important to note that individuals affected with CC, especially *BRCA1* carriers in our series, were older than the whole study group. Therefore, probably, longer survival is required for CC development in *BRCA1* carriers. In the case-control studies mentioned above,^{10–11} carriers affected with BC/OC are probably under-represented owing to a high mortality rate at younger age, which may have resulted in a lower carrier rate.

The risk of lymphoma was markedly elevated among *BRCA2* carriers, with an HR of 11.9 (95% CI 3.1 to 46.2, $p = 0.001$), whereas HR among *BRCA1* carriers was non-significantly reduced. In agreement with our results, the BCLC study reported an RR of 1.91 (95% CI 0.81 to 4.49) for non-Hodgkin's lymphoma and 1.48 (95% CI 0.4 to 5.48) for Hodgkin's disease in *BRCA2* carriers.⁴ The corresponding RRs in *BRCA1* carriers² were 0.23 (95% CI 0.09 to 0.60, $p < 0.001$) and 0 ($p = 0.15$), respectively. However, an RR of 2.6 was found for leukaemia and lymphomas, based on 649 patients with ovarian cancer (all *BRCA1* carriers).⁶ Again, in a case-control study of 286 Ashkenazi Jewish patients with lymphoma, only two *BRCA* carriers were found.¹² Whether the elevated lymphoma incidence we and others⁴ observed in *BRCA2* carriers is related to treatment, owing to the role of *BRCA2* in double-strand breaks repair, should be further investigated. Of the four *BRCA2* carrier patients with lymphoma in our series, two were diagnosed with lymphoma and treated with irradiation before BC diagnosis, the other two were diagnosed 5 and 34 years after the diagnosis of BC, and the causative role of the treatment for BC in the development of lymphoma is less clear.

In conclusion, our findings show an elevated risk of other cancers, especially that of CC, in a subset BC/OC-affected carriers. Our results partly explain the controversy between studies of high-risk carrier families and the case-control studies conducted in the general population. We speculate that the affected carriers, which comprise the majority of the carrier population in studies of high-risk families, are the main contributors to the elevated cancer risks found in these studies.^{1–7} In the case-control studies^{10–11} conducted in the general population, the BC/OC-affected carriers with early onset of disease are under-represented, owing to reduced survival. In the future, better treatment and surveillance in carriers may result in longer life expectancy and therefore higher risk for other cancers, especially CC, among carriers.

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CORRECTION

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approach in French-Canadian families with high risk of breast and ovarian cancer. *J Med Genet* 2007;**44**: 107–21.

The journal apologises for an error that has occurred in this paper in figure 4 on page 116, where the numbers 0 to ≥ 10 on the vertical axis of the graph should align with the horizontal dotted lines, starting with zero at the bottom. The correct figure is printed here.

Figure 4 Distribution of the 256 families according to the presence of ovarian cancer, the number of breast cancer cases diagnosed before (<) or after (≥) 50 years and their mutation status. BRCA1-positive (+) families are represented by either a red circle (families of subset A) or a red square (families of subset B). BRCA2-positive families are represented by either a black circle (families of subset A) or a black square (families of subset B). Families with no BRCA1/BRCA2 mutation detected are represented by either an open circle (families of subset A) or an open square (families of subset B). Female breast and ovarian cancer cases were at most third-degree relatives from the proband, whereas the presence of a male patient with breast cancer was considered at any degree from the proband. A dot in each form indicates the presence of male patients with breast cancer in the family.