ELECTRONIC LETTER

Hereditary ovarian cancer resulting from a non-ovarian cancer cluster region (OCCR) *BRCA2* mutation: is the OCCR useful clinically?

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Ovarian cancer is the fifth most common malignancy among North American women and the fourth leading cause of cancer death. Approximately 5 to 13% of all ovarian cancer cases are caused by the inheritance of cancer predisposing genes with an autosomal pattern of transmission.[1] Hereditary ovarian carcinoma has been described in association with mutations in four genes, *BRCA1*, *BRCA2*, *MLH1*, and *MSH2*, although usually ovarian carcinoma (OC) does not occur in a site specific fashion, but is associated with breast cancer (*BRCA1* and *BRCA2*) or colorectal and endometrial cancer (*MLH1* and *MSH2*). The large majority of hereditary OC is attributable to mutations in *BRCA1*. While mutations in *BRCA1* have been seen in large pedigrees with apparently site specific OC predisposition,[2] mutations in *BRCA2* that have been associated with site specific OC are rare, and have often been missense mutations.[3 4] The biological significance of such mutations can be uncertain.

Gayther *et al*[5] reported that mutations in a 3.3 kb segment of exon 11 of *BRCA2* were associated with a higher risk of OC relative to breast cancer than were mutations outside this region ($p = 0.0004$). They called this region of *BRCA2* the ovarian cancer cluster region (OCCR). In an expanded study from the same group, Thompson *et al*[6] estimated that mutations in the ovarian cancer cluster region (OCCR) of *BRCA2* are associated with an OC risk to the age of 70 of 19.5% (95% confidence interval (CI) 11.6 to 31.7), whereas the equivalent risk associated with mutations outside this region has been estimated at 10.9% (95% CI 5.5 to 20.9). Despite the concluding comments of the authors, urging a cautious interpretation of their data, if these estimates were to be used to counsel women who carry *BRCA2* mutations, those who carry mutations outside the OCCR might receive lower estimates of their risk than if a general gene wide risk were given. We report here a family (MON99-0085) where a non-OCCR *BRCA2* mutation appears to be highly penetrant for OC. We discuss the implications of these observations for the status of the OCCR and for counselling of this and other families.

Key points

- Female *BRCA2* mutation carriers are at increased risk of ovarian cancer.
- A previous study has defined a cluster region in *BRCA2* where the ratio of breast to ovarian cancers is decreased.
- This case report, along with more recent data, suggest that the main reason for the altered ratio is a decreased risk of breast cancer, rather than an increased risk of ovarian cancer.
- Caution should be exercised in counselling women with *BRCA2* mutations within the OCCR when the risk of ovarian cancer is discussed.

CASE REPORT

The proband (III.2) was referred to the Hereditary Cancer Clinic (HCC) at the Montreal General Hospital and first counselled in November 1999 on account of a family history of ovarian cancer (fig 1). She is of French Canadian origin and is currently in good general physical health. She was referred for genetic counselling because her mother (II.2) was diagnosed with ovarian carcinoma (OC) at the age of 68 and died at the age of 70 (fig 1). The pathology report on II.2 confirmed the presence of poorly differentiated serous cystadenocarcinoma of the right ovary. Her maternal aunt, II.3 (her mother's non-identical twin), was also diagnosed with OC at the age of 77. The pathology report received on II.3 confirmed the diagnosis of poorly differentiated serous cystadenocarcinoma of the left ovary. The maternal grandmother (I.2) was also reported to have died of OC at the age of 60, but this was not confirmed by the pathology report. One maternal uncle was believed to have died of prostate cancer at the age of 65. The proband's brother (III.1) was diagnosed with basal cell carcinoma at the age of 50, her father was believed to have died of prostate cancer at the age of 58, and one paternal aunt was reported to have died of breast cancer at the age of 55. We were unable to retrieve pathology records for these cases. No consanguinity was reported.

On account of the aggregation of three cases of ovarian cancer in this family, we offered II.3 (the only living affected subject) limited *BRCA1/2* genetic testing. When a reasonable probability of the presence of a cancer predisposing gene in a given family has been estimated, *BRCA1/2* genetic testing may be offered to an affected family member, usually the person most likely to carry the mutation. Therefore, we offered genetic testing to II.3 (fig 1).

Currently, as an initial screen, we offer clinical testing in Montreal for the five most common mutations found among French Canadian kindreds with hereditary breast/ovarian cancer.[7] Our panel includes 4446C>T, 2953del3+C in *BRCA1*, and 8765delAG, 6085G>T, and 6503delTT in *BRCA2*. No mutation was identified in II.3. Based on an estimation of the probability of finding a mutation in *BRCA1/2* despite the initial genetic screen, we decided to pursue full sequence *BRCA1/2* gene testing through Myriad Genetics Laboratories, Salt Lake City, UT.

Following complete sequencing of both genes, a mutation, *BRCA2*:2558insA, was identified. This allowed us to offer testing to other family members at high risk who became interested in genetic testing upon the provision of the above mentioned information. The results of further testing in this family are indicated in fig 1.

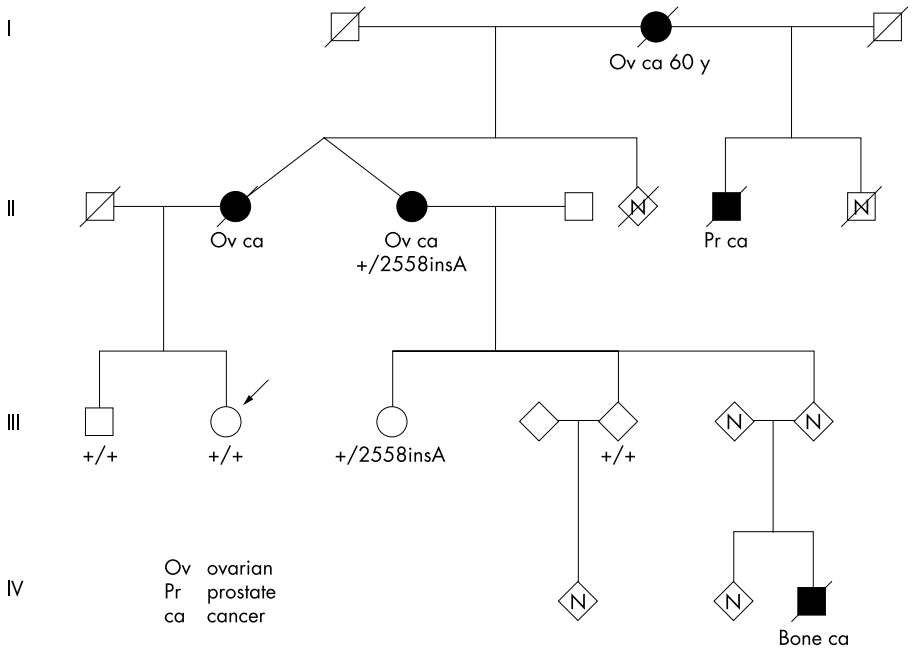

Figure 1 The pedigree for family MON99-0085 with hereditary ovarian cancer caused by a *BRCA2* mutation outside the OCCR. The presence of the *BRCA2* mutation, 2558insA, is indicated by +/2558insA. +/+ are tested wild type subjects. All other subjects in the pedigree are untested. Pathology block tissue is not available for dead subjects. Tested family members have agreed to the publication of this manuscript and will be supplied with a copy of the published work.

DISCUSSION

BRCA1 and *BRCA2* clearly predispose to OC, but germline mutations in *BRCA2* may confer a lower risk of OC (11%-27%) than mutations in *BRCA1* (12-68%).[1 8] It should be noted that while these estimates may appear to differ, they overlap substantially and some of the observed differences in the estimated penetrance of each gene may be the result of modifying genetic and environmental factors, ascertainment bias, or simply the result of chance, rather than being purely the effect of the gene under study.[9]

To study these differences further, Gayther *et al*[5] analysed the distribution of mutations in his study of a series of 25 families with multiple cases of breast/ovarian cancer ascertained in the United Kingdom. OC was more prevalent than breast cancer when *BRCA2* truncating mutations were located in a region of approximately 3.3 kb in exon 11 (nucleotides 3035 to 6629, the ovarian cancer cluster region or OCCR). An analysis of previously published data from 45 *BRCA2* families ascertained outside the United Kingdom provided support for this clustering.[5] Using these families, they delineated a so-called OCCR, whereby mutations in the central portion of *BRCA2* were found to be associated with a significantly higher ovarian cancer/breast cancer ratio in female carriers than were mutations 5′ or 3′ of this region. This region has been subsequently slightly modified, on statistical grounds, to include nucleotides 3059-4075 and 6503-6629.[9]

This later study seems to have confirmed the original observation of Gayther *et al*,[5] in that when 164 families were studied, mutations within the redefined OCCR were associated with an increased risk for OC (1.88, 95% CI 1.08 to 3.33, p=0.026) and, as before, a decreased risk of breast cancer (0.63, 95% CI 0.46 to 0.84, p=0.0012). However, as the authors point out, the increased risk for OC for "OCCR mutations" was only observed when the original 25 Cancer Research Campaign (CRC) families (on which the hypothesis was built) were included. When the analysis was restricted to the remaining 139 families, the significance was lost and the direction of the observed effect actually reversed, leading to point estimate of the risk for OC for mutations within the OCCR that was less than 1, although the result is still consistent with the findings in all 164 families (RR=0.85, 95% CI 0.39 to 1.85, p=0.2). The decreased risk for breast cancer persisted (RR=0.68, 95% CI 0.49 to 0.94, p=0.011).

Risch *et al*[10] in a population based series identified 60 mutations in 649 women with OC. They used a mutation analysis strategy that favoured the identification of *BRCA2* mutations within the OCCR. They also collected pedigree information, and so were able to study the risks of cancers in the relatives of carriers and non-carriers, and to correlate these risks with mutation position. In support of Thompson and Easton,[5] OC occurred among family members of cases carrying mutations only when the *BRCA2* mutation was within the OCCR, although this did not reach statistical significance (p=0.08). Interestingly, the effect did not seem to be limited to ovarian cancer, as the authors found a highly significant excess of colorectal, stomach, pancreatic, and prostate cancer in family members when the *BRCA2* mutation was within the OCCR (RR=3.1, 95% CI 1.75 to 7.0, p=0.0003). Of note, specifically for prostate cancer, the opposite effect was seen by Thompson and Easton,[5] where prostate cancer was less often found in association with OCCR *BRCA2* mutations (RR=0.52, 95% CI 0.24 to 1.00). These studies suggest that the statistical (and biological) significance of the OCCR remains uncertain, and this should be considered in the clinical management of women who carry *BRCA2* mutations and request OC risk estimates.

The affected subject II.3 carried *BRCA2*:2558insA, which clearly lies outside the OCCR, yet three cases of ovarian cancer occurred in this family. Our findings suggest that the validity of the OCCR as a discrete entity is questionable, and, certainly, caution should be exercised in counselling women regarding their risks of OC based on the position of the mutation along *BRCA2*. By contrast, the reduced risk for breast cancer within OCCR appears to be real. Perhaps the cluster region should be named the "diminished breast cancer risk region" (DBCRR). This is not to say that the risk of breast cancer outside this region is uniformly high (clearly it is not in the family we report here), but as has been argued previously by those who coined the term,[5] it does seem that within the so-called OCCR the reduced risk of breast cancer is a more likely reason for the observed excess of OC than is an increased risk of OC itself.

Hence the original term is a misnomer and could be replaced by DBCRR.

Interestingly, cases associated with mutations in the OCCR had a significantly older mean age at diagnosis of breast cancer than were seen in those outside this region (48 *v* 42 years, p=0.0005).[11] In pedigree MON99-0085 reported here, the mean age of diagnosis of OC was 68.3 years. This is in accordance with published reports in that the average age of onset of OC in *BRCA2* mutation carriers tends to be older than that seen in *BRCA1* mutation carriers with mean age at diagnosis being significantly older for *BRCA2* versus *BRCA1* linked patients (62 *v* 54 years).[1 12] We consider that women carrying *BRCA2* mutations who decide against preventive oophorectomy as a method of reducing breast cancer risk[13] may be able to delay oophorectomy until close to, or after, the onset of menopause without significant penalty. On the other hand, it may be prudent to discuss a broad range of risks for OC in association with a *BRCA2* mutation, wherever it may be situated along the gene.

In conclusion, we report here a family, with three cases of OC and no reported cases of breast cancer, which was found to be harbouring a disease causing mutation in *BRCA2* that lies outside the OCCR. On the basis of this, we would urge caution in counselling women carrying non-OCCR mutations that their risk of OC is lower than for women who carry mutations that lie in the OCCR. The name "diminished breast cancer risk region" or DBCRR perhaps more closely reflects the true relationship between mutations that fall within nucleotides 3059-4075 and 6503-6629 of *BRCA2* and the risk of breast and ovarian cancer.

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