Author's response to reviews

Title: Contribution of the PALB2 c.2323C>T [p. Q775X] founder mutation in well-defined breast and/or ovarian cancer families and unselected ovarian cancer cases of French Canadian descent

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Author's response to reviews: see over
26th November 2012

Prof Margareta Nordling
Editor
BMC Medical Genetics

Dear Prof Nordling

RE: MS: 1584287835803331 - Contribution of the PALB2 c.2323C>T [p. Q775X] founder mutation in well-defined breast and/or ovarian cancer families and unselected ovarian cancer cases of French Canadian descent

Thank you for your email dated 21-Nov-2012. We would like to thank the reviewers for their very helpful comments. On behalf of my co-authors I would like to resubmit this manuscript which has addressed the issues raised:

Associate Editor comments:

This is a well-written manuscript that evaluates the contribution of the PALB2 c.2323C>T mutation in hereditary breast cancer and ovarian cancer patients of French Canadian descent. However, the mutation has been reported previously in approximately the same frequency in breast cancer cases in this population and to establish the mutation as a founder mutation (as is stated in the title) haplotype analyses is needed. The manuscript could also benefit from a discussion about LOH in tumours and also regarding other PALB2-associated cancers (present or not) in F1469.

These comments have been addressed by referring to a previous published study which showed that haplotype analysis is consistent with this mutation being a founder. We have mentioned that PALB2 mutations can also predispose to pancreatic cancer, but have taken care not to over emphasize the significance of the cancer spectrum in F1469 as so far only the proband in this family is known to carry the mutation. We have also discussed our findings of no LOH in the context of other studies on this.

All the revisions suggested by Reviewer Kroupis need to be assessed. However, the haplotype analyses needs to be done if you state this is a founder mutation.

Furthermore:

1. Even if the control material is presented in previous reports you need to describe this further in this manuscript.
We have addressed this in the methods

2. Check "breast and/ovarian cancer", do you mean "breast and/or .."

This has been corrected

3. Check so that you get the naming of the mutation consistent throughout the manuscript (also the tables).

This has been done

4. Check the manuscript for minor grammatical errors, missing words etc.

This has been done

Reviewer Christos Kroupis comments

1. Authors should stress in the Discussion area the need for haplotype analysis in the future for mutation carriers in order to establish it as a founder mutation.

Haplotype analysis has been previously carried out and is consistent with this being a founder mutation. We now mention this in the discussion and cite the relevant paper.

2. The pedigree of the severely-hit family F1469 is very interesting and readers would like to know more precisely whether this family has been BRCA-analyzed by Myriad or only for the common French-Canadian mutations (it is not mentioned anywhere in the text). Also, about the testing for these common BRCA mutations: have the samples been checked for six or five mutations (or more as mentioned in the Tonin et al, 1998 paper)? If the number is the same for all samples, probably it would be of value to add this info throughout the text (abstract included).

We have added additional details regarding BRCA1/2-mutation screening in the Methods

Other minor or discretionary revisions
1. For the sake of readers, please rearrange citations in a consecutive way e.g. [19, 20, 23, 21,16, 22, 24] should be [16, 19-24].
2. In page 6 line 9, add next to the abbreviation LMP: (Low Malignant Potential).
3. For ovarian cancer staging, please add FIGO (and/or a citation) as this acronym is more easily recognized.
4. In p. 5 L. 11 remove Table 1 as it is mentioned twice. Next line, please correct to ...index “cases” ....were recruited...
5. In p.6 L.1 please add for clarity ...remaining 26 HBC and 14 HBOC cancer families were found...
6. In p. 9 L9, please add the BRCA2 variant; E2003K 7. In p. 9 L14 correct to “p.Q775X” carrier... 8. In p. 10, L. 21 suggest to change to “none of these two high-grade serous.....”

These have all been dealt with. Please find below a copy of the manuscript with tracked changes.
I hope that we have been able to answer all comments to your satisfaction and look forward to hearing from you.

Yours sincerely,

[Signature]

Dr Marc Tischkowitz
University Lecturer and Honorary Consultant in Medical Genetics
University of Cambridge
Contribution of the $PALB2$ c.2323C>T [p. Q775X] founder mutation in well-defined breast and/or ovarian cancer families and unselected ovarian cancer cases of French Canadian descent

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Abstract

The PALB2 c.2323C>T [p.Q775X] mutation has been reported in at least three breast cancer families and breast cancer cases of French Canadian descent and this has been attributed to common ancestors. The number of mutation-positive cases reported varied based on criteria of ascertainment of index cases tested. Although inherited PALB2 mutations are associated with increased risks of developing breast cancer, risk to ovarian cancer has not been fully explored in this demographically unique population. In this article we describe the contribution of PALB2 p.Q775X variant in 71 families with at least three cases of breast cancer (n= 48) or breast and ovarian cancers (n=23) that have previously been found negative for at least the most common BRCA1 and BRCA2 mutations reported in the French Canadian population. We also describe the frequency of PALB2 p.Q775X variant in 491 women of French Canadian descent who had invasive ovarian cancer and/or low malignant potential tumors of the major histopathological subtypes. We identified a PALB2 p.Q775X carrier in a breast cancer family, who had invasive ductal breast carcinomas at 39 and 42 years of age. We also identified a PALB2 p.Q775X carrier who had papillary serous ovarian cystadenocarcinoma at age 58 among the 238 serous subtype ovarian cancer cases investigated, who also had breast cancer at age 52. Our findings taking together with previous reports support adding PALB2 c.2323C>T p.Q775X to the list of cancer susceptibility genes for which founder mutations have been identified in the French Canadian population.

Keywords
PALB2, p.Q775X, p.Q775*, hereditary breast cancer, breast cancer risk; ovarian cancer, founder mutations, French Canadians
Introduction

Carriers of \(PALB2\) mutations in a heterozygous state have been associated with increasing the risk of developing breast cancer [1-10]. \(PALB2\) is a partner and localizer of the BRCA2 breast-ovarian cancer susceptibility protein to DNA damage sites [9, 11]. Penetrance estimation for conferring breast cancer risk has been hampered by the paucity of cases, although estimates of 2- to 6-fold increased risk to breast cancer have been suggested [12, 13], thus classifying \(PALB2\) as a moderate breast cancer risk allele [9, 12-14]. Germline mutations in \(PALB2\) have also been identified in familial pancreatic cancer [15, 16]. \(PALB2\) is comprised of 13 exons spanning a 38 kb region on chromosome 16p12.1 and mutation screening is complicated by the diversity of variants (including missense mutations) identified in cancer cases. The \(PALB2\) c.2323C>T mutation, which results in the introduction of a stop codon at amino acid position 775 (p.Q775X), has been reported in at least three French Canadian breast cancer families [5], and along with other protein truncating \(PALB2\) mutations found in breast cancer cases, is strongly suspected to be deleterious [17]. The French Canadian population of Quebec exhibits an unique genetic demography [18-20]. About 40% of French Canadian cancer families with at least three cases of breast and/ovarian cancer carry a pathogenic \(BRCA1\) or \(BRCA2\) mutation [20-25]. Although 15 different mutations in these genes have been reported in French Canadian cancer families, six specific mutations in \(BRCA1\) and \(BRCA2\) have been shown to account for a significant majority of mutation-positive families [20-26]. This has been attributed to a shared ancestry of mutation carriers due to common founders of the French Canadian population of Quebec [25-28].

The number of \(PALB2\) p.Q775X mutation-positive cases that have been reported thus far in studies involving the French Canadian population vary according to criteria and catchment area of ascertainment of index breast cases tested [5, 29]. To further assess the contribution of \(PALB2\) p.Q775X mutation in the French Canadian population, we report the results of screening this variant
in 71 well defined cancer families with at least three confirmed cases of breast and/or ovarian cancer found negative for the most common BRCA1 and BRCA2 mutation reported in this population. We report the cancer phenotype of a new p.Q775X mutation-positive family. We also report the screening 385 invasive ovarian cancer cases and 106 low malignancy potential ovarian tumors not selected for family history of cancer that were ascertained from the French Canadian population, and describe the cancer history of the p.Q775X cases identified in this screen. We describe our findings in the context of previous studies describing mutation screens of PALB2 in individuals of French Canadian descent.

Subjects, materials and methods

Subjects and cancer families

The study subjects fall within two defined groups. The first group contains index cases from 71 independently ascertained families (Table 1). The index cases tested for mutations were recruited to the study through the hereditary cancer clinics in Montreal as part of research studies assessing the contribution of BRCA1 and BRCA2 in breast and/or ovarian cancer families as described previously [21, 25]. They have a family history of breast cancer (n= 48) or breast and ovarian cancer (n=23) according to the following criteria: in addition to the index case affected with breast cancer at less than 66 years of age, the families contained at least two other confirmed cases of invasive breast and/or epithelial ovarian cancer in the same familial branch. The affected index cases from 26 breast cancer families (HBC) and 14 breast-ovarian cancer (HBOC) families were previously screened and found negative for BRCA1 and BRCA2 sequence variants by commercial DNA sequencing (Myriad Genetics, Myriad Genetics Laboratories, Salt Lake City, UT, USA). The index affected cases from the remaining 22 HBC and 9 HBOC families were found negative for 20 BRCA1 and BRCA2 mutations.
reported in French Canadian cancer families of Quebec which include the following most common BRCA1 (c.4327C>T (R1443X), c.2834_2836delGTGinsC) and BRCA2 (c.8537_8538delAG, c.5857G>T (E1953X), c.3167_3171delAAAAG) mutations reported in this population, as described previously [22, 23, 25]. All index cases in this study self-reported grandparental French Canadian ancestry. The second group contained 385 females with epithelial ovarian carcinomas and 106 low malignant potential tumors (Table 2), who were recruited to Banque de tissus et de données of the RR Cancer of the Fonds recherché Québec-santé tumor bank between April 1991 and October 2007. At least 88% of all women with malignant serous, endometrioid or undifferentiated malignant ovarian cancer cases from RR Cancer Tumor self-reported French Canadian ancestry (unpublished data). All women with serous LMP (Low Malignant Potential) tumors self-reported FC ancestry [30]. None of these subjects were selected for family history of cancer. Histopathology according to criteria established by the International Federation of Gynecology and Obstetrics (FIGO), age at diagnosis and personal history of cancer were provided for each case. Written consent to participate was obtained and the study protocols approved by the ethics review boards of the University of Montreal Hospital Center, McGill University Health Centre and Jewish General Hospital.

**PALB2 mutation analysis**

Mutation analysis was performed on DNA extracted from peripheral blood leukocytes from all study subjects. A sequence analysis of protein coding exons of PALB2 for the index cases of 14 families was performed as described previously [5, 10, 17] (Table 1). The targeted analysis for PALB2 c.2323C>T (p.Q775X) variant was performed using an allelic specific assay as described [5]. The variant-positive cases were confirmed by DNA sequencing using 3730XL DNA analyzer system platform from Applied Biosystems (Carlsbad, CA, USA) at the McGill University and Genome Quebec Innovation Centre.
(Montreal, PQ, CDN). Loss of heterozygosity (LOH) was inferred by sequence analysis of PALB2 locus containing the PALB2 c.2323C>T variant from DNA extracted from ovarian cancer specimen from the p.Q775X mutation-positive case. Sequences were compared with PALB2 NCBI Reference Sequence NM_024675 as described in GenBank (www.ncbi.nlm.nih.gov).

The PALB2 p.Q775X variant is also annotated as p.Q775* according to a recently proposed nomenclature alteration for nonsense changes by the Human Genome Variation Society (www.hgvs.org). However for historical purposes the p.Q775X designation is maintained in this report.

Results

PALB2 c.2323C>T [p.Q775X] carriers in breast and/or ovarian cancer families

One PALB2 p.Q775X positive case was identified among the cancer families not previously investigated for PALB2 mutations. The index carrier case was identified among the total of 48 (2.1%) HBC families or 71 (1.4%) HBC and HBOC families that share a phenotype defined by at least three or more confirmed cases of breast and/or ovarian cancer in the same familial branch (Table 1). These families were previously found negative for BRCA1 and BRCA2 mutations or the most common pathogenic mutations in these genes found in the French Canadian population.

The PALB2 carrier had bilateral invasive ductal carcinomas of the breast at ages 39 and 42 and is part of the breast cancer family F1469 (Fig. 1). Although breast cancer was reported in both paternal and maternal branches of her family (Fig. 1), only the aunt and cousin from the paternal branch of the family were confirmed to have had breast cancer. Her paternal aunt also had bilateral invasive ductal carcinoma at ages 41 and 42, as well as atypical stomach carcinoma that was identified at age 42 but not further explored due to death soon thereafter. The carrier’s paternal cousin had an
invasive breast cancer of mixed ductal and lobular histopathology at 52 and was still living at the time of pedigree analysis. Notable in this pedigree is that lack of ovarian cancer cases typified by BRCA1 or BRCA2 mutation carrier families. Her father had esophageal cancer and cancers of other sites reported (some confirmed) for both branches of her family. To our knowledge no other cases are available for genetic testing and thus transmission of the mutation is uncertain in this family. The family structure and associated phenotypes does not appear to overlap previously described PALB2 p.Q775X positive families [5].

**PALB2 c.2323C>T [p.Q775X] carriers in ovarian cancer cases**

One PALB2 p.Q775X positive case was identified among the 491 women with ovarian cancer or low malignant potential tumors. The carrier was diagnosed with a papillary serous cystadenocarcinoma at age 58. The carrier was identified among the 385 (0.3%) invasive ovarian carcinomas of all histopathological subtypes and among 238 (0.4%) invasive serous ovarian carcinomas (Table 2).

There were 21 cases that also had a prior personal history of breast cancer and the PALB2 p.Q775X carrier was in the group of 10 invasive serous ovarian carcinoma cases with this history (Table 2). The carrier had a breast cancer at age 52 years of undisclosed histological type. Genetic analysis of genomic DNA from ovarian cancer specimens did not indicate LOH of the PALB2 locus (Figure 2).

**Discussion**

Our results are consistent with previously established frequency of PALB2 c.2323C>T [p.Q775X] carriers in breast cancer families of French Canadian descent (Table 3). Initial reports of comprehensive screening of all of the protein encoding exons of PALB2, identified no variants in 38
breast cancer families, where 22 families had a prior probability of greater than 10% of harboring a
BRCA1 or BRCA2 mutation [10]. The same group reported one of 50 (2%) breast cancer families, and
two of 356 (0.6%) cases of early age (< 50 years) breast cancer with this mutation [5]. Pedigree
analysis of the index PALB2 p.Q775X positive cases from these three families indicated that they are
not immediately related to each other and haplotype analysis was consistent with this being a
founder mutation [5]. Four PALB2 p.Q775X positive cases were also identified in a subsequent study
involving 564 (0.7%) breast cancer cases not selected for family history of cancer, which also showed
that 6% of cases harbored common BRCA1, BRCA2 or CHEK2 mutations [29]. This latter study also
included the 356 early age breast cancer cases reported in a previous study, and one of these cases
was found related to a member of previously reported mutation-positive family (P28031) and two
other cases were the same carriers identified in a same previous study (P31030 and P26007) [5]
(Table 3). In an independent study involving the investigation of a new BRCA2 variant, c.9004G>A
(E3002K), a family (F1573) harboring both a BRCA2 variant and the PALB2 p.Q775X mutation was
reported [22]. However, pedigree inspection revealed that family F1573 was related to one of three
PALB2 p.Q775X (P28031) families described in the initial report of this variant in the French Canadian
breast cancer families [5]. The family history of PALB2 p.Q775X carrier P36470 also identified in a
screen of 564 breast cancer cases not selected for family history [29] appears not to be related to the
PALB2 p.Q775X carrier families described based on pedigree inspection, including family F1469
reported in this study. In summary, the six PALB2 p.Q775X breast cancer carriers which include five
occurring in apparently unrelated cancer families have thus far been identified in screening breast
cancer cases or breast cancer families.

In contrast, no PALB2 variants were reported in two other independent studies involving 99
Genealogy and genetic studies have reported variability of founder effects in various regions of Quebec [32], suggesting that demography may also be a factor in the paucity of \textit{PALB2} p.Q775X carriers in some studies of French Canadian cancer families. The majority of our cases were ascertained in Montreal [20], whereas independent groups have ascertained their families from the Quebec City region [33]. This possibility could also account for the lack of \textit{PALB2} p.Q775X carriers found in a screen of 6,440 newborns of French Canadian descent as the majority of these newborns were from the Quebec City region [5].

The young ages of breast cancer diagnoses and number of breast cancer cases per family in \textit{PALB2} p.Q775X carrier families suggest that carriers of this mutation are at high risk for breast cancer (Table 3), as has been posited with some \textit{PALB2} mutation carrier families [5, 10, 17]. Our findings here support this notion, as the \textit{PALB2} p.Q775X carrier identified had a bilateral case of breast cancer diagnosed before age 45 years and a strong family history of breast cancer (Fig. 1).

It is interesting that the \textit{PALB2} p.Q775X carrier found among the ovarian cancer cases examined in this study had a prior history of breast cancer (Table 3). Notable is that her personal history of cancer does not match any of the cases that appear in the pedigrees of \textit{PALB2} p.Q775X positive French Canadian cancer families described thus far (including the new carrier family identified in this study). The role of \textit{PALB2} in ovarian cancer is uncertain, as there have been few documented ovarian carcinoma cases harboring germline mutations in this gene. Two \textit{PALB2} mutation carriers were identified in a study of 339 unrelated ovarian cancer cases of Polish descent [3]. The carriers had high grade carcinomas of different histopathological types: serous (case diagnosed at 61 years) and endometrioid (case diagnosed at 54 years) subtypes, where the latter carrier also harbored a \textit{BRCA2} mutation [3]. Two (0.6\%) \textit{PALB2} mutation carriers were reported in a study of 360 ovarian cancer cases that were also screened for \textit{BRCA1}, \textit{BRCA2} and other recently
described cancer susceptibility genes [34]. None of these two high-grade serous carcinoma PALB2 mutation-carriers (diagnosed at ages 51 and 58) had a personal history of breast cancer, although the ovarian cancer case diagnosed at age 58 years had a family history of breast and/or ovarian cancer [34]. A low frequency of PALB2 carriers (0.4%) was also recently reported in an investigation of 253 ovarian cancer cases from the Volga-Ural region of Russia [35], with the only carrier identified in this study having a bilateral (moderate grade) serous ovarian carcinoma at age 46 and a prior history of melanoma. The low frequency of PALB2 mutation carriers identified thus far may argue a minor role for this gene in conferring ovarian cancer risk compared with higher frequency of mutation carriers observed in breast cancer cases and breast cancer families. This is consistent with recent findings estimating that PALB2 heterozygotes were 1.3-fold more likely to have a relative with ovarian cancer in the context of HBOC family history [2].

Our genetic analyses of the carrier ovarian cancer specimen harboring the PALB2 p.Q775X mutation did not exhibit evidence of LOH of the PALB2 locus. This could also be consistent with sufficient contamination of normal stromal DNA such that it would obscure an imbalance of alleles. It has been suggested that PALB2 contributes to carcinogenesis through haploinsufficiency and/or a dominant negative effect given the paucity of LOH observed in the majority of breast cancer cases from PALB2 carriers [3, 4, 6, 10]. However, few cases have been examined for LOH, and retention of PALB2 variant alleles have been reported in LOH analyses of breast [6] and ovarian [34] carcinoma specimens, with LOH reported for all ovarian cancer cases identified in one study [34]. Promoter methylation silencing has also been reported in four of 53 sporadic ovarian cancer cases [36]. The significance of these findings is unknown and warrants further investigation to elucidate the role of PALB2 in both breast and ovarian carcinogenesis.
In conclusion, the *PALB2* c.2323C>T [p. Q775X] mutation likely confers increased risk for breast cancer in the French Canadian population of Quebec. Although the frequency of carriers in significantly lower than that established for the high risk *BRCA1* and *BRCA2* alleles, the young age at diagnoses and associated familial history of breast cancer suggest that this variant could be added to the panel of deleterious mutations screened for assessing breast cancer risk in this unique population. Indeed during the preparation of this manuscript another *PALB2* carrier harboring the p.Q775X variant was identified in the Hereditary Cancer Clinics affiliated with McGill University Health Centre (William D. Foulkes, *per. commun.*). The carrier had bilateral breast cancer at ages 34 and 42 years and a strong family history of breast cancer further supporting with the notion that *PALB2* p.Q775X carriers are at increased risk for breast cancer.

**Acknowledgements**

We thank Lise Portelance and Suzanna L. Arcand for technical assistance. We also thank Laura Palma for providing information about a newly identified mutation positive proband. We acknowledge the Banque de tissus et de données of the RRCancer of the Fonds recherche Québec Santé (FRQS) which is affiliated with the Canadian Tumour Repository Network (CRTNet) for providing specimens from cancer families. The Research Institute of the McGill University Health Centre and the Centre de recherche du Centre hospitalier de l’Université de Montréal receive support from the FRQS. Marc Tischkowitz a recipient of the FRQS clinician-scientist award. This research was supported in part by a grant from the Cancer Research Society to Patricia N. Tonin, from grants from the Canadian Breast Cancer Research Alliance, Jewish General Hospital Weekend to End Breast Cancer and the Quebec Ministry of Economic Development to Marc Tischkowitz, and from a grant from the Susan G. Komen for the Cure to William D. Foulkes.
Conflict of interest

The authors declare that there are no conflicts of interest.

References


20. Tonin PN: [The limited spectrum of pathogenic BRCA1 and BRCA2 mutations in the French Canadian breast and breast-ovarian cancer families, a founder population of Quebec, Canada]. Bull Cancer 2006, 93(9):841-846.


Figure legends

**Fig. 1 Pedigree of PALB2 c.2323C>T [p.Q775X] mutation carrier family F1469.**

An arrow indicates the proband and only known mutation carrier in family F1469. Abbreviations: bilateral breast cancer (Bi Br), cerebral hemorrhage (CH) esophageal cancer (Eso), lung cancer (Lu), melanoma (Mel), stomach cancer (Sto), and uterine cancer (Ut). Age at ascertainment and/or death (d.) are indicated if known along with ages at diagnosis of cancer.

**Fig. 2 Mutation analysis of PALB2 c.2323C>T [p.Q775X] containing region.**

DNA sequencing chromatogram showing the region containing the c.2323C sequence of normal reference sample (Panel A) and corresponding interval from lymphocyte DNA of c.2323T mutation carrier (Panel B) and ovarian cancer specimen DNA from the same patient (Panel C). The arrow indicates the position of the mutation in the sequence chromatogram.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Number of families</th>
<th>Unilateral BC</th>
<th>Bilateral BC</th>
<th>BC and OC</th>
<th>OC</th>
<th>Mean age in years of BC (age range)</th>
<th>Mean age in years of OC (age range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBC</td>
<td>48 [10]</td>
<td>45</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>46 (30-65)</td>
<td>n/a</td>
</tr>
<tr>
<td>HBOC</td>
<td>23[4]</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>44 (25-55)</td>
<td>51 (31-74)</td>
</tr>
<tr>
<td>Total</td>
<td>71[14]</td>
<td>59</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>46 (25-65)</td>
<td>51 (31-74)</td>
</tr>
</tbody>
</table>

1The numbers in the brackets refer to number of index cases where the complete coding region of \( PALB2 \) genes was sequenced. Abbreviations: breast cancer (BC), hereditary breast cancer (HBC) hereditary breast and ovarian cancer (HBOC), and ovarian cancer (OC).
Table 2: Features of ovarian tumors examined for *PALB2* c.2323 C>T [p.Q775X] mutation

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Histology type</th>
<th>Number of cases</th>
<th>Prior history of BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>serous</td>
<td>238</td>
<td>10</td>
</tr>
<tr>
<td>Malignant</td>
<td>endometrioid</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Malignant</td>
<td>mucinous</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Malignant</td>
<td>clear cell</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Malignant</td>
<td>undifferentiated</td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>Low malignant</td>
<td>serous</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low malignant</td>
<td>endometrioid</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low malignant</td>
<td>mucinous</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>491</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviation: breast cancer (BC)
<table>
<thead>
<tr>
<th>Table 3: Summary of PALB2 c. 2323C&gt;T [p.Q775X] carriers identified in studies of French Canadian cancer families or cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Q775X positive cases [Family number]</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
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<td>1</td>
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<td>0</td>
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</table>
1  BC52;OC58  491  OC (see Table 2)  Not known  This study

1 Indicates cases identified in the pedigrees identified in independent studies involving 356 BC cases investigated in Foulkes et al. [5] overlap with series of 564 BC cases examined in a subsequent study reported by Ghadirian et al. [29].  
2 Pedigrees P28031 and F1573 have related family members and were reported in independent studies [5, 22]. Pedigree P28031 had two mutation-positives cancer cases, one as part of HBC family (BC 54) and the other recruited through BC<50 (BC 46) series. Abbreviations: breast cancer (BC), bilateral breast cancer (BiBC) ovarian cancer (OC) hereditary breast cancer (HBC), hereditary breast and ovarian cancer (HBOC).