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ORIGINAL ARTICLE

Risk of cancer other than breast or ovarian in individuals with *BRCA1* and *BRCA2* mutations

A. Moran · C. O'Hara · S. Khan · L. Shack · E. Woodward · E. R. Maher · F. Lalloo · D. G. R. Evans

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Abstract The risks of cancers other than breast and ovarian amongst *BRCA1* and *BRCA2* mutation carriers are based on relatively few family based studies with the risk of specific cancers tested in population based samples of cancers from founder populations. We assessed risks of "other cancers" in 268 *BRCA1* families and 222 *BRCA2* families using a person years at risk analysis from 1975 to 2005. Cancer confirmations were overall higher than in previous family based studies at 64%. There was no overall increase in risk for *BRCA1* carriers although oesophagus had a significant increased RR of 2.9 (95% CI 1.1–6.0) and stomach at 2.4 (95% CI 1.2–4.3), these were based mainly on unconfirmed cases. For *BRCA2* increased risks for cancers of the pancreas (RR 4.1, 95% CI 1.9–7.8) and prostate (RR 6.3, 95% CI 4.3–9.0) and uveal melanoma (RR 99.4, 95% CI 11.1–359.8) were confirmed. Possible new associations with oesophagus (RR 4.1, 95% CI 1.9–7.8) and stomach (RR 2.7, 95% CI 1.3–4.8) were detected but these findings should be treated with caution due to lower confirmation rates. In contrast to previous research a higher risk of prostate cancer was found in males with mutations in the *BRCA2* OCCR region. The present study strengthens the known links between *BRCA2* and pancreatic and prostate cancer, but throws further doubt onto any association with *BRCA1*. New associations with upper gastro-intestinal malignancy need to be treated with caution and confirmed by large prospective studies.

Keywords BRCA1 · BRCA2 · Pancreatic cancer · Prostate cancer · Oesophageal cancer · Uveal melanoma

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A. Moran · C. O'Hara · S. Khan · L. Shack
North West Cancer Intelligence Service, The Christie NHS Foundation Trust, Manchester M20 3LJ, UK

L. Shack
Preventative Oncology and Community Health Sciences, University of Calgary, Calgary, Canada

E. Woodward · E. R. Maher
Medical and Molecular Genetics, and Centre for Rare Diseases and Personalised Medicine, University of Birmingham School of Medicine, Birmingham B15 2TT, UK

E. Woodward · E. R. Maher
West Midlands Regional Genetics Service, Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham B15 2TG, UK

F. Lalloo · D. G. R. Evans (✉)
Genetic Medicine, Manchester Academic Health Science Centre, St. Mary's Hospital, Oxford Road, Manchester M13 9WL, UK
e-mail: gareth.evans@cmft.nhs.uk

Introduction

Since the identification of *BRCA1* and *BRCA2* in 1994 and 1995, respectively [1, 2], a large number of studies have evaluated the risk of breast and ovarian cancer associated with mutations in these genes [3–10]. However, relatively few studies have evaluated the risks of the cancer spectrum outside breast and ovarian cancer [11–15]. Whilst there is good evidence to support an increased risk of prostate and pancreatic cancer in *BRCA2*, the most recent large scale family study (as far back as 2002) has thrown doubt on whether there are any significantly elevated risks of cancer outside breast and ovarian cancer in *BRCA1* [13]. Indeed the editorial to that article called for more studies to evaluate the risks in *BRCA1* carriers [16]. We have

evaluated the cancer risks outside breast and ovarian cancer in a large cohort of 490 families with pathogenic *BRCA1* or *BRCA2* mutations.

Methods

Study subjects were identified from individuals who attended the Regional Genetics Clinics at Manchester and Birmingham. These clinics cover a population of about ten million in the overlapping regions of the North West and West Midlands of England. Breast and ovarian cancer families have been tested for *BRCA1/2* mutations (using a whole gene analysis including a test for large deletions) since 1996. Women who attend the specialist genetic clinics in these regions with a family history of breast/ovarian cancer have a detailed family tree elicited with all first, second and if possible third degree relatives recorded. If a *BRCA1/2* mutation is identified, further extensive attempts are made to ensure that all individuals at risk of inheriting the family mutation are represented on the pedigree. All cases of cancers are confirmed by means of hospital/pathology records, from the Regional Cancer Registries (data available from 1960) or from death certification. Once a family specific pathogenic *BRCA1/2* mutation is identified predictive testing is offered to all blood relatives. Where possible all affected women with breast/ovarian cancer are tested to establish the true extent of *BRCA1/2* involvement in the family. In many large families it is possible to establish "obligate" gene carriers by testing for the same mutation in different branches of the family, thereby establishing that intervening relatives carry the same mutation. Families were ascertained from 1987 onwards. All families meeting a 20% threshold for BRCA1/2 testing were included. However, testing also included in research studies isolated breast cancers $<$35 years of age and families with two instances of breast cancer. In all over 3,000 families were tested to arrive at the family cohort presented. Some of these families are very small. Given the large number of families utilised no adjustments were made for dependency.

All individuals diagnosed with a pathogenic mutation in *BRCA1* or *BRCA2* and who were the first in their family to be so diagnosed were eligible for this study and were termed index cases. Their first degree relatives (FDR) with mutations were also eligible. All known FDRs of mutation carriers were recorded on the mutation database. To make full use of the data collected in this study, it was decided to include in the analyses those FDRs who were not tested for mutations. All individuals were only counted once and FDRs testing negative were excluded.

A detailed family history was taken from study subjects, including any diagnosis of cancer. Individuals were actively followed-up and details of every cancer reported were checked against the records at the North West Cancer Intelligence Service or the West Midlands Cancer Intelligence Unit.

Analyses

Follow-up for the study subjects commenced on 1 January 1975 or on an individual's 15th birthday, whichever was the later. Follow-up ceased on the earliest of 31 December 2005, date of death or date of diagnosis of a given type of tumour. Patients diagnosed with one type of tumour continued to be considered at risk of other types of cancer.

Relative risks were calculated for all cancers combined (excluding breast, ovarian and non-melanoma skin cancers), for several common types of cancers and a few rarer cancers for which there is evidence of an increased risk. The risk of being diagnosed with a specific type of cancer in individuals with BRCA mutations compared with the general population of the same age and sex was estimated using the ratio of observed to expected number of cases. The expected number was calculated using population based incidence rates for the North West of England for the period 1 January 1975 to 31 December 2005. Age group-, sex-, and calendar period-specific person years at risk were multiplied by the corresponding age-specific incidence rates to estimate the number of expected cases.

Relative risks were calculated for (1) those who tested positive, (2) those not tested who carried the family mutation and (3) combined. As we did not know which of the untested individuals carried their family mutation, the number of cancers that occurred in carriers was calculated from the number of observed cancers in all those not tested. The following assumptions were made:

(a) 50% of those not tested carried the family BRCA mutation and 50% did not
(b) The number of years of follow-up and the age distribution during follow-up were similar for those who were and were not mutation carriers
(c) The risk of cancer in non-carriers was the same as for individuals in the general population of the same age and sex

Based on these assumptions, the number of cancers that occurred in the assumed non-carriers was taken as the same as the expected number of cancers in this group, which was half the expected number in all those not tested. This number was then subtracted from the observed number of cancers in those not tested to provide the estimate of the number of cancers that occurred in the assumed carriers (i.e. the "observed number"). In those instances where this calculation resulted in a negative value, the number of

observed cancers was taken as 0. Calculating observed numbers in this way produced many values that were not whole numbers.

A further analysis was undertaken on those sites for which significantly raised relative risks were obtained to overcome possible ascertainment bias. Relative risks were calculated including only follow-up up to the date on which the first member of the family was identified with a BRCA mutation.

In addition to the above an analysis of prostate cancer risk was carried out on an updated cohort extended to 1 June 2010. This contained additional cases ascertained since 31 December 2005. Kaplan–Meier analysis was used to assess cumulative risk of prostate cancer in *BRCA2* mutation carriers and their FDRs subdivided by mutation position.

The confidence intervals were calculated using the Byar's approximation of the exact Poisson distribution [17].

Results

For the initial analysis of all cancer risk, 3,836 individuals were identified who had either tested positive for *BRCA1* or *BRCA2* or who had not been tested though a relative had tested positive. 495 were excluded for the following reasons: 417 had died before the start of the follow-up period, 68 were neither index cases nor FDR of mutation positive cases, and essential information was not available for ten patients. After exclusions 3,341 individuals were included in the study; 1,148 who had tested positive, of whom 490 were index cases and 658 FDR, plus 2,193 who had not been tested but a FDR had tested positive. 268 cancers other than breast and ovary were reported in these individuals of which 258 occurred within the follow-up period of the study. 165 (64%) of these were confirmed. Table 1 shows the characteristics of the study population by gender and BRCA mutation. 1,815 had *BRCA1* mutations and 1,526 *BRCA2* mutations. Total follow-up was 75,555 person-years at risk (average = 22.6 years): 7% of which was at age 15–19, 64% at 20–49 years old, 23% in the 50–69 age group and 5% in the 70+. The age distribution of years of follow-up was similar for those tested and not tested (percentages for tested first): 7 and 7% for 15–19, 66 and 62% for 20–49 year olds, 23 and 25% for 50–69 year olds and 4 and 6% for 70+.

The relative risk for all cancers combined in those with *BRCA1* mutations is below the risk in the general population (RR = 0.7 95% CI 0.5–0.9: Table 2). Those with *BRCA2* mutations are at higher risk than the general population (RR = 1.5 95% CI 1.2–1.8). The increased risk is only seen in males (RR = 1.9 95% CI 1.5–2.4) with females having a RR of 1 (webappendix page 1).

Statistically significantly increased risks were found for individuals with *BRCA2* mutations for prostate (RR 6.3, 95% CI 4.3–9.0), oesophagus (RR 4.1, 95% CI 1.9–7.8), stomach (RR 2.7, 95% CI 1.3–4.8), pancreas (RR 4.1, 95% CI 1.9–7.8) and uveal melanoma (RR 99.4, 95% CI 11.1–359.8) (Table 2). However, for pancreas the increased risk was only in those not tested and was based on only two cases for uveal melanoma. Individuals with *BRCA2* mutations also had high, though statistically non-significant, rates for gall bladder and bile duct (RR 4.3, 95% CI 0.4–16.7) and cutaneous melanoma (RR 2.6, 95% CI 1.0–5.7). Increased risks in those with *BRCA1* mutations were calculated for oesophageal (RR 2.9, 95% CI 1.1–6.0) and stomach cancers (RR 2.4, 95% CI 1.2–4.3), though in both the increased risks were only in those not tested. When follow-up was censored at the date of the first positive mutation test in the family, the relative risks for those with *BRCA2* mutations were 4.2 (95% CI 2.4–6.7) for prostate cancer, 7.6 (95% CI 3.5–14.3) for oesophageal cancer, 3.2 (95% CI 1.4–6.2) for stomach cancer and 6.3 (95% CI 2.7–12.2) for pancreatic cancer. The equivalent values for BRCA1 carriers were 3.2 (95% CI 0.9–7.8) for oesophagus and 2.6 (95% CI 1.1–5.4) for stomach.

OCCR assessment

The numbers of prostate cancers were too low to assess the effect of the Ovarian Cancer Cluster Region (OCCR) in the initial cohort. However, we have assessed this amongst an expanded set of 336 *BRCA2* families containing 1,018 male mutation carriers and FDRs. There were 33 prostate cancers (8.6%) amongst 385 males from the OCCR (4/56 in 6174DelT mutation families), but only 32/633 (5.1%) amongst males from families with mutations outside the OCCR (Fishers exact Chi square $P = 0.03$). The cumulative risk of prostate cancer was 15.9% (95% CI 12.8–19.0%) in OCCR related men by aged 70 years compared to 5.9% (95% CI 4.4–7.5% Hazard ratio 2.92 95% CI 1.54–5.54, Fig. 1) in males from families with mutations outside the OCCR.

Discussion

The current study has confirmed that an increased risk of cancer as a whole outside breast and ovarian cancer was confined to men with *BRCA2* mutations. The study has confirmed the increased risk of prostate cancer in *BRCA2* mutation carriers. A new association of increased risk with *BRCA2* mutations was found for oesophageal cancer (RR 4.1, 95% CI 1.9–7.8), and increased risks were also reported for gastric (RR 2.7, 95% CI 1.3–4.8) and pancreatic cancers (RR 4.1, 95% CI 1.9–7.8). Those with *BRCA1* mutations had

Table 1 Study subjects by gender, BRCA mutations and number of cancers

		Females				Males			All persons
		N study subjects	N (%) breast cancers	N (%) ovarian cancers	N (%) other cancers	N study subjects	N (%) breast cancers	N (%) other cancers	N study subjects
BRCA 1	Index	266	186 (70)	84 (32)	12 (5)	2	2 (100)	0 (0)	268
	FDR positive	285	113 (41)	65 (24)	10 (4)	78	0 (0)	11 (14)	363
	FDR not tested	549	116 (21)	69 (13)	36 (7)	635	1 (0.2)	54 (9)	1,184
BRCA 2	Index	211	173 (82)	34 (16)	12 (6)	11	8 (73)	5 (50)	222
	FDR positive	224	84 (34)	21 (8)	9 (4)	71	2 (3)	22 (31)	295
	FDR not tested	496	118 (24)	38 (8)	31 (6)	513	7 (1)	76 (15)	1,009
Totals		2,031	790	311	110	1,310	20	168	3,341

an increased risk of oesophageal cancer (RR 2.9, 95% CI 1.1–6.0) and stomach cancer (RR 2.4, 95% CI 1.2–4.3). The finding that the relative risks for these sites remained high after follow-up past the first positive *BRCA* test in the family was excluded makes ascertainment bias a less likely explanation for these results.

Care needs to be taken in interpreting results for those sites where increased risks occurred only in those assumed to be positive. Nonetheless, the results identified in this study appear valid as they confirm unequivocal associations without creating multiple new associations. Ideally, such findings would be confirmed in larger prospective studies with sufficient numbers of positive individuals to provide relative risks with narrow confidence intervals.

The risk for malignancies at other sites has so far been addressed using two types of study: (a) Family-based studies, which compare the observed *and* expected number of cases of a specific malignancy and (b) Studies which compare rates of *BRCA1/BRCA2* mutations in unselected cases of a specific malignancy with mutation rates in controls or in the general population (these are usually only carried out in founder populations). In family-based studies, cancers other than breast or ovarian cancer were confirmed by pathology or clinical records in only about half of the cases [13, 15]. This compares to the 64% in the present study. Whilst, inability to confirm cancers was more difficult in the previous studies based on family members from multiple generations, absence of confirmation in previous studies is not a criticism, but failure to confirm especially in more distant relatives and in previous generations makes the diagnosis far less certain.

Prostate cancer risk was previously assessed in 173 Breast cancer Linkage Consortium (BCLC) *BRCA2* families [12] showing a RR of 4.65 (95% CI 3.48–6.22), corresponding to a cumulative 7.5% (95% CI 5.7–9.3%) risk by age 70 years. A Dutch study of *BRCA2* carriers [15] showed a cumulative risk of 5.2% (95% CI 1.7–8.7%) by age 70 years, with an RR of 2.5 (95% CI 1.6–3.8) [15]. BCLC family-based studies found that prostate cancer risk in *BRCA2* carriers depend on age and *BRCA2* mutation location. Relative prostate cancer risk was higher in men younger than 65 years (RR 7.3, 95% CI 4.7–11.5) [12]. The lower risk in OCCR mutations 95% CI 0.24–1.00) may explain why prostate cancer risk has not been consistently elevated in studies of *BRCA2* in the Jewish population where the 6174DelT mutation predominates [18]. However, a population based study of breast cancer in Australia found the prostate cancer RR in FDRs of *BRCA2* carriers was 18.55 (95% CI 4.64–74.17) [19]. Our study has shown a 6.3 fold RR of prostate cancer although this did drop to 4.2 after excluding the follow up period after mutation testing to remove cancers diagnosed by screening tests precipitated by the finding of a family mutation. Unfortunately given the numbers of prostate cancers an assessment of the OCCR region was not possible in the initial cohort. However, an updated analysis throws considerable doubt on whether there is a lower risk with OCCR mutations with a significantly increased risk found for OCCR versus non OCCR mutations. From previous studies it is less clear whether *BRCA1* mutations increase prostate cancer risk. In the BCLC *BRCA1* families, there was some evidence of an increased risk of prostate cancer from both studies [13, 14]. The first study based on only 33 families with linkage to *BRCA1* found a RR for prostate cancer of 3.33 (95% CI 1.78–6.20) [14]. The second, larger study only found an increased risk for men younger than 65 years (RR 1.82, 95% CI 1.01–3.29), but not for those aged 65 years or older (RR 0.84, 95% CI 0.53–1.33) [13]. Studies in Jewish populations have yielded conflicting results [18]. The present study shows no evidence for increased prostate cancer risk in *BRCA1* carriers (RR 1.0) and this is supported by a population based study in Poland [20].

Table 2 Relative risk of cancer in individuals with BRCA mutations

Type of cancer	Observed*	Expected	Relative risk	Confidence intervals (95%)
All cancers (excluding breast, ovarian and non-melanoma skin cancers)				
BRCA1	54.4	80.3	0.7	0.5–0.9
BRCA2	105.7	70.3	1.5	1.2–1.8
Oesophagus				
BRCA1	6.8	2.4	2.9	1.1–6.0
BRCA2	8.9	2.2	4.1	1.9–7.8
Stomach				
BRCA1	10.4	4.4	2.4	1.2–4.3
BRCA2	10.7	4.0	2.7	1.3–4.8
Gall bladder and bile duct				
BRCA1	1.0	0.5	2.2	0.0–12.3
BRCA2	1.8	0.4	4.3	0.4–16.7
Pancreas				
BRCA1	1.8	2.4	0.8	0.1–2.9
BRCA2	8.9	2.2	4.1	1.9–7.8
Cutaneous melanoma				
BRCA1	2.4	2.6	0.9	0.1–3.1
BRCA2	6.0	2.3	2.6	1.0–5.7
Uveal melanoma				
BRCA1	0.0	0.0	0.0	
BRCA2	2.0	0.02	99.4	11.1–359.8
Prostate				
BRCA1	6.1	5.8	1.0	0.4–2.3
BRCA2	31.7	5.0	6.3	4.3–9.0
Haematological				
BRCA1	6.5	6.5	1.0	0.4–2.1
BRCA2	1.0	5.9	0.2	0.0–1.0
Colorectal				
BRCA1	11.0	11.4	1.0	0.5–1.7
BRCA2	10.4	10.3	1.0	0.5–1.8
Larynx				
BRCA1	0.9	1.1	0.9	0.0–5.0
BRCA2	0.0	1.0	0.0	
Trachea, bronchus and lung				
BRCA1	8.2	14.2	0.6	0.3–1.1
BRCA2	10.9	13.2	0.8	0.4–1.5
Cervix				
BRCA1	1.8	4.0	0.4	0.0–1.7
BRCA2	1.8	3.5	0.5	0.1–2.0
Body of uterus				
BRCA1	4.3	2.1	2.0	0.6–5.0
BRCA2	4.0	2.0	2.0	0.6–5.2
Urinary bladder				
BRCA1	4.0	4.5	0.9	0.2–2.3
BRCA2	2.0	4.1	0.5	0.1–1.8
Brain				
BRCA1	0.7	1.8	0.4	0.0–2.8
BRCA2	1.2	1.6	0.8	0.0–3.7

* The observed number is often not a whole number due to the method used in allocating the observed number of cancers in all untested FDRs into those in individuals who would have tested (i) positive and (ii) negative, as only (i) are included

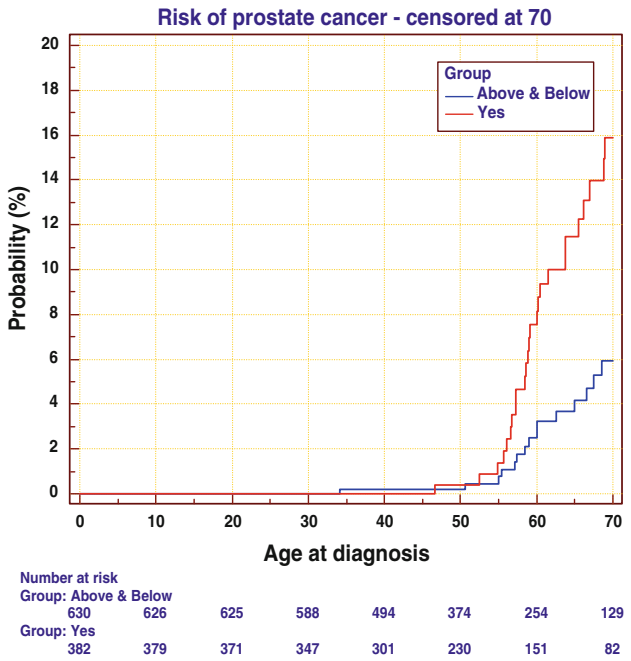

Fig. 1 Cumulative incidence of prostate cancer on Kaplan–Meier analysis in males with mutations in the BRCA2 OCCR and their FDRs compared to males from families with mutations outside the OCCR

Amongst 1,793 prostate cancers *BRCA1* mutations were less frequent than in 4,570 controls RR 0.9, although risk did vary between the three common mutations.

Pancreatic cancer is the only other malignancy for which there is unequivocal evidence for increased risk in *BRCA1/2* carriers. In *BRCA1* carriers pancreatic cancer risk from a family based study by age 70 years has been estimated to be 1.16% (95% CI 0.83–1.61%) in men, and 1.26% (95% CI 0.92–1.72%) in women, reflecting a twofold RR [13]. However, the evidence for this is not supported from population based cancer studies in either Polish or Jewish founder populations [21, 22]. No mutations were identified amongst 88 pancreatic cancers in Poland and only two amongst 144 (1.3%) in a Jewish study. These compare with founder expected frequencies of 0.5 and 1.1% in the background populations. The absence of any evidence for increased pancreatic cancer risk in the present study throws further doubt on any association. In *BRCA2* carriers, the largest previous study was of 177 families, which included data on 566 malignancies other than breast or ovarian cancers. This BCLC study estimated pancreatic cancer risk in *BRCA2* carriers with a RR of 3.51 (95% CI 1.87–6.58) and a cumulative risk of pancreatic cancer by age 70 years of 2.1% (95% CI 1.2–3.0%) in men, and 1.5% (95% CI 0.9–2.1%) in women [12]. The smaller Dutch study, based on 199 malignancies other than breast or ovarian cancer, estimated pancreatic cancer RR in *BRCA2* carriers as 5.9 (95% CI 3.2–10.0), and cumulative risk by age 70 years at 4.1% (95% CI 1.0–7.3%) in men and 1.4% (95% CI 0–3.4%) in women [15]. These risk estimates are also consistent with the 4–7% rate of *BRCA1* and *BRCA2* mutations among unselected pancreatic cases [18]. We also found an increased risk of gall bladder and bile duct cancer for BRCA2 based on two confirmed cases in FDRs. This supports the risks found in the large BCLC study (RR 4.97, 95% CI 1.50–16.52) [12].

Colon and rectal cancer risk was originally thought to be increased in *BRCA1,* but not *BRCA2* carriers [12, 14]. However, the second larger BCLC study, showed that colorectal cancer risk was not increased [13] and a large study of 225 unselected Jewish colon cancer cases did not find increased rates of either *BRCA1* or *BRCA2* mutations [23]. Malignant melanoma, both cutaneous and ocular, has been reported in *BRCA2* families [11], and an excess risk has been reported in the BRCA2-BCLC families [12]. This has not been confirmed in a smaller Dutch study [15]. A study of 385 unselected uveal melanoma cases has not shown excess rates of *BRCA2* mutations [24]. However, the current study shows a RR of 99.4 (95% CI 11.1–359.8) with two confirmed cases in carriers. The relative risk for cutaneous melanoma was 2.6 (95% CI 1.0–5.7) in this study, just falling short of statistical significance. Taken together, these results suggest that melanoma (including uveal) risk may be elevated in specific *BRCA2* families, but not for all *BRCA2* carriers. Non melanoma skin cancer is difficult to study, as it is not reliably reported on cancer registries. One study does suggest that this may be elevated for *BRCA2* [25].

Determining the risk of stomach cancer risk is problematic due to the use of ‘stomach’ by lay people to refer to any abdominal cancer [26]. Even in FDRs, confirmation rates for abdominal cancers are not impressive [26]. The BCLC study found an increased stomach cancer risk (RR 2.59, 95% CI 1.46–4.61) [12] in *BRCA2* carriers, but this was not supported by the Dutch study (non-significant RR 1.2) [15]. We found a significant RR of 2.7 (95% CI 1.3–4.8) for stomach cancer based on four confirmed cases in carriers and 9 confirmed cases in untested FDRs. Confirmation of cancers is an important issue when risk estimates are based on a small number of cases. Liver and bone cancers may represent distant metastases from other sites. In English parlance ‘throat’ cancer might be interpreted as oesophageal, pharyngeal or laryngeal cancer. The Dutch study that achieved cancer verification in only 46% of cases found significant RR for both bone (14.4, 95% CI 2.9–42.1) and pharynx (7.3, 95% CI 2.0–18.6). We did not find an increased risk for pharynx, but did find one for oesophagus. This was nonetheless based on only one confirmed case of eight in FDRs although the three mutation carriers were confirmed. Nonetheless the possible association is supported by a study in Iran [27]. A nonsense variant, K3326X, was identified in 9

of 197 cases (4.6%) versus 2 of 254 controls (0.8%) (OR 6.0, 95% CI 1.3–28; $P = 0.01$).

The first study of *BRCA1* carriers did suggest an increased risk of non ovarian gynaecological cancer [14] but this was not supported by the larger follow up BCLC study [12]. Our own study appeared to show increased risks amongst proven mutation carriers for both *BRCA1* and BRCA2, but this was not seen in FDRs and overall RRs for endometrial cancer were not significantly increased. Any increased risk in carriers could be related to concomitant breast cancer and tamoxifen treatment which occurred in 2/4 *BRCA1* and three of four *BRCA2* carriers with the endometrial cancers occurring 6–15 years after primary breast cancer.

This study represents the largest family based study of cancer risks based on 268 *BRCA1* families and 222 *BRCA2* families. Cancer confirmations were overall higher than in previous family based studies. The current study has confirmed increased risks for prostate and pancreatic cancers in *BRCA2* carriers equivalent to a four-fold risk. Possible excess risks of oesophageal and stomach cancer are also reported, but *BRCA1* carriers now look to have negligible excess risks with the possible exception of cancers of the upper gastrointestinal tract. Until large prospective studies of mutation carriers are available studies of this kind are useful in assessing other cancer risks in *BRCA1/2* carriers.

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