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BRCA1 and *BRCA2* mutations among 233 unselected Finnish ovarian carcinoma patients

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Germline mutations of *BRCA1* and *BRCA2* predispose to hereditary breast-ovarian cancer syndrome. In Finland, 20 different *BRCA1/2* mutations have been identified, and 13 of them are founder mutations that account for the vast majority of Finnish *BRCA1/2* families. The purpose of our study was to determine the prevalence of *BRCA1/2* mutations in unselected Finnish ovarian carcinoma patients and to evaluate the relationship between mutation carrier status and personal/family history of cancer. Two hundred and thirty-three patients were screened for all the 20 *BRCA1/2* mutations known in the Finnish population. Additionally, a subgroup of patients with personal history of breast cancer and/or family history of breast and/or ovarian cancer was screened for novel *BRCA1/2* mutations. Thirteen patients (5.6%) had mutations: eleven in *BRCA1* and two in *BRCA2*. All the mutation-positive patients were carriers of the previously known Finnish *BRCA1/2* mutations, and seven recurrent founder mutations accounted for 12 of the 13 mutations detected. A logistic regression analysis was used to determine the odds of mutation for ovarian carcinoma patients. The most significant predictor of a mutation was the presence of both breast and ovarian cancer in the same woman, but family history of breast cancer was also strongly related to mutation carrier status. Although *BRCA1/2* mutation testing is not warranted in the general Finnish ovarian cancer patient population, patients who have also been diagnosed with breast cancer or have family history of breast or breast and ovarian cancer could benefit from referral to genetic counselling and mutation testing. *European Journal of Human Genetics* (2001) **9**, 424–430.

Keywords: *BRCA1*; *BRCA2*; founder mutations; ovarian carcinoma; Finland

Introduction

Inherited mutations of *BRCA1* and *BRCA2* predispose to hereditary breast-ovarian cancer syndrome. The lifetime risk of ovarian carcinoma has been estimated to be ~60% in *BRCA1* mutation carriers[1] and ~30% in *BRCA2* mutation carriers.[2] However, these estimates were based on families with multiple cases of breast and/or ovarian cancer, and studies that have consisted of patients not selected for their strong family history have suggested considerably lower risks.[3–5] Furthermore, the location of the mutation in *BRCA1* and *BRCA2* may affect cancer phenotype.[5–7] A higher ovarian cancer risk, in relation to breast cancer risk, has been reported to be associated with mutations in the 5′ end of the *BRCA1* gene,[5,6] and in exon 11 of *BRCA2*, in a region known as the ovarian cancer cluster region.[5,7]

Hundreds of distinct mutations, most of which are unique, have been identified throughout the entire coding sequences of both *BRCA1* and *BRCA2*,[8] which makes large-scale mutation screening laborious. In certain ethnic groups and populations, the presence of individual, highly recurrent

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founder mutations facilitates mutation carrier detection. Among Ashkenazi Jews, three *BRCA1/2* founder mutations have been found to be present in about 40% of unselected ovarian carcinoma patients.[4] In addition to the Ashkenazi Jews, the frequencies of *BRCA1* and/or *BRCA2* mutations have been studied thus far in the UK, Hungary, Iceland, Canada, and the US, where the mutation frequencies have been observed to be considerably lower (varying from 2 to 10% for *BRCA1* and from 1 to 8% for *BRCA2*).[5,9–17]

In the Finnish population 20 different *BRCA1/2* mutations have been identified.[18–23] Thirteen of the mutations, six in *BRCA1* and seven in *BRCA2*, are recurrent founder mutations that account for the vast majority of all mutations detected. Due to the high coverage of the multiple founders, the impact of both *BRCA1* and *BRCA2* mutations can be studied efficiently and reliably at the population level in Finland. In the present study, all *BRCA1/2* mutations known in the Finnish population were screened in a series of 233 unselected ovarian carcinoma patients. Furthermore, novel mutations were screened in a subset of patients with personal history of breast cancer and/or family history of breast and/or ovarian cancer. Mutation carrier status was correlated with personal and family history of breast and ovarian cancer.

Patients and methods

Patients

The study group consisted of 233 women with invasive epithelial ovarian carcinoma treated at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Finland during the years 1989–1998. The Finnish population is well represented in the Helsinki University Central Hospital region: a quarter of the Finns reside in the region, and because of recent migration patterns in Finland, the patients diagnosed in the Helsinki University Central Hospital have their ancestral origins throughout Finland. Altogether 573 invasive epithelial ovarian carcinoma patients were treated at the Department during the years 1989–1998, and at the end of the year 1998, 220 of those patients were alive. After initial treatment the patients routinely attend the clinic at least once a year for a time period of 10 years. In conjunction with such visits during the years 1997 and 1998, a blood sample and a written informed consent were obtained from the patients. Information concerning family history of cancer was collected by questionnaire interviews. The cohort studied covers 91% of all epithelial ovarian carcinoma patients who were alive during the study period. The distribution of clinical and histopathological characteristics in the present study cohort and in the general Finnish ovarian cancer patient population are shown in Table 1. The study was approved by the Ethical Committee of the Department of Obstetrics and Gynecology, and appropriate permissions were obtained from the Ministry of Social Affairs and Health in Finland.

Detection of known mutations

All 233 DNA samples were screened for 12 *BRCA1* and eight *BRCA2* mutations identified previously in the Finnish population.[18–23] Genomic DNA was extracted by standard procedures and amplified by polymerase chain reaction (PCR). Mutation detection was carried out using allele specific oligonucleotide hybridisation (ASO)[24] or restriction fragment length polymorphism (RFLP) analysis. The RFLP analyses were designed such that incomplete digestion would lead to a false positive, hence minimising the possibility of false negative result. Sequences of the PCR primers and ASO probes, as well as the enzymes used for digestions are available upon request. The mutation results were confirmed by direct sequencing using an ABI PRISM 310 Genetic Analyzer and Dye Terminator Cycle Sequencing Ready Reaction Kit according to the manufacturer's instructions (PE Applied Biosystems, Foster City, CA, USA).

Screening for new mutations

Protein truncation test (PTT) was used in screening *BRCA1* exon 11[25] and *BRCA2* exons 10 and 11[26] for new mutations in 38 patients who reported: (1) two or more 1st and/or 2nd degree relatives diagnosed with breast or ovarian cancer; (2) a 1st, 2nd, or 3rd degree relative with ovarian cancer; (3) a 1st degree relative with breast cancer; and/or (4) a 1st degree relative with both breast and ovarian cancer or had themselves been diagnosed with both cancers.

In order to detect possible large genomic rearrangements and deletions in *BRCA1*, Southern analysis was performed on eleven patient samples and two healthy population control individuals. Genomic DNA (5 μg) was digested with *Eco*RI according to the supplier's protocol (New England Biolabs, Beverly, MA, USA). Complete digests were run on agarose gels and separated DNA was denatured and transferred to nylon membranes (Hybond-N^+, Amersham Pharmacia Biotech, Uppsala, Sweden) according to the protocol published by Petrij-Bosch *et al*.[8,27] The probes consisted of PCR products amplified from cloned DNA containing the complete *BRCA1* cDNA (pcBRCA1-385, a kind gift from Dr Lawrence Brody, NHGRI, NIH, MD, USA) and purified with the Qiaquick PCR purification kit (Qiagen GmbH, Hilden, Germany). Probes 1, 2, and 3 were obtained with primers F(forward)5′-GATTTATCTGCTCTTCGC-3′ and R(reverse)5′-CTTGACCATTCTGCTCC-3′ (nucleotides (nt) 123-1752), F5′-CTAACCAAACGGAGCAG-3′ and R5′-AACAAGTGTTGGAAGCAG-3′ (nt 1726-3791), and F5′-TTCCCTGCTTCCAACAC-3′ and R5′-TGCTACACTGTCCAACACC-3′ (nt 3787-5648), respectively. Purified fragments were labelled with [α-^{32}P]dCTP using Rediprime DNA labelling system (Amersham Pharmacia Biotech) according to the supplier's protocol. Prehybridisation, hybridisation, and washing were carried out as described by Petrij-Bosch *et al*.[8,27] Filters were exposed overnight to Hyperfilm MP autoradiography film (Amersham Pharmacia Biotech) at -70°C.

Table 1 Clinical and histopathological characteristics

Variable	*The present study cohort* (n=233)	*General ovarian cancer patient population*[a] (%)
(a) Stage available	133 (57%)	
I	60 (45%)	27
II	8 (6%)	13
III	57 (43%)	47
IV	8 (6%)	13
(b) Grade available	155 (67%)	
1	69 (44%)	27
2	38 (25%)	20
3	48 (31%)	53
(c) Histology available	233 (100%)	
Serous	118 (51%)	45
Mucinous	49 (21%)	13
Endometrioid	33 (14%)	10
Mesonephroid	19 (8%)	9
Poorly differentiated	14 (6%)	23
(d) Age at ovarian cancer diagnosis, years mean $\pm$ SD, range	55 $\pm$ 13, 23–96	58 $\pm$ 13

SD, standard deviation; [a]according to the study by Venesmaa. [44]

Statistical methods

A logistic regression analysis was used to determine the odds of mutation for ovarian cancer patients using personal and family history variables as explanatory variables. Fisher's exact test was used to study the association between mutation carrier status and young age (<50 years) at breast cancer onset.

Results and Discussion

Germline mutations of *BRCA1/2* were detected in 13 (5.6%) of the 233 unselected Finnish ovarian carcinoma patients. Mutations detected and personal and family history of cancer of the mutation carriers are presented in Table 2. No new mutations were identified in this study, and seven recurrent founder mutations accounted for 12 of the 13 mutations detected, emphasising the significance of the *BRCA1/2* founder mutations in Finland. Thus about 5% of the ovarian carcinoma patients were carriers of the recurrent *BRCA1/2* founder mutations. The only unique mutation had been identified previously[21] in the same patient that also belonged to the present study cohort. Large genomic deletions that have been identified as major *BRCA1* founder mutations in the Netherlands[27] do not seem to be significant in the Finnish population; no such mutations were found among the 11 ovarian carcinoma patients studied here or in another study of 80 Finnish breast and/or ovarian cancer families (R Winqvist, personal communication).

In the Finnish ovarian carcinoma patient, the frequency of *BRCA1* mutations (4.7%) was notably higher than the frequency of *BRCA2* mutations (0.9%). In contrast, in a population-based study of 1035 unselected Finnish breast cancer patients, *BRCA2* mutations were considerably more prevalent (with the frequency of 1.4%) than *BRCA1* mutations (with the frequency of 0.4%).[22] Overall, *BRCA1/2* mutations are more prevalent in unselected Finnish ovarian cancer (5.6%) than breast cancer patients (1.8%).

The frequency of *BRCA1/2* mutations (5.6%) in the Finnish ovarian carcinoma patients is far lower than in the Ashkenazi Jewish population where three highly recurrent *BRCA1/2* founder mutations were detected in 41.3% (86/208) of unselected ovarian carcinomas.[4] Among French Canadians, few *BRCA1* and *BRCA2* founder mutations were found in 8.1% (8/99) of unselected ovarian carcinoma patients,[16] while in a population-based series of unselected Canadian ovarian carcinoma patients, 26 distinct *BRCA1* and 19 distinct *BRCA2* mutations were detected with the frequency of 7.6% (39/515) and 4.1% (21/515), respectively.[5] In the isolated Icelandic population, one strong *BRCA2* founder mutation was present in 7.9% (3/38) of ovarian carcinomas,[15] and in Hungary, three *BRCA1* founder mutations accounted for 11.1% (10/90) of unselected ovarian carcinoma patients, whereas none of the patients carried either of the two *BRCA2* founder mutations known in the Hungarian population.[13]

The frequencies of *BRCA1* (4.7%) and *BRCA2* (0.9%) the mutations in Finland are more similar to those reported in the UK and the US.[9–12,14,17] In the screening for *BRCA1* mutations, 1.9–3.9% of unselected ovarian carcinoma patients were found to be mutation-positive in California and North Carolina.[9,10,12] In Pennsylvania, the frequency of *BRCA1* mutations has been reported to be as high as 8.6%.[14] However, in that study the ethnicity of the patients was unknown, whereas in the other American studies Ashkenazi Jews were known not to be overrepresented.[9,10,12,14] *BRCA2* mutations have been detected in 0.9–3.1% of American ovarian carcinomas.[14,17] In the UK, 3.5% (13/374) of unselected ovarian carcinoma patients were found to be mutation-positive in the screening for *BRCA1* mutations.[11] The mutation detection sensitivity was estimated to be 70%, hence the true *BRCA1* mutation frequency would be 5%.[11] The *BRCA1/2* mutation frequency of 5.6% reported in our study obviously also represents an underestimate. New mutations were searched in a subset of patients with personal history of breast cancer and/or family history of breast and/or ovarian cancer, whereas all patients were screened for all 20 *BRCA1/2* mutations known to be present in the Finnish population. We believe that our result is well representative of the *BRCA1/2* mutation burden because founder mutations have been found to account for the vast majority of *BRCA1/2* families in Finland.[18–21] The significance of these founder mutations was also observed in this independent study. Ovarian carcinomas of high grade are typical for *BRCA1/2* mutation carriers.[4] Such carcinomas were, however, slightly underrepresented in our study cohort (Table 1); thus the real mutation frequencies might be somewhat higher. However, the possible effects of retrospectively collected study cohort are hard to evaluate as contradictory results on survival of *BRCA1/2* mutation carriers have been reported.[28–31]

Table 2 Mutations detected and personal and family history of cancer of the mutation-positive patients

Patient number	*Gene and mutation*[a]	*Type of cancer and age at onset*[b]	*Number of 1st and 2nd degree relatives with breast and/or ovarian cancer (type of cancer, age at onset, and degree of relatedness)*	*Other cancer cases in the family*	*Bc at any age*[c]	*Bc and oc in the same person*[d]	*Bc< 50 years*[d]	*Bc and oc in the same person and/or bc< 50 years*[d]
	BRCA1							
654	ex11, 3604delA	bc 41, oc 44		Endometrium	yes	yes	yes	yes
911	ex11, 3604delA	oc 42	1 (bc 55, 2nd)	Esophagus, melanoma	yes	no	no	no
913	ex11, 3604delA	oc 42	1 (bc 46, 1st)	–	yes	no	yes	yes
1000	ex11, 3604delA	oc 53	2 (bc 58, oc 46, 1st; bc 50, 2nd)	Leukemia, lung × 2, skin	yes	yes	no	yes
816	ex11, 3744delT	oc 43		Abdominal cancer[e], endometrium	no	no	no	no
673	ex11, 4153delA	bc 32, oc 48		Melanoma, meyloma	yes	yes	yes	yes
723	int11, 4216nt-2A→G	oc 59		Abdominal cancer[e] × 4	no	no	no	no
883	int11, 4216nt-2A→G	bc 52, oc 58	1 (bc n.k., 1st)	Lung	yes	yes	no	yes
87	ex13, 4446C→T	bc 48, oc 58	3 (bc 52, 1st; bc n.k., 2nd; bc n.k., 2nd)	–	yes	yes	yes	yes
656	ex13, 4446C→T	bc 37, oc 40		Breast × 2, lung × 2, sarcoma	yes	yes	yes	yes
257	ex20, 5370C→T	bc 50, oc 57	1 (bc 60, 1st)	Breast	yes	yes	no	yes
	BRCA2							
488	ex11, 5797G→T	oc 52	2 (bc d37, 1st; oc 55, 1st)	–	yes	no	yes	yes
983	int23, 9346nt-2A→G	oc 70	1 (bc 43, 1st)	–	yes	no	yes	yes
					11/13 (85%)	7/13 (54%)	7/13 (54%)	10/13 (77%)

bc, breast cancer; d, deceased; n.k., not known; oc, ovarian cancer; [a]All mutations detected in this study have been identified previously in the Finnish population,[19–21,23] and all but 4153delA in *BRCA1* are recurrent founder mutations; [b]The mean ± SD age at ovarian cancer onset is 51 ± 9 years; [c]Index and/or 1st and/or 2nd degree relative(s); [d]Index or 1st degree relative; [e]unspecified.

In most populations *BRCA1/2* mutations are relatively uncommon among ovarian cancer patients. Therefore, it is important to identify risk factors that predict the likelihood of finding a *BRCA1/2* mutation, so that mutation screening could be directed to potential mutation carriers.[32] Among the 13 mutation carrier patients, 11 (85%) had a personal and/or family history of breast cancer (Table 2). Breast and ovarian cancer had been diagnosed in the same woman (index or a relative) in seven cases (54%), and also seven of the mutation carriers had a history of breast cancer diagnosed below the age of 50 years (index or a relative). Altogether, the presence of breast and ovarian cancer in the same woman and/or early onset (<50 years) breast cancer was characteristic of the majority (77%) of the mutation carriers. When a logistic regression analysis was used to determine the odds of a *BRCA1/2* mutation for ovarian carcinoma patients, the single most significant predictor of a mutation was the presence of both breast and ovarian cancer in the same patient (Table 3). The odds ratio also independently increased for patients who reported at least two relatives with breast or ovarian cancer and for patients who reported one relative with breast cancer only (Table 3). The likelihood of finding a mutation also increased when the age at breast cancer onset became younger (Table 4). However, there was no statistically significant association between the mutation carrier status and young age (<50 years) at breast cancer onset (P=0.40, Fisher's exact test). This may be due to the small number of breast cancer cases for which the information on the age at onset was available. In addition to personal and family history of breast and ovarian cancer, bilateral breast cancer, young age at breast cancer onset, and Ashkenazi Jewish descent have been reported to be predictive of a *BRCA1* or *BRCA2* mutation.[33–36]

Ovarian cancer histology might also be predictive of *BRCA1* mutations since almost all *BRCA1*-associated ovarian carcinomas have been reported to be of serous histology,[5,11] while *BRCA2* mutation carriers have been reported to have carcinomas of various histological subtypes.[17] In our study, all mutation-positive patients except for one had serous or poorly differentiated carcinoma (Table 4). Of all serous carcinomas, *BRCA1* mutation was found in 6.8% and *BRCA2* mutation in 1.7%. None of the mutation carriers had a carcinoma of mucinous or endometrioid subtype. However, the tumour histology variable did not independently increase the odds of mutation in the logistic regression analysis. Since there is evidence that the molecular pathogenesis of various histological forms of ovarian carcinoma might be distinct,[37] it seems likely that somatic mutations that occur in association with the inactivation of the *BRCA1* gene may lead to the serous subtype of ovarian carcinoma.

No mutations were detected among the thirteen patients who reported one 1st or 2nd degree relative with ovarian cancer only (Table 4). Also in the study of Gayther *et al*[38] *BRCA1/2* mutations were detected in only 20% of families

Table 3 Logistic regression analysis of the association between personal and family history of breast and ovarian cancer and *BRCA1/2* mutation carrier status

Variable	*Coefficient*	*SE*	*OR (95% CI)*
Intercept	−4.21	0.59	0.02 (0.01 – 0.05)
Breast and ovarian cancer in the same person[a]	4.59	0.99	98.69 (14.11 – 690.15)
Family history of breast and ovarian cancer[b]			
One relative with breast cancer	1.83	0.85	6.22 (1.17 – 33.16)
One relative with ovarian cancer	−3.00	6.20	0.05 (2.65×10^{-7} – 9402.47)
Two or more relatives with breast or ovarian cancer	2.70	1.16	14.84 (1.53 – 143.61)

CI, confidence interval; OR, odds ratio; SE, standard errror; [a]Index or 1st degree relative; [b]In 1st and 2nd degree relatives.

Table 4 Mutation prevalences according to personal/family history of breast/ovarian cancer, age at breast/ovarian cancer onset, and ovarian cancer histology

Variable	*Number of cases tested* (n=233)	*Number of cases with mutation* *BRCA1* (n=11) *(5%)*	*BRCA2* (n=2) *(1%)*	*BRCA1/2* (n=13) *(6%)*	*Number of cases without mutation* (n=220) *(94%)*
(a) Family history of breast and ovarian cancer[a]					
None	182 (78%)	5 (3%)	0	5 (3%)	177 (97%)
One relative with breast cancer	30 (13%)	4 (13%)	1 (3%)	5 (16%)	25 (84%)
One relative with ovarian cancer	13 (6%)	0	0	0	13 (100%)
Two or more relatives with breast or ovarian cancer	8 (3%)	2 (25%)	1 (13%)	3 (38%)	5 (62%)
(b) Breast and ovarian cancer in the same person[b]	9 (4%)	7 (78%)	0	7 (78%)	2 (22%)
(c) Age at onset					
Breast cancer[b]					
<40 years	4 (2%)	2 (50%)	1 (25%)	3 (75%)	1 (25%)
<50 years	13 (6%)	5 (39%)	2 (15%)	7 (54%)	6 (46%)
$\geqslant 50$ years	10 (4%)	3 (30%)	0	3 (30%)	7 (70%)
$\geqslant 60$ years	4 (2%)	0	0	0	4 (100%)
Ovarian cancer[c]					
<50 years	96 (41%)	7 (7%)	0	7 (7%)	89 (93%)
$\geqslant 50$ years	137 (59%)	4 (3%)	2 (1%)	6 (4%)	131 (96%)
(d) Histology[c]					
Serous	118 (51%)	8 (7%)	2 (2%)	10 (9%)	108 (91%)
Mucinous	49 (21%)	0	0	0	49 (100%)
Endometrioid	33 (14%)	0	0	0	33 (100%)
Mesonephroid	19 (8%)	1 (5%)	0	1 (5%)	18 (95%)
Poorly differentiated	14 (6%)	2 (14%)	0	2 (14%)	12 (86%)

[a]In 1st and 2nd degree relatives; [b]Index or 1st degree relative; [c]Index.

with two cases of ovarian cancer alone, while they were detected in 66% of families with either three or more cases of ovarian cancer or four or more cases of breast or ovarian cancer. A combination of chance clustering of sporadic cases, non-genetic familial factors, and incomplete sensitivity of mutation detection may account for a significant fraction of *BRCA1/2* mutation-negative ovarian carcinoma families. However, still unidentified, possible low-penetrance genes may be important in some families.[39]

Ovarian carcinoma also occurs as part of the hereditary nonpolyposis colorectal cancer syndrome (HNPCC), which is caused by germline mutations in DNA mismatch repair genes.[40] Mutations in these genes have been reported in 1.7% of unselected ovarian carcinoma patients.[14] Instability of several microsatellites, which is a characteristic of inherited mismatch repair system deficiency,[41,42] ie HNPCC, has been detected in one out of 62 (1.6%) serous ovarian carcinomas in the present study cohort;[43] thus mutations in the genes that predispose to HNPCC are likely to account for only a small fraction of the ovarian carcinomas in our series.

In conclusion, *BRCA1/2* founder mutations account for about 5% of ovarian carcinomas in Finland. Since screening of all ovarian carcinoma patients for *BRCA1/2* mutations is not clinically and ethically justified, it is important to identify those women who have high probability of carrying a deleterious *BRCA1/2* mutation.[32] Our results indicate that ovarian carcinoma patients who have also been diagnosed with breast cancer or have family history of breast or breast and ovarian cancer could benefit from referral to genetic counselling and mutation testing.

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