UC Irvine
UC Irvine Previously Published Works

Title
Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer

Permalink
https://escholarship.org/uc/item/2s0829vb

Journal
European Journal of Cancer, 36(10)

ISSN
0959-8049

Authors
Anton-Culver, H
Cohen, PF
Gildea, ME
et al.

Publication Date
2000-06-01

DOI
10.1016/s0959-8049(00)00110-6

Peer reviewed

Characteristics of *BRCA1* mutations in a population-based case series of breast and ovarian cancer

H. Anton-Culver *, P.F. Cohen, M.E. Gildea, A. Ziogas

Epidemiology Division, College of Medicine, 224 Irvine Hall, University of California, Irvine, Irvine, CA 92697–7550, USA

Abstract

Breast and ovarian cancers account for approximately 210 000 newly diagnosed cases per year. More than half a million American women are estimated to be carriers of a breast cancer susceptibility gene. The purpose of this study was to assess the association of characteristics such as, age at diagnosis, race/ethnicity and family history of cancer with inherited *BRCA1* mutations in a population-based sample of breast and ovarian cancer cases. No selection was made by race, age at diagnosis or positive family history of breast or ovarian cancer. The population under study was all breast cancer cases diagnosed in Orange County, CA, during the 1-year period beginning 1 March 1994 and all ovarian cancer cases diagnosed in Orange County during the 2-year period beginning 1 March 1994. This report focuses on the first consecutively ascertained 802 participating probands enrolled in the study, of which 9 were male breast cancer probands, 673 were female breast cancer probands and 120 were ovarian cancer probands. We observed 11 *BRCA1* mutations or 1.6% (95% CI: 0.8–2.9) among the 673 female breast cancer probands and 4 *BRCA1* mutations or 3.3% (95% CI: 0.8–8.3) among the 120 ovarian cancer probands. No *BRCA1* mutations were identified among the 98 non-white breast and ovarian cancer probands. The prevalence of *BRCA1* mutations in non-Hispanic-white breast cancer cases below the age of 50 years was 2%. Positive family history of breast or ovarian cancers was significantly associated with *BRCA1* mutation status among breast cancer probands. Similarly, positive family history of breast or ovarian cancer was significantly associated with *BRCA1* mutation status among the ovarian cancer probands. In summary, we present results on the prevalence of *BRCA1* mutations in a significantly larger sample of population-based breast and ovarian cancer cases than previously reported. The results indicate that, using a conservative approach to targeted genotyping of *BRCA1*, the frequency of mutations was consistent with those reported using similar methods of population-based case ascertainment. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Keywords: BRCA1; Breast cancer; Ovarian cancer; Population-based

1. Introduction

Breast cancer is the most common cancer and ovarian cancer is the fifth most common cancer in women in the US. Breast and ovarian cancers account for approximately 210 000 newly diagnosed cases per year [1]. Of the 180 000 new breast cancer cases diagnosed yearly in the US, the estimated number of cases associated with a breast cancer susceptibility gene(s) is more than 10 000 [2,3]. More than half a million American women are estimated to be carriers of a breast cancer susceptibility gene. Some of these women may have a significantly increased risk of developing breast cancer and perhaps additional cancers over their lifetime depending on the degree of family history of cancer [2,4]. For these women, a prevention and early detection strategy is an essential aspect of managing their risk.

Early genetic linkage studies using multiple case families have suggested that mutations in the *BRCA1* gene account for 45% of hereditary breast cancer and 80–90% of breast and ovarian cancer [4–7]. Based on some of these studies, it was determined that *BRCA1* mutation carriers had a lifetime risk of 85% for breast cancer and 63% for ovarian cancer. More recent studies have included breast cancer families that are not highly selected for their strong family history of breast and ovarian cancer. These studies suggest that risk estimates are far lower than previously reported [8–15]. These

* Corresponding author. Tel.: +1-949-824-7416; fax: +1-949-824-4773.

E-mail address: hantoncu@uci.edu (H. Anton-Culver).

studies also suggest that mutations in *BRCA1* are attributable to only 16% of women with a family history of breast or ovarian cancer [13]. The study by Whittemore and colleagues [14] indicated that the risk of ovarian cancer among carriers is 27.8% based on population-based case–control studies of ovarian cancer.

In the present study, we describe the frequency of *BRCA1* mutations in a population-based series of 682 consecutive breast cancer probands and 120 consecutive ovarian cancer probands. We further describe the characteristics of breast and ovarian cancer probands with *BRCA1* mutations with respect to age at diagnosis, demographic characteristics including race and ethnicity, family history (presence of breast or ovarian cancer among first-degree or first- and second-degree relatives of the proband) and presence of multiple primary cancer. Thus, the purpose of the present study was to assess the characteristics of inherited *BRCA1* mutations in a population-based sample that was not selected by race, age at diagnosis or family history of breast or ovarian cancer.

2. Patients and methods

2.1. Patients

The population under study is all breast (female and male) cancer cases older than 18 years of age diagnosed in Orange County, CA, during the 1-year period beginning 1 March 1994 and all ovarian cancer cases diagnosed in Orange County during the 2-year period beginning 1 March 1994 (Internal Review Board No. HS91–137). Eligible probands were ascertained through the population-based cancer registry of the Cancer Surveillance Program of Orange County (CSPOC). Description of CSPOC and details of data collection methods have been reported previously [16–20].

Protocols for population-based ascertainment of breast and ovarian cancer have been established [21]. Breast cancer probands were identified within 6 months of diagnosis. However, for ovarian cancer probands we have incorporated a rapid reporting system to identify ovarian cancer cases within 4 weeks of diagnosis. Physicians were notified that their patient(s) would be contacted regarding study participation. This was followed by a letter of introduction sent to the patient, then by a telephone interview regarding the family history of cancer. Positive family history was determined as at least 1 first-degree relative with breast or ovarian cancer or no first-degree relative with breast or ovarian cancer but at least 2 second-degree relatives with breast or ovarian cancer on the same side of the family. Trained interviewers elicited information on dates of birth, types of cancer and diagnosis and death dates on all first- and second-degree relatives and first cousins of the proband,

including both affected and unaffected family members. After the subject signed a consent form, an 18-ml blood sample was drawn, and the proband completed an epidemiological risk factor questionnaire. All reported malignancies among family members were verified whenever possible by obtaining pathology reports, tumour tissue, clinical records, interview of another family member besides the proband and, if applicable, death certificates.

The population ascertained consisted of 2030 probands, of whom 342 were ovarian cancer cases, 17 male breast cancer cases, and 1671 female breast cancer cases. All probands were invited to participate in this breast and ovarian cancer family registry study. The distribution of the probands by race/ethnicity shows that 86.6% were non-Hispanic white, 7.2% Hispanic, 0.5% African-American and 5.7% Asian. The age distribution of contacted cases was: 8% below the age of 40 years, approximately 21% in each 10-year interval from 40 to 80 years of age and 10% for 81 years of age or older. More than 78% of the patients agreed to complete the family history interview. For breast cancer, 362 patients declined to participate (361 females and 1 male), and for ovarian cancer, 70 patients declined to participate. Of the non-participants, the most common reasons given for non-participation were 'not interested' (40%), 'bad health' (20%) and 'time commitment' (19%). Participants and non-participants did not differ significantly with respect to age and race/ethnicity. Details about participation status of the above-referenced population were presented by Ziogas and colleagues [22].

Overall 1598 probands were enrolled in the study (16 male cancer, 1310 female breast cancer and 272 ovarian cancer cases). This report focuses on the first consecutively ascertained 802 participating probands enrolled in the study, of which 9 were male breast cancer probands, 673 were female breast cancer probands and 120 were ovarian cancer probands. Approximately 4.5% of breast cancer probands were Ashkenazi Jewish and among the ovarian cancer probands 3.3% were Ashkenazi Jewish. 29% of the breast cancer probands were under the age of 50 years at diagnosis, and approximately 38% of the ovarian cancer probands were under the age of 50 years at diagnosis. Among the families with no family history of breast or ovarian cancer, there was an average of 7.6 female first- or second-degree relatives compared with 8.5 among families with positive family history.

Reported malignancies for the study in probands and family members were verified by obtaining pathology reports, clinical records, an interview of another family member in addition to the proband and review of death certificates. All probands' tumours were verified by pathology. 76% of first-degree relatives affected with breast or ovarian cancer were verified, whereas approximately 65% of affected second-degree relatives were verified. Details about verification of cancer

among first- and second-degree relatives in the population under study were presented in Ziogas and colleagues [22].

2.2. Laboratory methods

The details of the laboratory procedures have been described previously [23,24]. Allele-specific oligonucleotide (ASO) assays for *BRCA1* mutations 185delAG, 5382insC, R1443X, int5-11T-G, 4184delTCAA, R841W and 2594delC among breast cancer probands were performed using appropriate reverse transcriptase polymerase chain reaction (RT-PCR) or genomic PCR products prepared with nucleic acids purified from buffy coat samples as described elsewhere [23]. Of the 120 ovarian cancer cases, 13 were screened for mutations in the coding region of the *BRCA1* gene using the same ASO methods as in the breast cancer cases and 107 were screened for mutations usin the Rnase Mismatch Cleavage Assay (NIRCA; Ambion, Austin, TX, USA). Laboratory methods for genotyping of ovarian cancer probands have been presented elsewhere [24].

2.3. Statistical analysis

Proportions and 95% confidence intervals (CIs) for the two groups (breast and ovary) and for subgroups categorised by race, age-at-diagnosis and family history were computed by exact binomial probabilities. Tests for trends were computed by use of unconditional logistic regression.

3. Results

The characteristics of the 682 breast cancer probands and 120 ovarian cancer probands with respect to *BRCA1* status are presented in Table 1. Using the laboratory methods outlined above, where targeted mutations were tested in the breast cancer cohort and a full screening was done on the *BRCA1* gene in the ovarian cancer group, we observed 11 *BRCA1* mutations or 1.6% (95% CI: 0.8–2.9) among the 673 female

breast cancer probands and 4 *BRCA1* mutations or 3.3% (95% CI: 0.8–8.3) among the 120 ovarian cancer probands. The mean age at onset in female breast cancer probands was 54.0±14.5 years among the *BRCA1* carriers versus 58.4±13.0 years among non-carriers. Among the ovarian cancer probands the mean age at onset among *BRCA1* carriers was 49.8±5.7 years compared with 55.5±15.7 among the non-carriers. Both breast and ovarian cancer probands who were *BRCA1* carriers tended to be younger than non-carriers. However, the differences observed were not statistically significant.

Male breast cancer probands were genotyped for both *BRCA1* and *BRCA2* gene. No *BRCA1* mutations were identified among the nine male breast cancer probands. However, we detected two *BRCA2* mutations among the male breast cancer probands. Of the two *BRCA2* mutations among the male breast cancer probands, one occurred in a proband with no family history of breast or ovarian cancer among first- or second-degree relatives and the other occurred in a proband with family history of breast cancer in a first-degree relative. The mean age at onset of male breast cancer probands was 67.0±11.3 years (Table 1), whereas the mean age at onset of the 2 *BRCA2* mutation carriers was 61±1.4 years. Since the number of male breast cancer probands was small, the following analyses are limited to female breast or ovarian cancer families.

No *BRCA1* mutations were identified among the 98 non-white breast and ovarian cancer probands. Thus, the proportion of *BRCA1* carriers among the 592 non-Hispanic-white breast cancer probands was estimated to be 1.9% (95% CI: 0.9–3.3) and among the 103 non-Hispanic-white ovarian cancer probands was 3.9% (95% CI: 1.1–9.6) (Table 2). In addition, among the 30 breast cancer Ashkenazi probands, 6.7% were carriers of a *BRCA1* mutation. No statistically significant differences were observed among breast or ovarian cancer probands with respect to *BRCA1* status and tumour differentiation, histology or presence of multiple primaries. Since no *BRCA1* mutations were identified among the non-white breast or ovarian cancer probands, subsequent analyses include only the non-Hispanic-white probands.

Table 1
Type of proband by *BRCA1* mutation status and age of diagnosis

Type of proband	*BRCA1* Negative		*BRCA1* Positive		Total	
	n (%)	Mean age at diagnosis (years) ±SEM[a]	n (%)	Mean age at diagnosis (years)±SEM	n	Mean age at diagnosis (years)±SEM
Male breast	9 (100)	67.0±11.3	0	–	9	67.0±11.3
Female breast	662 (98.4)	58.4±13.0	11 (1.6)	54.0±14.5	673	58.4±13.1
Ovarian	116 (96.7)	55.5±15.7	4 (3.3)	49.8±5.7	120	55.3±15.5
Total	787 (98.1)	58.1±13.5	15 (1.9)	52.9±11.6	802	58.0±13.5

[a] SEM, standard error of the mean.

Table 2
General characteristics in female breast and ovarian cancer probands by *BRCA1* mutation status

Characteristic	Breast cancer probands		Ovarian cancer probands	
	BRCA1 negative (%) *n* = 662	*BRCA1* positive (%) *n* = 11	*BRCA1* negative (%) *n* = 116	*BRCA1* positive (%) *n* = 4
Race/ethnicity				
White	581 (87.8)	11 (100)	99 (85.3)	4 (100)
African-American	4 (0.6)	0	0	0
Hispanic	42 (6.3)	0	12 (10.3)	0
Asian	35 (5.3)	0	5 (4.3)	0
Race/ethnicity among whites	*n* = 581	*n* = 11	*n* = 99	*n* = 4
Non-Askhenazi	553 (95.2)	9 (81.8)	95 (96.0)	4 (100)
Askhenazi	28 (4.8)	2 (18.2)	4 (4.0)	0
Age at diagnosis (years)	*n* = 662	*n* = 11	*n* = 116	*n* = 4
< 40	39 (5.9)	2 (18.2)	17 (14.7)	0
40–49	153 (23.1)	2 (18.2)	26 (22.4)	3 (75)
50–59	161 (24.3)	4 (36.4)	23 (19.8)	1 (25)
60–69	147 (22.2)	1 (9.1)	22 (19.0)	0
⩾ 70	162 (24.5)	2 (18.2)	28 (24.1)	0
Multiple primaries	*n* = 662	*n* = 11	*n* = 116	*n* = 4
No	580 (87.6)	10 (90.9)	97 (83.6)	4 (100)
Yes	82 (12.4)	1 (9.1)	19 (16.4)	0

Of the 11 breast cancer probands with *BRCA1* mutations, 4 had the 185delAG mutation, 4 had the R841W mutation, 1 had the int5-11T-G, 1 had the 2594delC, and 1 had the 5382insC mutation. Among the 4 ovarian cancer probands with *BRCA1* mutations, 1 had the 5382insC mutation, 1 had the R841W, 1 had the 3600del-AAGATACTAGT, and 1 had the 962delCTCA mutation (Table 3). The mean age at onset of individuals identified with the R841W mutation was 66.0±9.5 years whereas for individuals with the 185delA-G mutation, mean age at onset was 48.8±9.2 years.

Positive family history of breast or ovarian cancer was significantly associated with *BRCA1* mutation status among breast cancer probands (*P* = 0.018) (Table 4). Similarly, positive family history of breast or ovarian

cancer was significantly associated with *BRCA1* mutation status among the ovarian cancer probands (*P* = 0.0028). However the frequency of *BRCA1* mutations was higher for ovarian cancer probands than for breast cancer probands. In particular, the association of ovarian cancer family history with the presence of *BRCA1* mutations in both breast and ovarian cancer probands was statistically significant (*P* = 0.019 and *P* = 0.029, respectively). *BRCA1* mutations were responsible for 4.0% of breast cancer probands with positive family history of breast or ovarian cancer and 16% of ovarian cancer probands with positive family history of breast or ovarian cancer. In addition, *BRCA1* mutations were responsible for 3 of 15 breast cancer probands (20%) with positive family history of ovarian cancer and 2 of 8 ovarian cancer probands (25%) with positive family history of ovarian cancer.

We also observed statistically significant trends between *BRCA1* status and the number of breast and ovarian cancers among first-degree or first- and second-degree relatives in both breast and ovarian cancer probands (Table 5). The proportion of *BRCA1* positive breast cancer probands with 2 or more first-degree relatives with breast or ovarian cancer was 2 out of 31 (6.5%) compared with 5 out of 437 (1.1%) for probands with negative family history (test for trend *P* = 0.032). Significant trends were also observed for ovarian cancer probands when we included in the family history second-degree relatives with breast and ovarian cancer (Table 5). When we classified the data considering the age of onset of breast cancer of the affected relatives (less than the age of 50 years and aged 50 years or more), we observed statistically significant trends between

Table 3
BRCA1 mutations and mean age at diagnosis in breast and ovarian cancer probands

Mutation	Breast cancer probands		Ovarian cancer probands		Total	
	n	Mean age at diagnosis (SD)[a]	*n*	Mean age at diagnosis (SD)	*n*	Mean age at diagnosis (SD)
R841W	4	68.0 (9.6)	1	58.0	5	66.0 (9.5)
185delAG	4	48.8 (9.2)	–	–	4	48.8 (9.2)
Int5-11T-G	1	39	–	–	1	39
2594delC	1	33	–	–	1	33
5382insC	1	55	1	45	2	50 (7.1)
3600delAAG-ATACTAGT	–	–	1	48	1	48
962delCTCA	–	–	1	48	1	48

[a] SD, standard deviation.

Table 4

Characteristics of family history among female breast and ovarian cancer probands

Characteristic	Breast cancer probands		Ovarian cancer probands	
	BRCA1 negative n = 581 (%)	*BRCA1* positive[a] n = 11 (%)	*BRCA1* negative n = 99 (%)	*BRCA1* positive[a] n = 4 (%)
Family history based on breast or ovarian cancer phenotype				
Negative	415 (71.4)	4 (36.4)	78 (78.8)	0
Positive	166 (28.6)	7 (63.6)	21 (21.2)	4 (100)
Family history based on breast only, ovarian only and breast and ovarian cancer phenotype				
Negative	415 (71.4)	4 (36.4)	78 (78.8)	0
Breast only	154 (26.5)	4 (36.4)	15 (15.2)	2 (50)
Ovarian only	4 (0.7)	1 (9.1)	5 (5.1)	1 (25)
Breast and ovarian	8 (1.4)	2 (18.1)	1 (1.0)	1 (25)
Test for trend	P = 0.0009		P = 0.0012	
Family history based on breast cancer phenotype only				
Negative	419 (72.1)	5 (45.5)	83 (83.8)	1 (25)
Positive	162 (27.9)	6 (54.5)	16 (16.2)	3 (75)
Family history based on ovarian cancer phenotype only				
Negative	569 (97.9)	8 (72.7)	93 (93.9)	2 (50)
Positive	12 (2.1)	3 (27.3)	6 (6.1)	2 (50)

[a] Positive family history was considered for probands having either at least one first-degree relative with the defined phenotype or no first-degree relative and at least two maternal or paternal second-degree relatives.

Table 5

Trends in *BRCA1* mutation frequency in probands by number of breast or ovarian cancer, breast only and ovarian only in first-degree or first- and second-degree relatives

Characteristic	Breast cancer probands		Ovarian cancer probands	
	BRCA1 negative n = 581 (%)	*BRCA1* positive n = 11 (%)	*BRCA1* negative n = 99 (%)	*BRCA1* positive n = 4 (%)
Number of first-degree relatives with breast or ovarian cancer				
0	432 (98.9)	5 (1.1)	81 (100)	0
1	120 (96.8)	4 (3.2)	17 (85.0)	3 (15.0)
2+	29 (93.5)	2 (6.5)	1 (50.0)	1 (50.0)
Number of first-degree relatives with breast cancer only				
0	437 (98.6)	6 (1.4)	86 (98.9)	1 (1.1)
1	117 (96.7)	4 (3.3)	12 (80.0)	3 (20.0)
2+	27 (96.4)	1 (3.6)	1 (100)	0
Number of first-degree relatives with ovarian cancer only				
0	570 (98.6)	8 (1.4)	93 (97.9)	2 (2.1)
1	11 (78.6)	3 (21.4)	6 (75.0)	2 (25.0)
Number of first- and second-degree relatives with breast or ovarian cancer				
0	264 (99.6)	1 (0.4)	51 (100)	0
1	165 (97.6)	4 (2.4)	32 (97.0)	1 (3.0)
2+	152 (96.2)	6 (3.8)	16 (84.2)	3 (15.8)
Number of first- and second-degree relatives with breast cancer only				
0	278 (99.6)	1 (0.4)	59 (100)	0
1	162 (97.0)	5 (3.0)	26 (92.9)	2 (7.1)
2+	141 (96.6)	5 (3.4)	14 (87.5)	2 (12.5)
Number of first- and second-degree relatives with ovarian cancer only				
0	533 (98.5)	8 (1.5)	87 (98.9)	1 (1.1)
1	40 (93.0)	3 (7.0)	10 (83.3)	2 (16.7)
2+	8 (100)	0	2 (66.7)	1 (33.3)

Table 6

Number of female breast and ovarian cancer probands by *BRCA1* mutation status and the presence of at least one first- or second-degree relative diagnosed with breast cancer < 50 years old

Characteristic	Breast cancer probands		Ovarian cancer probands	
	BRCA1 negative $n = 581$ (%)	*BRCA1* positive $n = 11$ (%)	*BRCA1* negative $n = 99$ (%)	*BRCA1* positive $n = 4$ (%)
At least one first-degree relative with breast cancer diagnosed at < 50 years old				
Negative FamHx	415 (99.0)	4 (1.0)	78 (100)	0
No < 50 years[a]: positive FamHx	119 (97.5)	3 (2.5)	16 (88.9)	2 (11.1)
Yes < 50 years[b]: positive FamHx	47 (92.2)	4 (7.8)	5 (71.4)	2 (28.6)
Test for trend	$P = 0.0068$		$P = 0.0021$	
At least one first- or second-degree relative with breast cancer diagnosed at < 50 years old				
Negative FamHx	394 (99.0)	4 (1.0)	74 (100)	0
No < 50 years[c]: positive FamHx	104 (98.1)	2 (1.9)	14 (93.3)	1 (6.7)
Yes < 50 years[d]: positive FamHx	83 (94.3)	5 (5.7)	11 (78.6)	3 (21.4)
Test for trend	$P = 0.00019$		$P = 0.0017$	

FamHx, family history.
[a] No first-degree relative with breast cancer diagnosed below the age of 50 years.
[b] At least one first-degree relative with breast cancer diagnosed below the age of 50 years.

BRCA1 status of the breast and ovarian cancer probands and the presence of a first- and/or second-degree relative with breast cancer below the age of 50 years (Table 6). In particular, *BRCA1* mutations were responsible for 7.8% of breast cancer probands with positive family history of breast cancer diagnosed below the age of 50 years (test for trend $P = 0.0068$) and 28.6% of ovarian cancer probands with such a family history (test for trend $P = 0.0021$).

Of the 11 breast cancer probands who carried *BRCA1* mutations, 1 did not report a history of breast or ovarian cancer among first-degree or first- and second-degree relatives (Table 5). However, of the 4 ovarian cancer probands who carried a *BRCA1* mutation, all 4 reported a history of breast or ovarian cancer among first- or second-degree relatives.

Colon and stomach cancer among first- or second-degree relatives of the breast cancer probands was reported more frequently among carriers of *BRCA1* mutation compared with families of non-carriers (Table 7). Similarly, in addition to family history of ovarian cancer among first- and second-degree relatives of the ovarian cancer probands, positive family history of kidney cancer was more frequent among mutation carriers compared with non-carriers (Table 7).

4. Discussion

In this paper we report *BRCA1* mutation frequency in 120 population-based ovarian cancer cases. For a majority of cases (107), the mutation analysis was

Table 7

Percentages of carriers and non-carriers of *BRCA1* mutations with a family history among first- and second-degree relatives for selected cancers

Type of cancer	Breast cancer		Ovarian cancer		Total	
	BRCA1 negative $n = 581$ (%)	*BRCA1* positive $n = 11$ (%)	*BRCA1* negative $n = 99$ (%)	*BRCA1* positive $n = 4$ (%)	*BRCA1* negative $n = 680$ (%)	*BRCA1* positive $n = 15$ (%)
Breast	247 (42.5)	8 (72.7)	32 (32.3)	4 (100)[a]	279 (41.0)	12 (80.0)[b]
Ovary	37 (6.4)	3 (27.3)[a]	9 (9.1)	3 (75.0)[b]	46 (6.8)	6 (40.0)[b]
Pancreas	39 (6.7)	1 (9.1)	9 (9.1)	1 (25.0)	48 (7.1)	2 (13.3)
Lung	124 (21.3)	2 (18.2)	21 (21.2)	1 (25.0)	145 (21.3)	3 (20.0)
Prostate	115 (19.8)	0	19 (19.2)	1 (25.0)	134 (19.7)	1 (6.7)
Colon	129 (22.2)	7 (63.6)[b]	20 (20.2)	1 (25.0)	149 (21.9)	8 (53.3)[b]
Kidney	19 (3.3)	1 (9.1)	6 (6.1)	2 (50.0)[a]	25 (3.7)	3 (20.0)[a]
Stomach	87 (15.0)	5 (45.5)[a]	18 (18.2)	1 (25.0)	105 (15.4)	6 (40.0)[a]
Brain	33 (5.7)	2 (18.2)	7 (7.1)	0	40 (5.9)	2 (13.3)
Any cancer	510 (87.8)	10 (90.9)	92 (92.9)	4 (100)	672 (98.8)	15 (100)

[a] $P < 0.05$ for comparison with non-carriers.
[b] $P < 0.01$ for comparison with non-carriers.

carried out through a full screening of mutations throughout the *BRCA1* gene using RNase mismatch cleavage assay (NIRCA; Ambion, Austin, TX, USA) method. However, the *BRCA1* mutation testing in the breast cancer group in this study was done through screening for targeted mutations using ASO methods. The frequencies of *BRCA1* mutations in a population-based series of non-Hispanic-white breast (592 cases) and ovarian (103 cases) cancer probands found in this study were 1.9% and 3.9% respectively.

Several studies in the literature reported *BRCA1* frequencies in series of breast cancer patients to evaluate the population mutation prevalence and penetrance as well as lifetime risk of developing breast cancer in mutation carriers and non-carriers. It is clear that there is a wide range of variability in these estimates, which may be attributed to differences in the characteristics and the origin of study populations. Thus, it is important when making comparisons in mutation frequencies between studies to do so only if the study populations are comparable at least with respect to age distribution, ascertainment source (high-risk versus population-based series), and ethnic/racial origin. In this study, we found that the overall frequency of *BRCA1* mutations in population-based, non-Hispanic-white breast cancer patients was 1.9%. The age range of our non-Hispanic-white breast cancer series was older than 18 years. Newman and colleagues [9] reported a frequency of 3.3% in a series of breast cancer cases ranging in age from 20–74 years. When we compared the frequency for non-Hispanic-white women below the age of 40 years, in our study 6.1% (data not included in tables) were found to have *BRCA1* mutations compared with 3.6% in the Australian women in the same age group cited in Newman [9]. Furthermore, in breast cancer probands below the age of 50 years, the frequency of *BRCA1* mutations in our study was 2% compared with 1.4% reported by Newman [9]. Malone and colleagues [25] reported a 6.2% frequency of *BRCA1* mutations in cases diagnosed below the age of 35 years, none of whom were selected on the basis of family history, and a 7.2% frequency in cases diagnosed below the age of 45 years who had a first-degree relative with breast cancer.

Clearly, the age of the groups studied is important in estimating the frequency of *BRCA1* mutations. Among breast cancer probands, we estimated the probability of developing breast cancer among carriers by the age of 40 years to be 0.17 and by the age of 70 years to be 0.48 [22]. It is important to point out that the mutation frequencies among the breast cancer group are probably underestimated since the mutation analysis was targeted to specific mutations using ASO methodology. Although this is a potential weakness in this study, a full sequencing of the *BRCA1* gene in a large population-based series is prohibitively expensive and the yield is low, particularly in population-based series such as in this study.

Most of the current literature on *BRCA1* mutations in ovarian cancer has been concerned with its occurrence in Ashkenazi Jews [26,27], and frequencies in other populations were only based on estimates from family studies [8,5]. In our study of 103 population-based, non-Hispanic-white women with ovarian cancer, the frequency of *BRCA1* using full sequencing of the gene [24] was found to be 3.9% (95% CI: 1.2–9.6). No mutations were found in the age groups below 40 years or above 60 years of age. The mutation frequency in women of 40–49 years of age was 3/29 (10.3%) and for women 50–59 years was 1/24 (4.2%).

In 81 non-white breast cancer probands and 17 non-white ovarian cancer probands there were no mutations found in *BRCA1*. This could possibly be due to the small number of non-whites in this study (4 African-American, 42 Hispanic and 35 Asian breast cancer patients and 12 Hispanic and 5 Asian ovarian cancer patients). Mutations in *BRCA1* were previously identified in high-risk African-American families [28,29]. However, in a series of 76 African-American women with breast cancer, no mutations were detected [9]. In the study by Newman and colleagues [9], the cases were selected from a population-based registry and, therefore, it is likely that *BRCA1* mutations in African-American women associated with breast cancer are extremely rare and probably limited to very high-risk families with early-onset disease similar to those included in the study by Gao and colleagues [29].

Cases that were positive for *BRCA1* in our study were younger than those who were mutation-negative. The mean age at onset for female breast cancer probands who were *BRCA1* positive was 54 years compared with 58.4 years in *BRCA1* mutation-negative cases. For ovarian cancer, *BRCA1* mutation-positive probands were younger than mutation-negative probands, 49.8 compared with 55.5 years. The difference was not statistically significant, and the difference of 6 years in the age of onset among carriers and non-carriers might not be epidemiologically meaningful. Similar data were observed in a study of *BRCA1* mutations among Jewish women with ovarian cancer, where mutation-positive patients had a mean age of 48.3 years while negative patients had a mean age of 55.5 years [30]. Thus, although the frequency of *BRCA1* mutations in ovarian cancer in Ashkenazi Jews was higher than in our non-Hispanic-white probands, the ages of onset were quite similar. In this study the frequency of *BRCA1* mutations in the Ashkenazi subgroup of breast cancer probands was 6.7%.

The age of onset may also vary between cases with specific mutations. In our study, the mean age at onset of individuals identified with the R841W mutation was 66 years, whereas for cases with the 185delAG mutation the mean age at onset was 48.8 years. We did not find differences in the mutation frequency when we classified

our patients by histology or differentiation. It may be of importance to report specific mutations and patient and tumour characteristics to further define the *BRCA1* mutation-positive phenotype.

Positive family history of breast or ovarian cancer was significantly associated with *BRCA1* mutation status among breast cancer probands (Table 4). Similarly, positive family history of breast or ovarian cancer was significantly associated with *BRCA1* mutation status among the ovarian cancer probands. However, the frequency of *BRCA1* mutations was higher for ovarian cancer probands than for breast cancer probands.

5. Conclusions

In summary, the frequencies of *BRCA1* mutations in this population-based study of breast cancer were consistent with those reported using a similar approach and similar study populations ascertainment. There were no *BRCA1* mutations found in non-white breast and ovarian cancer probands. In this study we found that the frequency of *BRCA1* mutations in ovarian cancer patients was significantly higher than that for breast cancer for the same age groups however the number of mutation carriers was small. In addition, the age of onset of cases with positive *BRCA1* mutations was younger than cases negative for *BRCA1* mutation. Furthermore, the frequency of *BRCA1* mutations in ovarian cancer in Ashkenazi Jewish cases in our study group was higher than in our non-Ashkenazi Jewish/non-Hispanic-white probands, although the age of onset was quite similar in the two groups. The frequency of *BRCA1* mutations in the Ashkenazi subgroup of breast cancer probands was 6.7%. Finally, the proportion of *BRCA1* positive breast cancer probands with 2 or more first-degree relatives with breast or ovarian cancer was 6.5% compared with 1.1% for probands with negative family history. In particular, the *BRCA1* mutations were responsible for 7.8% of breast cancer probands with positive family history of a first-degree relative with breast cancer diagnosed at an age below 50 years and 28.6% of ovarian cancer probands with such a family history. In addition, *BRCA1* mutations were responsible for 20% of breast cancer probands with positive family history of ovarian cancer and 25% of ovarian cancer probands with positive family history of ovarian cancer.

Acknowledgements

References

1. American Cancer Society. *Cancer Facts and Figures — 1997*. Atlanta, GA, American Cancer Society, 1997.
2. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the Cancer and Steroid Hormone Study. *Am J Hum Genet* 1991, **48**, 232–242.
3. Børresen AL. Role of genetic factors in breast cancer susceptibility. *Acta Oncol* 1992, **31**, 151–155.
4. Easton DF, Bishop DT, Ford D, Crockford GP, Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 1993, **52**, 678–701.
5. Easton DF, Ford D, Bishop DT, Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. *Am J Hum Genet* 1995, **56**, 265–271.
6. Rebbeck TR, Couch FJ, Kant J, *et al*. Genetic heterogeneity in hereditary breast cancer: role of *BRCA1* and *BRCA2*. *Am J Hum Genet* 1996, **59**, 547–553.
7. Narod SA, Goldgar D, Cannon-Albright L, *et al*. Risk modifiers in carriers of *BRCA1* mutations. *Int J Cancer* 1995, **64**, 394–398.
8. Ford D, Easton DF, Stratton M, *et al*. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1998, **62**, 676–689.
9. Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC. Frequency of breast cancer attributable to *BRCA1* in a population-based series of American women. *JAMA* 1998, **279**, 915–921.
10. Fodor FH, Weston A, Bleiweiss IJ, *et al*. Frequency and carrier risk associated with common *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish breast cancer patients. *Am J Hum Genet* 1998, **63**, 45–51.
11. Hamann U, Häner M, Stosiek U, Bastert G, Scott RJ. Low frequency of *BRCA1* germline mutations in 45 German breast/ovarian cancer families. *J Med Genet* 1997, **34**, 884–888.
12. Hakansson S, Johannsson O, Johansson U, *et al*. Moderate frequency of *BRCA1* and *BRCA2* germ-line mutations in Scandinavian familial breast cancer. *Am J Hum Genet* 1997, **60**, 1068–1078.
13. Couch FJ, DeShano ML, Blackwood MA, *et al*. *BRCA1* mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* 1997, **336**, 1409–1415.
14. Whittemore AS, Gong G, Intyre J. Prevalence and contribution of *BRCA1* mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. *Am J Hum Genet* 1997, **60**, 496–504.
15. Southey MC, Tesoriero AA, Andersen CR, *et al*. *BRCA1* mutations and other sequence variants in a population-based sample of Australian women with breast cancer. *Br J Cancer* 1999, **79**, 34–39.
16. Anton-Culver H, Culver BD, Kurosaki T, Osann KE, Lee JB. Incidence of lung cancer by histological type from a population-based registry. *Cancer Res* 1988, **48**, 6580–6583.
17. Seiffert JE, Price WT, Gordon B. The California tumor registry: a state-of-the-art model for a regionalized, automated, population-based registry. *Top Health Rec Manag* 1990, **11**, 59–73.

18. Gordon B, ed. *Standards for Cancer Registries*. Vol I, Data Exchange Standards and Record Description. Sacramento, CA, North American Association of Central Cancer Registries, 1994.

19. Seiffert J, ed. *Standards for Cancer Registries*. Vol II, Data Standards and Data Dictionary. Sacramento, CA, North American Association of Central Cancer Registries, 1997.

20. Seiffert J, ed. *Standards for Cancer Registries*. Vol III, Standards for Completeness, Quality, Analysis, and Management of Data. Sacramento, CA, North American Association of Central Cancer Registries, 1997.

21. Anton-Culver H, Kurosaki T, Taylor TH, Gildea M, Brunner D, Bringman D. Validation of family history of breast cancer and identification of the *BRCA1* and other syndromes using a population-based cancer registry. *Genet Epidemiol* 1996, **13**, 193–205.

22. Ziogas A, Gildea M, Cohen P, *et al.* Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. *Cancer Epidemiol Biomark Prev* 2000, **9**, 103–111.

23. Barker DF, Almeida ER, Casey G, *et al. BRCA1* R841W: a strong candidate for a common mutation with moderate phenotype. *Genet Epidemiol* 1996, **13**, 595–604.

24. Janezic SA, Ziogas A, Krumroy LM, *et al.* Germline *BRCA1* alterations in a population-based series of ovarian cancer cases. *Hum Molec Genet* 1999, **8**, 889–897.

25. Malone KE, Daling JR, Thompson JD, O'Brien CA, Francisco LV, Ostrander EA. *BRCA1* mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 with first-degree family history. *JAMA* 1998, **12**, 922–929.

26. Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E. High frequency of *BRCA1* and *BRCA2* germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. *Gyneco Oncol* 1997, **67**, 123–126.

27. Levy-Lahad E, Catane R, Eisenberg S, *et al.* Founder *BRCA1* and *BRCA2* mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. *Am J Hum Genet* 1997, **60**, 1059–1067.

28. Mefford HC, Baumbach L, Panguluri RC, *et al.* Evidence for *BRCA1* founder mutation in families of West African ancestry. *Am J Hum Genet* 1999, **65**, 575–578.

29. Gao Q, Neuhausen S, Cummings S, Luce M, Olopade OI. Recurrent germ-line *BRCA1* mutations in extended African American families with early-onset breast cancer. *Am J Hum Genet* 1997, **60**, 1233–1236.

30. Menczer J, Theodor L, Friedman E. *BRCA1* 185delAG mutation in a non-Ashkenazi Jewish woman with early-onset breast and ovarian cancer. *Am J Ob Gyn* 1997, **176**, 731.