ORIGINAL ARTICLE

Prevalence of *BRCA1/2* germline mutations in 21 401 families with breast and ovarian cancer

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ABSTRACT

Purpose To characterise the prevalence of pathogenic germline mutations in *BRCA1* and *BRCA2* in families with breast cancer (BC) and ovarian cancer (OC) history.

Patients and methods Data from 21 401 families were gathered between 1996 and 2014 in a clinical setting in the German Consortium for Hereditary Breast and Ovarian Cancer, comprising full pedigrees with cancer status of all individual members at the time of first counselling, and *BRCA1/2* mutation status of the index patient.

Results The overall *BRCA1/2* mutation prevalence was 24.0% (95% CI 23.4% to 24.6%). Highest mutation frequencies were observed in families with at least two OCs (41.9%, 95% CI 36.1% to 48.0%) and families with at least one breast and one OC (41.6%, 95% CI 40.3% to 43.0%), followed by male BC with at least one female BC or OC (35.8%; 95% CI 32.2% to 39.6%). In families with a single case of early BC (<36 years), mutations were found in 13.7% (95% CI 11.9% to 15.7%). Postmenopausal unilateral or bilateral BC did not increase the probability of mutation detection. Occurrence of premenopausal BC and OC in the same woman led to higher mutation frequencies compared with the occurrence of these two cancers in different individuals (49.0%; 95% CI 41.0% to 57.0% vs 31.5%; 95% CI 28.0% to 35.2%).

Conclusions Our data provide guidance for healthcare professionals and decision-makers to identify individuals who should undergo genetic testing for hereditary breast and ovarian cancer. Moreover, it supports informed decision-making of counselees on the uptake of genetic testing.

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INTRODUCTION

Women with pathogenic germline mutations in the *BRCA1* and *BRCA2* genes are at an increased lifetime risk for breast cancer (BC) and ovarian cancer (OC) compared with the general population.[1] Identification of mutation carriers is an important prerequisite for targeted clinical management. The probability of finding a deleterious germline mutation in a woman affected with BC or OC depends on her familial cancer history in terms of type, number and ages of onset of these cancers.[2–5] To date, the decision to perform mutation testing is mainly guided by the presence of a family cancer history, which is indicative for a BRCA mutation with a certain probability.[6–8] Consequently, to define appropriate clinical selection criteria, precise knowledge on expected mutation frequencies for individual family histories is required. Since the discovery of the *BRCA1* and *BRCA2* genes, several studies have analysed the relationship between family history and BRCA mutation prevalence.[9–14] In the largest study so far, Frank *et al*[11] correlated familial disease histories of 10 000 consecutively enrolled individuals with mutation status, resulting in detailed tabulations of empiric mutation prevalences.

In 1996, the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) had established a panel of clinical criteria for genetic testing of individuals in a clinical setting, based on familial BC and OC history.[7] By the end of 2014, a total of 21 401 families suspected of having a deleterious BRCA mutation according to this panel of clinical criteria were enrolled into the central registry of GC-HBOC. Based on this data set, we aimed to comprehensively analyse the correlation of family history of BC and OC with BRCA mutation frequencies. We were particularly interested in the predictive value of the number of premenopausal versus postmenopausal BCs in the family, and the presence of premenopausal or postmenopausal bilateral breast cancer (bBC) versus unilateral cancer. With this analysis, we aim to provide guidance for counsellors, counselees and decision-makers on the offer and uptake of genetic testing.

MATERIALS AND METHODS

The GC-HBOC comprises 15 university centres. Using standardised clinical criteria (table 2),

Table 1 Family characteristics

	Total	*BRCA1*	*BRCA2*	Negative
Families, no	21 401	3398	1766	16 265
Members				
Total number	617 578	99 708	52 861	466 013
Median per family	25	26	26	25
Members with cancer, no				
uBC_{50-}	26 236	4996	2519	18 770
uBC_{51+}	24 452	2789	2033	19 655
bBC_{50-}	4132	1304	427	2414
bBC_{51+}	1896	239	168	1492
OC	7250	2650	730	3897
BC and OC	1917	805	202	916
Male BC	671	62	193	420
Age of onset (mean)*				
BC	49.0	44.4	47.5	50.2
OC	51.5	49.8	55.6	51.9
Male BC	58.0	56.9	60.4	57.0

*Mean ages of onset for BC and OC were significantly different in all pairwise group comparisons (p<0.001). For male BC, mean age of onset was significantly different between *BRCA2*-positive and *BRCA1/2*-negative families (p=0.006).
bBC, bilateral breast cancer; BC, breast cancer; OC, ovarian cancer.

families with clustering or early onset of BC or OC are registered and tested for the presence of deleterious germline mutations in *BRCA1* and *BRCA2*. Comprehensive data on familial cancer history, including a detailed pedigree, pathology reports and results of molecular testing, are documented in a central database using standardised electronic case report forms.

A total number of 21 401 families, who were registered from 1996 until 2014, were included in the present analysis. All families fulfilled the clinical inclusion criteria shown in table 2. Families who were ascertained through a known pathogenic mutation rather than by clinical criteria were not included. If possible, the family member with the most severe phenotype (defined as bBC, BC and OC, or earliest age of onset) was chosen as the index patient and was searched for *BRCA1* and *BRCA2* mutations. In case that no DNA from an affected family member could be obtained, mutation analysis was performed in unaffected individuals. BC included ductal carcinoma in situ. OC included cancers of the fallopian tube and primary peritoneal cancers irrespective of histopathological subtype and grading. BC cases with an age of onset of 50 years or earlier are hereafter referred to as premenopausal BC (BC_{50-}). BC at the age from 51 years onwards are referred to as postmenopausal BC (BC_{51+}). For bBC, the age of onset of the first cancer was considered. The present study did not include families with single cases of OC or single cases of male breast cancer (mBC) since these families were not part of the clinical inclusion criteria.

Mutation analysis

Mutation analysis was performed using direct sequencing or a pre-screening step followed by direct sequencing of suspect fragments. Pre-screening methods comprised mainly denaturing high-performance liquid chromatography and high-resolution melting.[15 16] Before the year 1999, single-strand conformation polymorphism and protein truncation test were used. If no deleterious sequence alterations were found in these steps, an additional screening for large genomic alterations was performed using multiplex ligation-dependent probe amplification. In the present study, 88.4% of all *BRCA1/2*-negative index patients were searched for large genomic alterations. Mutations were classified according to the International Agency for Research on Cancer (IARC) system and considered pathogenic or likely pathogenic (class 4 or 5) based on literature evidence, multifactorial likelihood and functional analyses of the ENIGMA consortium that comprises genetic data of the GC-HBOC database.[17–19]

Statistical analysis

IBM SPSS 22 was used for statistical analysis. The 95% CIs for mutation frequencies were calculated using Wilson's score

Table 2 Familial breast and ovarian cancer histories used as inclusion criteria for *BRCA1/2* mutation testing in German Consortium for Hereditary Breast and Ovarian Cancer and observed mutation prevalences

	Families		Families with pathogenic mutation								
			BRCA1/2			*BRCA1*			*BRCA2*		
Distinct groups of familial BC and OC history (including proband)	N	% of total	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)
Total	21 401	100.0	5136	24.0	23.4 to 24.6	3398	15.9	15.4 to 16.4	1766	8.3	7.9 to 8.6
≥3 females with BC_{51+} (no BC<51, no OC, no mBC)	684	3.2	25	3.7	2.5 to 5.3	9	1.3	0.7 to 2.5	17	2.5	1.6 to 3.9
≥2 females with BC, of these ≥1 with BC_{50-}(no OC, no mBC)	12 996	60.7	2379	18.3	17.7 to 19.0	1439	11.1	10.5 to 11.6	949	7.3	6.9 to 7.8
Single female with unilateral BC_{35-}(no further female BC, no OC, no mBC)	1267	5.9	173	13.7	11.9 to 15.7	116	9.2	7.7 to 10.9	57	4.5	3.5 to 5.8
Single female with bBC_{50-} (no further female BC, no OC, no mBC)	480	2.2	109	22.7	19.2 to 26.7	73	15.2	12.3 to 18.7	36	7.5	5.5 to 10.2
≥1 females with BC and ≥1 female with OC (no mBC)	5072	23.7	2111	41.6	40.3 to 43.0	1624	32.0	30.7 to 33.3	500	9.9	9.1 to 10.7
≥2 females with OC (no female BC, no mBC)	260	1.2	109	41.9	36.1 to 48.0	77	29.6	24.4 to 35.4	34	13.1	9.5 to 17.7
≥1 male with BC and ≥1 females with BC or OC	642	3.0	230	35.8	32.2 to 39.6	60	9.3	7.3 to 11.8	173	26.9	23.7 to 30.5

bBC, bilateral breast cancer; BC, breast cancer; mBC, male breast cancer; OC, ovarian cancer; Prev, prevalence.

method. For comparison of mutation frequencies between groups, the χ^2 test was used. p Values <0.05 were considered significant.

RESULTS

Basic characteristics of the study population are summarised in table 1. Of 21 401 families, 3398 (15.9%) had a pathogenic mutation in *BRCA1* and 1766 (8.3%) in *BRCA2*. Of these, 28 families had mutations in both genes, *BRCA1* and *BRCA2*. The median number of family members documented in each pedigree was 25, regardless of BRCA mutation status. The mean age at cancer diagnosis was 44.4 years for BC and 49.8 years for OC in *BRCA1*-positive families compared with 47.5 and 55.6 years, in *BRCA2*-positive families, and 50.2 and 51.9 years in BRCA-negative families. The mean age at diagnosis of mBC in *BRCA1*-positive families was 56.9 years, which was younger than in *BRCA2* mutation carriers (60.4 years) and equal to *BRCA1/2*-negative families (57.0 years).

The families were classified into seven mutually exclusive groups of aggregated familial cancer histories (table 2). These groups cover the inclusion criteria of the GC-HBOC established in 1996. The overall *BRCA1/2* mutation prevalence was 24.0% (95% CI 23.4% to 24.6%). The highest mutation frequencies were seen in families with at least two OC (41.9%, 95% CI 36.1% to 48.0%) and families with at least one BC and one OC (41.6%, 95% CI 40.3% to 43.0%) followed by families with mBC and at least one additional female with BC or OC (35.8%, 95% CI 32.2% to 39.6%). *BRCA1* mutations were more frequent in families with OC, whereas *BRCA2* mutations were more frequent in families with mBC. The largest group comprises families with at least two cases of BC, at least one that was diagnosed before the age of 51 (n=12.996, 60.7% of all families). The lowest mutation frequencies (3.7%, 95% CI 2.5% to 5.3%) were observed in families with three or more cases of postmenopausal BC, but no occurrence of premenopausal BC, OC or male BC.

To characterise mutation frequencies in more detail, the familial cancer histories were further refined. Table 3 shows the mutation prevalences in families, in which exclusively female BC was present (72.1% of all families). Group 1a comprises families with exclusive occurrence of unilateral cases of BC (53.1% of all families), whereas groups 1b (14.6%) and 1c

Table 3 BRCA mutation prevalence in families with female breast cancer only

Familial cancer history (including proband)			Families		Families with pathogenic mutation								
					BRCA1/2			*BRCA1*			*BRCA2*		
Group	BC_{50-}	BC_{51+}	N	% of total	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)
Group 1a:	0	≥3	522	2.4	20	3.8	2.5 to 5.8	6	1.1	0.5 to 2.5	15	2.9	1.7 to 4.7
female unilateral BC	1*	0	1267	5.9	173	13.7	11.9 to 15.7	116	9.2	7.7 to 10.9	57	4.5	3.5 to 5.8
(no bBC, OC, mBC)	1	1	2577	12.0	227	8.8	7.8 to 10.0	118	4.6	3.8 to 5.5	109	4.2	3.5 to 5.1
	1	2	1239	5.8	102	8.2	6.8 to 9.9	54	4.4	3.4 to 5.6	48	3.9	2.9 to 5.1
	1	≥3	579	2.7	43	7.4	5.6 to 9.9	14	2.4	1.4 to 4.0	29	5.0	3.5 to 7.1
	2	0	1725	8.1	302	17.5	15.8 to 19.4	187	10.8	9.5 to 12.4	116	6.7	5.6 to 8.0
	2	1	1256	5.9	204	16.2	14.3 to 18.4	99	7.9	6.5 to 9.5	105	8.4	7.0 to 10.0
	2	2	477	2.2	76	15.9	12.9 to 19.5	33	6.9	5.0 to 9.6	43	9.0	6.8 to 11.9
	2	≥3	239	1.1	41	17.2	12.9 to 22.4	15	6.3	3.8 to 10.1	26	10.9	7.5 to 15.5
	≥3	0	739	3.5	225	30.4	27.2 to 33.9	143	19.4	16.7 to 22.4	82	11.1	9.0 to 13.6
	≥3	1	462	2.2	127	27.5	23.6 to 31.7	83	18.0	14.7 to 21.7	45	9.7	7.4 to 12.8
	≥3	2	177	0.8	50	28.2	22.1 to 35.3	33	18.6	13.6 to 25.0	17	9.6	6.1 to 14.8
	≥3	≥3	103	0.5	25	24.3	17.0 to 33.4	13	12.6	7.5 to 20.4	12	11.7	6.8 to 19.3
	Total		**11 362**	**53.1**	**1615**	**14.2**	**13.6 to 14.9**	**914**	**8.0**	**7.6 to 8.6**	**704**	**6.2**	**5.8 to 6.7**
Group 1b:	1	0	480	2.2	109	22.7	19.2 to 26.7	73	15.2	12.3 to 18.7	36	7.5	5.5 to 10.2
female BC,	1	1	482	2.3	101	21.0	17.6 to 24.8	69	14.3	11.5 to 17.7	32	6.6	4.7 to 9.2
of these ≥1bBC_{50-}	1	2	204	1.0	41	20.1	15.2 to 26.1	28	13.7	9.7 to 19.1	13	6.4	3.8 to 10.6
(no OC, mBC)	1	≥3	99	0.5	14	14.1	8.6 to 22.3	10	10.1	5.6 to 17.6	4	4.0	1.6 to 9.9
	2	0	588	2.7	190	32.3	28.7 to 36.2	140	23.8	20.5 to 27.4	52	8.8	6.8 to 11.4
	2	1	348	1.6	109	31.3	26.7 to 36.4	76	21.8	17.8 to 26.5	34	9.8	7.1 to 13.3
	2	2	131	0.6	40	30.5	23.3 to 38.9	26	19.8	13.9 to 27.5	14	10.7	6.5 to 17.1
	2	≥3	55	0.3	14	25.5	15.8 to 38.3	9	16.4	8.9 to 28.3	5	9.1	3.9 to 19.6
	≥3	0	361	1.7	183	50.7	45.6 to 55.8	135	37.4	32.6 to 42.5	49	13.6	10.4 to 17.5
	≥3	1	222	1.0	96	43.2	36.9 to 49.8	72	32.4	26.6 to 38.8	27	12.2	8.5 to 17.1
	≥3	2	95	0.4	44	46.3	36.6 to 56.3	26	27.4	19.4 to 37.1	18	18.9	12.3 to 28.0
	≥3	≥3	64	0.3	22	34.4	23.9 to 46.6	13	20.3	12.3 to 31.7	9	14.1	7.6 to 24.6
	Total		**3129**	**14.6**	**963**	**30.8**	**29.2 to 32.4**	**677**	**21.6**	**20.2 to 23.1**	**293**	**9.4**	**8.4 to 10.4**
Group 1c:	0	≥3	162	0.8	5	3.1	1.3 to 7.0	3	1.9	0.6 to 5.3	2	1.2	0.3 to 4.4
female BC,	1	1	197	0.9	19	9.6	6.3 to 14.6	3	1.5	0.5 to 4.4	16	8.1	5.1 to 12.8
of these ≥1bBC_{51+}	1	2	175	0.8	14	8.0	4.8 to 13.0	4	2.3	0.9 to 5.7	10	5.7	3.1 to 10.2
(no bBC_{50-}, OC, mBC)	1	≥3	132	0.6	14	10.6	6.4 to 17.0	4	3.0	1.2 to 7.5	10	7.6	4.2 to 13.4
	2	1	75	0.4	13	17.3	10.4 to 27.4	7	9.3	4.6 to 18.0	6	8.0	3.7 to 16.4
	2	2	69	0.3	9	13.0	7.0 to 23.0	7	10.1	5.0 to 19.5	2	2.9	0.8 to 10.0
	2	≥3	62	0.3	11	17.7	10.2 to 29.0	3	4.8	1.7 to 13.3	8	12.9	6.7 to 23.4
	≥3	1	24	0.1	10	41.7	24.5 to 61.2	7	29.2	14.9 to 49.2	3	12.5	4.3 to 31.0
	≥3	2	12	0.1	6	50.0	25.4 to 74.6	2	16.7	4.7 to 44.8	4	33.3	13.8 to 60.9
	≥3	≥3	28	0.1	7	25.0	12.7 to 43.4	6	21.4	10.2 to 39.5	1	3.6	0.6 to 17.7
	Total		**936**	**4.4**	**108**	**11.5**	**9.6 to 13.7**	**46**	**4.9**	**3.7 to 6.5**	**62**	**6.6**	**5.2 to 8.4**

*≤35 years.
bBC, bilateral breast cancer; BC, breast cancer; mBC, male breast cancer; OC, ovarian cancer; Prev, prevalence.

(4.4%) include also cases of premenopausal and postmenopausal bilateral BC, respectively. These groups were further stratified by the number of women with premenopausal and postmenopausal BC. The highest mutation frequency was seen in families with at least three females with premenopausal BC, at least one of which was bilateral (50.7%, 95% CI 45.6% to 55.8%). Mutations were detected significantly more frequent in families with a single case of premenopausal bilateral BC than in families with two different women with premenopausal BC (22.7%, 95% CI 19.2% to 26.7% vs 17.5%, 95% CI 15.8% to 19.4%, p=0.012). In families with a single case of very early BC before the age of 36, mutations were found in 13.7% (95% CI 11.9% to 15.7%). In all subgroups, the occurrence of additional cases of postmenopausal BC did not considerably change mutation frequencies. In contrast, additional cases of premenopausal BC increased the mutation frequencies considerably.

Table 4 lists families with OC only (group 2a, 1.2% of all families), families with BC and OC (group 2b, 23.7%) and families with occurrence of mBC (group 3, 3.0%). In families with one case of BC and one case of OC, mutation frequencies were considerably higher when the BC case was premenopausal (31.5% 95% CI 28.0% to 35.2% vs 19.2%, 95% CI 15.3% to 23.8%). Double primary premenopausal BC and OC in one individual was associated with a much higher mutation prevalence than the occurrence of premenopausal BC and OC in two different women (49.0%, 95% CI 41.0% to 57.0% vs 31.5%, 95% CI 28.0% to 35.2, p<0.001). However, there was no significant difference in mutation prevalence between double primary BC and OC (BCOC) and occurrence of BC and OC in two different women (BC/OC) when the BC was postmenopausal instead of premenopausal (20.3%, 95% CI 14.1% to 28.5% vs 19.2%, 95% CI 15.3% to 23.8, p=0.788).

In families with mBC (table 4, group 3) and an additional case of female BC, no significant difference in mutation frequencies could be detected depending on menopausal status of the BC (16.5%, 95% CI 10.4% to 25.1% vs 23.2%, 95% CI 16.0% to 32.5%, p=0.284). In families with mBC and additional cases of OC, mutation frequencies for *BRCA1* and *BRCA2* mutations were similar in contrast to families without additional OC cases.

DISCUSSION

Based on a large sample of 21 401 families, the present study provides a detailed characterisation of *BRCA1/2* mutation prevalences for defined patterns of familial BC and OC. The underlying data were collected over a period of almost 20 years (1996–2015) in a standardised way within a German multicentre consortium of interdisciplinary university centres specialised in providing healthcare for families with HBOC. All families suspected of having HBOC were selected for genetic testing according to a set of defined clinical criteria that were compulsory for all participating centres.

The German HBOC consortium has defined inclusion criteria for *BRCA1/2* testing based on at least three generation pedigree analysis.[6] Currently, GC-HBOC offers genetic testing to index patients if the expected BRCA mutation probability is ≥10% based on the individual family cancer history. In our study, the overall mutation prevalence was 24.0%. The decision threshold of 10% is exceeded in almost all subgroups of HBOC families including mBC. However, families with exclusive occurrence of three or more postmenopausal BC cases (3.2% of all families) were below the 10% threshold with a mutation of prevalence of only 3.7%. The latter finding is in line with the study of Frank *et al*,[11] who reported a prevalence of 3.9%. Interestingly, the low prevalence observed in our study was independent of whether bilateral cases were present among the postmenopausal BCs in the family (3.1%) or not (3.8%). Moreover, mutation prevalences did not increase with the number of postmenopausal BC cases in the family. On the contrary, in a previous study we showed that an increasing number of females with BC diagnosed at an age of 60 or later was associated with a decreasing *BRCA1/2* mutation frequency.[20]

In contrast to postmenopausal BC, mutation prevalence increased considerably with each additional case of premenopausal BC both in families with exclusive occurrence of BC and in families with BC and OC. This agrees well with the results of the study of Frank *et al*.[11] In our study, mutation prevalence was even higher if at least one case of premenopausal BC was bilateral. In contrast, the presence of postmenopausal bilateral BC did not increase the chance to detect a deleterious mutation. This observation is in line with a previous study of Gershoni-Baruch *et al*,[21] who suggested that bBC per se is not reflective of genetic predisposition, unless associated with early age of onset. However, other studies came to the conclusion that mutation frequencies are similar if two cancers (bBC or BCOC) occurred in one individual compared with two separate individuals.[10 22–24] In our study, mutations were detected significantly more often in families with a single case of premenopausal bilateral BC than in families with two independent premenopausal BC (22.7% vs 17.5%, p=0.012).

In accordance with other studies, the highest mutation rates were observed in families with BC and OC.[4 9 11 12] As observed in families with exclusive occurrence of BC, mutation prevalence was considerably higher if BC cases were premenopausal. Moreover, mutation prevalence was significantly higher in individuals with double primaries of ovarian and premenopausal BC than if these two cancers occurred in different women.

Our study comprised 642 families with mBC. Due to the inclusion criteria, these families had at least one additional case of female BC or OC. As described in previous studies, *BRCA2* mutations were found more frequently than *BRCA1* mutations in families with mBC but without occurrence of OC. In cases where additional OC cases were present in these families, a similar prevalence of mutations was found in *BRCA1* and *BRCA2*. The additional presence of a premenopausal versus postmenopausal BC increased the mutation prevalence from 16.5% to 23.2%, although this difference was not significant due to low sample sizes in these groups.

The present study revealed a mutation prevalence of 13.7% (9.2%, 95% CI 7.7% to 10.9% for *BRCA1* and 4.5%, 95% CI 3.5% to 5.8% for *BRCA2*) for individuals with early unilateral BC before the age of 36 years without further cancer cases in their family. This is in line with results from two other studies.[25 26] However, there is evidence in the literature that the prevalence of *BRCA1* and *BRCA2* mutations is high in women with triple-negative breast cancer (TNBC) and that *BRCA1/2* mutations are not restricted to young women or patients with a positive family history.[27] Thus, single cases of TNBC might be considered in *BRCA1/2* genetic testing guidelines with an extended age of onset that requires further exploration to confirm a potential cut-off at the age of 60 years as suggested by the data of Couch *et al*.[27]

Comparison of our data to empiric mutation frequencies of other groups is difficult due to varying inclusion criteria. For example, in high-risk HBOC families of Czech ancestry an overall detection rate of 29% was reported compared with 24.0% by us.[12] That work was restricted to first-degree and second-degree relatives in the maternal line and to third-degree

Table 4 BRCA mutation prevalence in families with ovarian cancer (OC) only (group 2a), both breast cancer (BC) and OC (group 2b), and male breast cancer (mBC) (group 3)

		Families		Families with pathogenic mutation								
				BRCA1/2			*BRCA1*			*BRCA2*		
Group	Familial cancer history (including proband)	N	% of total	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)	n	Prev (%)	95% CI (%)
Group 2a: OC only	2 OC (no BC, mBC)	194	0.9	79	40.7	34.1 to 47.8	50	25.8	20.1 to 32.4	29	14.9	10.6 to 20.6
	≥3 OC (no BC, mBC)	66	0.3	30	45.5	34.0 to 57.4	27	40.9	29.9 to 53.0	5	7.6	3.3 to 16.5
	Total	**260**	**1.2**	**109**	**41.9**	**36.1 to 48.0**	**77**	**29.6**	**24.4 to 35.4**	**34**	**13.1**	**9.5 to 17.7**
Group 2b: OC and female BC, but no mBC	1 BC_{51+}OC (no mBC)	118	0.6	24	20.3	14.1 to 28.5	17	14.4	9.2 to 21.9	7	5.9	2.9 to 11.7
	1 BC_{50-}OC (no mBC)	145	0.7	71	49.0	41.0 to 57.0	56	38.6	31.1 to 46.7	15	10.3	6.4 to 16.4
	≥2 BCOC (no mBC)	11	0.1	7	63.6	35.4 to 84.8	7	63.6	35.4 to 84.8	0	0.0	0.0 to 25.9
	≥2 BCOC+≥1 BC/OC (no mBC)	1482	6.9	796	53.7	51.2 to 56.2	641	43.3	40.8 to 45.8	160	10.8	9.3 to 12.5
	1 BC_{51+}+1 OC (no mBC, BCOC)	333	1.6	64	19.2	15.3 to 23.8	39	11.7	8.7 to 15.6	26	7.8	5.4 to 11.2
	1 BC_{50-}+1 OC (no mBC, BCOC)	645	3.0	203	31.5	28.0 to 35.2	155	24.0	20.9 to 27.5	48	7.4	5.7 to 9.7
	1 BC+≥2 OC (no mBC, BCOC)	248	1.2	113	45.6	39.5 to 51.8	100	40.3	34.4 to 46.5	13	5.2	3.1 to 8.8
	≥2 BC+≥1 OC (no mBC, BCOC)	2090	9.8	833	39.9	37.8 to 42.0	609	29.1	27.2 to 31.1	231	11.1	9.8 to 12.5
	Total	**5072**	**23.7**	**2111**	**41.6**	**40.3 to 43.0**	**1624**	**32.0**	**30.7 to 33.3**	**500**	**9.9**	**9.1 to 10.7**
Group 3: mBC	1 mBC+1 BC_{51+} (no OC)	97	0.5	16	16.5	10.4 to 25.1	3	3.1	1.1 to 8.7	13	13.4	8.0 to 21.6
	1 mBC+1 BC_{50-} (no OC)	99	0.5	23	23.2	16.0 to 32.5	5	5.1	2.2 to 11.3	18	18.2	11.8 to 26.9
	1 mBC+≥2 BC (no OC)	331	1.5	128	38.7	33.6 to 44.0	29	8.8	6.2 to 12.3	100	30.2	25.5 to 35.4
	≥2 mBC+≥1 BC (no OC)	23	0.1	15	65.2	44.9 to 81.2	1	4.3	0.8 to 21.0	15	65.2	44.9 to 81.2
	1 mBC+≥1 OC (no BC)	15	0.1	8	53.3	30.1 to 75.2	4	26.7	10.9 to 52.0	4	26.7	10.9 to 52.0
	≥1 mBC+≥1 BC +≥1 OC	77	0.4	40	51.9	41.0 to 62.7	18	23.4	15.3 to 34.0	23	29.9	20.8 to 40.8
	Total	**642**	**3.0**	**230**	**35.8**	**32.2 to 39.6**	**60**	**9.3**	**7.3 to 11.8**	**173**	**26.9**	**23.7 to 30.5**

Prev, prevalence.

relatives in the case of paternal transmission. In the work of Frank *et al*,[11] the overall detection frequency was 15.7% in non-Ashkenazi individuals, but postmenopausal BC was not taken into account.

Some limitations have to be mentioned. First, in our study only aggregated familial cancer histories were correlated with mutation prevalence, that is, the pedigree size and family structure was not considered. Mutation prediction algorithms such as BOADICEA, BRCAPRO or IBIS, which use the pedigree structure and an underlying genetic model of inheritance, might have a better predictive performance.[28–31] Second, it is known that *BRCA1/2*-associated OCs are characterised by a high grade (G2/3) serous histology.[32–34] In our study, we did not restrict the analysis to OC with specific pathological features since pathology information was not available for all OC. Thus, we cannot exclude that a restriction to this specific type of OC would have led to larger mutation frequencies.

In summary, we provide a detailed overview on empiric *BRCA1/2* mutation frequencies for at-risk individuals with different familial cancer histories. The number of postmenopausal BC failed to show a systematic correlation with mutation frequency. Bilateral BC or premenopausal BC and OC in one affected family member conferred a higher mutation prevalence than two primaries in separate individuals. Our analysis provides a simple means to get an overview about expected mutation probabilities during clinical and genetic counselling before mutation testing is considered for both counsellors and counselees. Moreover, our results provide guidance for healthcare professionals and decision-makers to define consistent clinical criteria for decision-making to undergo genetic testing for individuals with suspected HBOC.

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