

HER-2/*neu* Status and Tumor Morphology of Invasive Breast Carcinomas in Ashkenazi Women with Known BRCA1 Mutation Status in the Ontario Familial Breast Cancer Registry

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Supported by Ontario Cancer Genetics Network, the Canadian Breast Cancer Research Initiative, the Cooperative Familial Registry for Breast Cancer Studies, and a Public Health Service Grant U01CA69467 from the National Cancer Institute and the National Institutes of Health.

The authors thank the women who participated in this study. They also thank Elaine Maloney, Judy Morell, Ellen Shi, and all the staff of the Ontario Familial Breast Cancer Registry.

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Received April 24, 2002; revision received June 17, 2002; accepted June 21, 2002.

BACKGROUND. The prevalence of BRCA1 germline mutations is greater in the Ashkenazi Jewish population than in the general North American population. The Ontario Familial Breast Cancer Registry collects clinical and family history data in familial breast carcinoma cases, and unselected Ashkenazi breast carcinomas, and acts as a tumor tissue repository.

METHODS. Using this resource, we examined the tumor morphology, hormone receptor status, and HER-2/*neu* protein overexpression in Canadian Ashkenazi breast carcinoma patients whose germline BRCA1 mutation status is known.

RESULTS. Thirty-eight tumors from 32 BRCA1 carriers and 354 tumors from 334 noncarriers were analyzed. The tumors in BRCA1 mutation carriers were more likely to be high grade ($P < 0.0001$) and estrogen receptor negative ($P < 0.004$). There was an increased frequency of typical medullary carcinomas in mutation carriers when all tumors were analyzed. However, this difference did not remain statistically significant when only the first tumor diagnosed in each patient was included in the analysis. There was no difference in HER-2/*neu* protein overexpression between the two groups overall ($P = 0.07$). However, when the analysis was restricted to Grade III tumors, there were significantly fewer HER-2/*neu*-positive tumors in the mutation carriers versus noncarriers (3.1% vs. 21.5%, $P = 0.012$). No significant differences were found in the incidence of lymph node status, progesterone receptor status, lymphatic vessel invasion, degree of lymphocytic infiltration, or in the presence of ductal carcinoma in situ associated with the invasive tumors.

CONCLUSIONS. Increasing awareness of the morphologic and immunophenotypic features more commonly found in BRCA1-associated breast carcinomas may lead to a wider use of these characteristics in genetic screening programs and provide further clues to their pathogenesis. *Cancer* 2002;95:2068-75.

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DOI 10.1002/cncr.10949

KEYWORDS: BRCA1, *erbB-2*, estrogen receptor, breast neoplasms.

The prevalence of BRCA1 germline mutations in the general population is approximately 0.1%,¹ 10 times lower than the reported prevalence of approximately 1% for the 185delAG and 5382insC founder mutations common among the Ashkenazi Jewish population.²⁻⁴ Penetrance for breast carcinoma is estimated to be about 60% by age 70 for Ashkenazi women who carry one of these mutations.^{5,6} Among Canadian Ashkenazi breast carcinoma patients not selected for age at diagnosis or family history, the BRCA1 germline mutation

prevalence is reported to be 8.2–11.9%.^{5–7} Comparable prevalence figures for Ashkenazi women with breast carcinoma have been reported from Israel, the United Kingdom, and the United States.^{8–10}

Breast carcinomas arising in BRCA1 mutation carriers differ from sporadic breast tumors by having a higher frequency of Grade III tumors. They are also estrogen (ER) and progesterone receptor (PR) negative and have an increased incidence of medullary histology.^{11–13} Fewer studies have considered other features with possible prognostic implications, such as the presence of lymphatic vessel invasion and HER-2/*neu* status, the presence of ductal carcinoma in situ (DCIS), or a lymphocytic infiltrate associated with these invasive carcinomas.^{14–16}

The Ontario Familial Breast Cancer Registry (OFBCR) offers testing for three Ashkenazi BRCA gene founder mutations, the BRCA1 mutations 185delAG and 5382insC and the BRCA2 6174delT mutation. These are offered to Ashkenazi Jewish women with a personal history of breast carcinoma irrespective of family history. Patients may also consent to retrieval of tissue specimens from the hospitals at which their breast carcinoma diagnoses were originally made, with representative tissue retained by the OFBCR's tumor repository. Results of review of tissue histology by a pathologist are recorded in the OFBCR's computerized database.

MATERIALS AND METHODS

This study was conducted as a substudy of an OFBCR research protocol investigating the prevalence of germline mutations in BRCA1 and BRCA2 among Ashkenazi Jewish women with a personal history of breast carcinoma. Recruitment occurs two ways. The population-based ascertainment included all those under 55 years and 35% of those aged 55–69 (randomly selected from the Ontario Cancer Registry) who responded to a questionnaire that included ethnic background. Those who indicated Jewish ancestry on the family history questionnaire were included in the Ashkenazi substudy. In addition, prevalent cases of breast carcinoma in Ashkenazis were identified through breast cancer clinics. They were invited to participate in the OFBCR and provided family history information. All individuals recruited gave written informed consent to participate in the OFBCR research protocol, including blood testing for germline BRCA gene mutations and consent for archival paraffin-embedded tissue to be obtained from the institutions at which the breast carcinoma diagnoses were made. In Ashkenazi patients, BRCA1 testing was limited to the two common founder mutations in this population (i.e., 185delAG and 5382insC) as these account for

almost all the BRCA1 mutations that occur in this population. The methods of determination of BRCA1 status in this protocol have been described previously.¹⁷ The research protocol was approved by the ethics committee of the University of Toronto.

There are 491 Ashkenazi participants in the OFBCR. Slides and blocks were obtained for 410 individuals (83.5%). Those who had the BRCA2 6174delT mutation as well as those with pure DCIS or DCIS with micro-invasion were excluded from the current study. Detailed pathology reviews were performed for the remaining 366 Ashkenazi patients for whom adequate paraffin-embedded tissue was available. All reviews were performed by a pathologist (L.A.Q. or F.P.O.) using standardized pathology reporting forms. Grading was by the method of Bloom and Richardson as modified by Elston and Ellis.¹⁸ To evaluate the extent of the mononuclear inflammatory cell infiltrate in and around the invasive carcinomas, the following arbitrary scale was used: absent = no mononuclear inflammatory cell infiltrate; mild = peritumoral infiltrate not involving the central area of the tumor; moderate = intratumoral infiltrate involving the central part of the tumor, but in which the mononuclear inflammatory cells represent less than one-half of the cells in a high power field ($\times 40$ objective); and marked = intratumoral infiltrate in which more than one-half of the cells in one or more high power fields are mononuclear inflammatory cells. Hematoxylin and eosin-stained sections of all available tissue from the breast carcinoma surgeries were reviewed, including nontumorous tissue and axillary lymph nodes. Thirty-eight invasive carcinomas from 32 BRCA1 mutation carriers were available for review, as were 354 invasive carcinomas from 334 noncarriers. All pathology reviews were blinded to the BRCA1 mutation status of the patients.

Determination of HER-2/*neu* status was made in 298 cases by standard avidin-biotin immunohistochemistry using diaminobenzidine as the chromogen and hematoxylin as the counterstain. Positive and negative cell line controls were used. Two monoclonal antibodies (CB11, Novocastra, New Castle-Upon-Tyne, UK, dilution 1/200; TAB250, Zymed, San Francisco, CA, dilution 1/150 with a Ficin incubation step for antigen retrieval for TAB250) were used in each case. A semiquantitative scoring system was used in which the proportion score for the percentage of cells staining positively (0 = none; 1 = < 1%; 2 = 1–10%; 3 = 10–33%; 4 = 34–67%; and 5 = > 67%) was added to the score for staining intensity (0 = no staining; 1 = weak; 2 = intermediate; 3 = strong staining) to give a final score of 0–8.¹⁹ A score of 5 or greater was counted as positive.²⁰ Individual tumors were counted

as positive if the result with either or both antibodies was positive. All determinations of HER-2/*neu* status were blinded to the BRCA1 mutation status of the patients.

Results for ER and PR status were obtained from the original pathology reports from the hospitals at which the breast carcinoma surgeries were performed. Results were either from biochemical or immunohistochemical tests. We were able to obtain ER status reports for 299 tumors and PR status reports for 296 tumors.

Due to the low frequencies in some cells, all statistical analyses were done using exact permutational statistical methods by StatXact-3 (Cytel Software, Cambridge, MA). Tests for all ordinal variables (e.g., tumor grade) used the exact version of the Wilcoxon–Mann–Whitney test. Nominal (e.g., type of carcinoma) variables used the Fisher exact test. Odds ratios (OR; and corresponding significance tests and exact 95% confidence intervals [CI]) were calculated for all binary variables (e.g., lymph node status), as well as for each level of the ordinal variables. All *P* values and ORs from these tests were based on the exact permutational distribution of the data and “mid-*P* adjusted” to correct for the usual conservativeness of exact tests compared with their asymptotic counterparts. Two-sided tests were used for testing the significance of the OR, as well as for analysis in which the Mann–Whitney test was used. *P* values were considered statistically significant if *P* was less than 0.05. As tumor grade was strongly associated with the other tumor characteristics (except DCIS), all analyses (*P*- values and ORs) in Tables 1–3 controlled for grade by stratification. To assess the impact of the intrasubject correlation in the 26 patients who had bilateral tumors in the study, the analysis was repeated using only data from the patient’s first tumor (except where that data were missing). As the two approaches yielded similar results, only the analysis on the complete dataset will be reported in full.

RESULTS

In tumors from both germline BRCA1 mutation carriers (*n* = 38) and non-carriers (*n* = 354), the most common histologic type of invasive breast carcinoma was no special type (invasive ductal, not otherwise specified), which accounted for greater than 88% of tumors in each group of patients (Table 4). Typical medullary type carcinomas were overrepresented in the mutation-carrier patients, with 2 of 38 tumors occurring in these patients, versus 1 of 354 in the noncarrier group (*P* = 0.013). The two medullary tumors in the BRCA1 mutation group occurred as bilateral, metachronous tumors in the same patient.

TABLE 1
Hormone Receptor Status^a and HER-2 Expression Status in Invasive Carcinomas

	BRCA-1 mutation carriers (%)	Noncarriers (%)	Odds ratio (95% CI)
Estrogen receptor status in all tumor grades (<i>P</i> = 0.004) ^b			
Positive	4 (15.4)	205 (75.1)	1.0 (reference)
Borderline	7 (26.9)	20 (7.3)	10.3 (2.4, 50.3)
Negative	15 (57.7)	48 (17.6)	5.6 (1.7, 22.8)
Totals	26	273	
Progesterone receptor status in all tumor grades (<i>P</i> = 0.34) ^c			
Positive	8 (30.8)	178 (65.9)	1.0 (reference)
Borderline	4 (15.4)	23 (8.5)	1.37 (0.30, 5.6)
Negative	14 (53.8)	69 (25.6)	1.64 (0.60, 4.7)
Totals	26	270	
HER-2/ <i>neu</i> protein overexpression in all tumor grades (<i>P</i> = 0.07) ^d			
Positive	2 (5.7)	34 (12.9)	0.25 (0.04, 1.03)
Negative	33 (94.3)	229 (87.1)	1.0 (reference)
Totals	35	263	
HER-2/ <i>neu</i> protein overexpression in Grade III tumors (<i>P</i> = 0.012) ^e			
Positive	1 (3.1)	14 (21.5)	0.12 (0.005, 0.73)
Negative	31 (96.9)	51 (78.5)	1.0 (reference)
Totals	32	65	

CI: confidence interval.

^a From the original pathology reports generated at the time of diagnosis in various hospitals.

^b Wilcoxon–Mann–Whitney test with 2 df, controlling for tumor grade. The *P* value changed to 0.002 when the analysis was limited to one tumor per patient.

^c Wilcoxon–Mann–Whitney test with 2 df, controlling for tumor grade. The *P* value changed to 0.63 when the analysis was limited to one tumor per patient.

^d Significance test that odds ratio is unity, controlling for tumor grade. The *P* value changed to 0.12 when the analysis was limited to one tumor per patient.

^e Significance test that odds ratio is unity. The *P* value changed to 0.022 when the analysis was limited to one tumor per patient.

Therefore, when the second tumors were excluded from the analysis, the excess in medullary tumors was no longer significant (*P* = 0.09). As well, when atypical medullary carcinoma, or medullary features were included (Table 5), there was no evidence of a difference between BRCA1 mutation carriers and noncarriers.

Comparing the two groups by histologic tumor grade shows a very different distribution among the three grades depending on BRCA1 status (*P* < 0.0001; Table 6). There were no Grade I/III tumors in the mutation carriers, whereas more than one-third of the carcinomas in the noncarriers were Grade I/III. Of 38 carcinomas in the mutation carriers, 34 (89%) were Grade III/III. Tumors in the noncarriers were distrib-

TABLE 2
Mononuclear Inflammatory Cell Infiltration in Invasive Carcinomas

	BRCA-1 mutation carriers (%)	Noncarriers (%)	Odd ratio (95% CI)
Mononuclear inflammatory cell infiltrate in all tumor grades ($P = 0.57$) ^a			
Absent	11 (30.6)	142 (42.4)	1.0 (reference)
Mild	10 (27.8)	116 (34.6)	1.09 (0.39, 3.1)
Moderate	6 (16.7)	61 (18.2)	0.38 (0.11, 1.2)
Marked	9 (25.0)	16 (4.8)	2.0 (0.62, 6.3)
Totals	36	335	

Absent: no infiltrate; mild: peritumoral infiltrate not involving the central area of the tumor; moderate: intratumoral infiltrate involving the central part of the tumor, but in which the mononuclear inflammatory cells represent less than one-half of the cells in a high power field ($\times 40$); marked: intratumoral infiltrate in which more than one-half of the cells in one or more high power fields are mononuclear inflammatory cells; CI: confidence interval.

^a Wilcoxon–Mann–Whitney test with 3 df, controlling for tumor grade. The P value changed to 0.88 when the analysis was limited to one tumor per patient.

uted more evenly among the three grades, with Grade II/III being the most frequent (40%), and only 25% being Grade III/III.

Tumors from mutation carriers were more often ER negative, even after controlling for tumor grade ($P = 0.004$). There was no statistical evidence of a difference in PR status, after controlling for grade (Table 1).

Of the 298 tumors in which HER-2/*neu* status was determined, there was no significant differences in HER-2/*neu* protein overexpression controlling for tumor grade ($P = 0.07$). However, when the analysis was restricted to Grade III tumors, there were significantly fewer HER-2/*neu*-positive tumors among the mutation carriers ($P = 0.012$; Table 1). There was only one HER-2/*neu*-positive tumor among the 32 Grade III tumors in the mutation carriers (3.1%) compared with 21.5% in the 65 noncarrier Grade III tumors (OR: 0.12, 95% CI: 0.005–0.73). The rate of HER-2/*neu* overexpression in both groups was lower than usually reported (5.7% in mutation carriers vs. 12.9% in noncarriers).

The BRCA1 mutation carriers and noncarriers did not differ with respect to the degree of mononuclear inflammatory cell infiltrate (Table 2), presence of lymphatic vessel invasion, positive lymph node status, the presence of DCIS associated with the invasive carcinomas, circumscribed margins, or syncytial growth (Table 3).

DISCUSSION

The invasive breast carcinomas of Ashkenazi women in the OFBCR display the features associated with

TABLE 3
Lymphatic Vessel Invasion, Lymph Node Status, DCIS, Circumscribed Margins, and Syncytial Growth Associated with Invasive Carcinomas

	BRCA-1 mutation carriers (%)	Noncarriers (%)	Odds ratio (95% CI)
Lymphatic vessel invasion in all tumor grades ($P = 0.29$) ^a			
Present	12 (31.6)	89 (25.3)	0.63 (0.28, 1.38)
Absent	26 (68.4)	263 (74.7)	1.00 (reference)
Totals	38	352	
Lymph node status in all tumor grades ($P = 0.08$) ^a			
Positive	9 (28.1)	113 (35.8)	0.45 (0.18, 1.06)
Negative	23 (71.9)	203 (64.2)	1.00 (reference)
Totals	32	316	
DCIS associated with invasive carcinoma in all tumor grades ($P = 0.38$) ^a			
Present	22 (59.5)	225 (63.7)	0.74 (0.34, 1.61)
Absent	15 (40.5)	128 (36.3)	1.00 (reference)
Totals	37	353	
Circumscribed margins in all tumor grades ($P = 0.57$) ^a			
Present	3 (11.1)	11 (3.6)	1.48 (0.29, 6.2)
Absent	24 (88.9)	292 (96.4)	1.00 (reference)
Totals	27	303	
Syncytial growth in all tumor grades ($P = 0.52$) ^a			
Positive	5 (19.2)	21 (7.0)	0.63 (0.19, 1.9)
Negative	21 (80.8)	281 (93.0)	1.00 (reference)
Totals	26	302	

DCIS: ductal carcinoma in situ; CI: confidence interval.

^a Significance test that odds ratio is unity, controlling for tumor grade. All P values remained nonsignificant when the analysis was limited to one tumor per patient.

BRCA1 in other reports (Table 7). These reports originate from several countries, include persons of different ethnic origins, and record several different mutations of the BRCA1 gene.

An increased frequency of high-grade tumors is reported in all but two studies: one found weak evidence of an increase in high-grade tumors²³ and the other is a smaller study of 10 tumors from BRCA1 mutation carriers.²⁵ Eighty-nine percent of the tumors in mutation carriers were Grade III in our study. Figures reported by others for the percentage of Grade III tumors in mutation carriers range from 57%²³ to 100%.^{13,16,22,34} An increased frequency of medullary or atypical medullary histology is noted in a number of studies (Table 7). These reports come from several nations, including a small study of five BRCA1-associated carcinomas in Chinese women in Hong Kong.³⁵ In one study of 10 BRCA1-associated tumors, 6 were

TABLE 4
Histologic Types of Invasive Carcinomas

	BRCA-1 mutation carriers No. (%)	Noncarriers No. (%)
No. of patients	32	334
No. of carcinomas	38	354
Histologic type in all tumors (<i>P</i> = 0.13) ^a		
No special type	34 (89.5)	312 (88.1)
Typical medullary ^b	2 (5.3)	1 (0.3)
Classic lobular	0	11 (3.1)
Pleomorphic lobular	1 (2.6)	12 (3.4)
Tubular	0	9 (2.5)
Mucinous	0	5 (1.4)
Metaplastic	1 (2.6)	2 (0.6)
Micropapillary	0	1 (0.3)
Cribriform	0	1 (0.3)

^a Fisher exact test with 8 df. The *P* value changed to 0.33 when the analysis was limited to one tumor per patient.

^b Odds ratio = 19.3 (95% confidence interval: 1.4–588, *P* = 0.013) relative to all other tumor types. The *P* value changed to 0.09 when the analysis was limited to one tumor per patient.

TABLE 5
Medullary Features (Including Atypical Medullary Carcinoma)

	BRCA-1 mutation carriers (%)	Noncarriers (%)	Odds ratio (95% CI)
Medullary features in all tumors (<i>P</i> = 0.076) ^a			
Absent	34 (89.5)	338 (95.5)	1.0 (reference)
Present	4 (10.5)	16 (4.5)	2.5 (0.68, 7.5)
Totals	38	354	

CI: confidence interval.

^a *P* value for the significance test that odds ratio is unity. The *P* value changed to 0.13 when the analysis was limited to one tumor per patient.

found to be of atypical medullary type.¹³ Using the more rigorous Ridolfi criteria³⁶ to define typical medullary carcinomas, a frequency of up to 19% was found (in 32 tumors).³¹ Comparisons of BRCA1-associated breast carcinomas with BRCA2-associated tumors and non-BRCA-associated familial breast carcinomas suggest that this increased frequency of medullary histology in familial carcinomas is only seen with mutations of BRCA1.^{12,13,27,28,33,37} Enthusiasm for linking medullary features to BRCA1 mutation status must be tempered, however, by the equally numerous reports showing no significant increase in the occurrence of medullary histology in BRCA1-associated carcinomas (Table 7). A smaller number of studies included an assessment of the degree of mononuclear inflammatory cell infiltrate present in and around invasive

TABLE 6
Histologic Grades of Invasive Carcinomas

	BRCA-1 mutation carriers (%)	Noncarriers (%)	Odds ratio (95% CI)
Histologic grade (<i>P</i> < 0.0001) ^a			
I	0	124 (35.0)	0.0 (0.0, 0.07)
II	4 (10.5)	143 (40.4)	0.07 (0.02, 0.20)
III	34 (89.5)	87 (24.6)	1.0 (reference)
Totals	38	354	

CI: confidence interval.

^a Wilcoxon-Mann-Whitney test with 2 df. The *P* value was unchanged when the analysis was limited to one tumor per patient.

breast carcinomas in BRCA1 mutation carriers.^{13,15,31,37} The larger studies have shown that the stroma of these tumors are more frequently infiltrated by mononuclear inflammatory cells and that these infiltrates are denser than in noncarriers.^{14,15,30,31} The percentages obtained in our study for the presence of a lymphocytic infiltrate in tumors from mutation carriers are in very close agreement with those reported by Lakhani and co-workers in the largest studies in which this factor was evaluated^{30,37} (69% in our study vs. 66% in theirs). Our study, however, did not show a statistically significant increase in mononuclear inflammatory infiltrate associated with tumors in the BRCA1 carrier group. This was largely due to the fact that the degree of inflammatory infiltrate was highly correlated with tumor grade and our analysis controlled for tumor grade. Two smaller studies, one comprising 10 tumors,¹³ and one involving 12 BRCA1-associated carcinomas in a pool of 17 BRCA1/2 tumors¹⁶ did not show an increased inflammatory cell infiltrate in tumors from BRCA1 mutation carriers.

There is no consensus as to whether or not DCIS is less frequently seen in association with invasive carcinomas in BRCA1 mutation carriers (Table 7). The larger studies have favored a relative absence of DCIS. In our Ashkenazi patients, there was no difference between patients with and without a BRCA1 mutation in this regard.

The frequency of lymphatic vessel invasion did not differ between the two groups in our study. This is consistent with findings in all but one other study (Table 7). There was no significant difference in lymph node involvement between our two groups of patients, in agreement with all but one published report.⁹

An increased frequency of ER-negative tumors is universally described in BRCA1-associated breast carcinomas (Table 7). The majority of reports also note an increased frequency of PR-negative tumors (Table 7),

TABLE 7
Features Commonly Identified in Invasive Breast Carcinomas from BRCA1 Mutation Carriers: More Frequent in BRCA1-Associated Breast Carcinomas than in Controls^a

Reference	No. of tumors in mutation carriers	Study group limited by age	Country	High grade	Medullary or atypical medullary histology	Mononuclear inflammatory cell infiltrate present	Lymphatic vessel invasion	ER negative	PgR negative	p53 mutated	HER-2/ <i>neu</i> overexpression less than or equal to controls	Absence of associated DCIS	Lymph node status differs significantly
Robson et al. ¹⁶	12 of 17 ^b	< 42	USA	Yes	No	No	No	Yes	—	No	Yes	No	No
Robson et al. ²¹	23 of 30	< 42	USA	Yes	No	—	—	Yes	No	—	—	—	No
Turchetti et al. ²²	6 ^b	< 35	Italy	Yes	Yes	—	—	Yes	No	—	—	—	No
Wagner et al. ²³	34	No	Austria	No	Yes	—	—	Yes	Yes	—	—	—	c
Robson et al. ⁹	27 of 35 ^b	No	USA	—	No	—	—	Yes	—	—	—	—	Yes
Vaziri et al. ²⁴	31	No	USA	c	c	—	—	Yes ^d	Yes ^d	No	Yes ^d	—	—
de Bock et al. ²⁵	10	No	The Netherlands	No	—	—	No	Yes	Yes	No	Yes	No	No
Armes et al. ²⁶	10	< 40	Australia	—	—	—	—	Yes	No	Yes	Yes	—	—
Pierce et al. ²⁷	53	No	USA and Canada	Yes	Yes	—	—	Yes	Yes	—	—	—	—
Stoppa-Lyonnet et al. ²⁸	50	No	France	Yes	Yes	—	—	Yes	Yes	—	—	—	No
Phillips et al. ²⁹	13	No	Canada	Yes	—	—	—	Yes	—	Yes	—	—	—
Chappuis et al. ⁷	24 of 32 ^b	No	Canada	—	—	—	—	Yes	—	—	—	—	No
Marcus et al. ¹¹	90	No	USA	Yes	Yes	—	—	—	—	—	—	—	—
Karp et al. ⁵	17	< 65	Canada	—	No	—	—	Yes	Yes	—	—	—	No
Lakhani et al. ³⁰	114	No	e, see below	—	Yes	Yes	—	—	—	—	—	Yes	—
Eisinger et al. ³¹	32	No	France	—	Yes	Yes	—	—	—	—	—	Yes	—
Eisinger et al. ¹⁴	32	No	France	Yes	—	Yes	No	Yes	Yes	Yes	Yes	Yes	—
Lynch et al. ³²	32	No	USA	Yes	No	—	—	Yes	Yes	Yes	Yes	—	—
Breast Cancer Linkage Consortium. ¹²	118	No	e, see below	Yes	Yes	—	—	—	—	—	—	Yes	—
Foulkes et al. ⁴³	16	< 65	Canada	—	—	—	—	Yes	—	Yes	—	—	—
Loman et al. ⁴⁴	27	No	Sweden	—	—	—	—	Yes	Yes	—	—	—	—
Verhoog et al. ⁴⁵	49	No	The Netherlands	—	No	—	—	Yes	Yes	—	—	—	No
Hamann et al. ⁴⁶	36	No	Germany	Yes	No	—	—	—	—	—	—	—	No
Johannsson et al. ⁴⁷	40	No	Sweden	—	No	—	—	Yes	Yes	—	—	—	—
Eerola et al. ³³	32	No	Finland	—	Yes	—	—	—	—	—	—	—	No
Armes et al. ¹³	10	< 40	Australia	Yes	Yes ^f	No	No	—	—	—	—	No	No
Johannsson et al. ⁵	40	No	Sweden, Iceland	Yes	No	Yes	—	Yes	Yes	No	Yes	—	—
OFBCR Ashkenazi (this study)	38	No	Canada	Yes	Yes	No ^g	No	Yes	No ^g	—	Yes ^h	No	No

ER: estrogen receptor; PR: progesterone receptor; DCIS: ductal carcinoma in situ.

^a Yes: significantly more frequent in BRCA1-associated cases than in controls; No: not significantly different from controls; —: not reported.

^b Study included a minority of BRCA2 mutation carriers admixed with the BRCA1 carrier group.

^c Matched in study.

^d Only significant in patients younger than 50 years at diagnosis.

^e UK, USA, Ireland, France, Germany, Iceland, Switzerland, The Netherlands.

^f No typical medullary, all atypical medullary.

^g Controlled for tumor grade.

^h In grade III tumors only.

although three previous studies found no significant differences in PR status between BRCA1 mutation carriers and noncarriers.^{21,22,26} Investigations of HER-2/*neu* status in BRCA1-associated tumors have either found no difference in HER-2/*neu* overexpression

compared with controls^{14,24,25,32} or a lower frequency of overexpression in BRCA1-associated tumors, as in the current study.^{15,16,21} In contrast, several groups, including our own, have reported a higher frequency of p53 mutations in BRCA1 mutation carriers com-

pared with controls.^{14,29,32} The increased frequency of high-grade, ER-negative invasive breast carcinomas as described in the Ashkenazi OFBCR patients is consistent with reports published by other authors in various countries. The importance of recognizing histologic and immunophenotypic features more frequently found in BRCA1-associated invasive breast carcinomas is reinforced by recent successful attempts to use the factors of poor tumor differentiation, ER-negative status,³⁸⁻⁴⁰ and the presence of typical medullary histology³¹ to improve the yield of genetic testing for BRCA1 carrier status.

The relatively homogeneous phenotype of BRCA1-associated breast carcinomas may also have important implications for their treatment and prevention. The low frequency of HER-2/*neu* overexpression in BRCA1-associated breast carcinomas suggests that this is a subgroup of tumors for which treatment with the biologic agent trastuzumab is unlikely to be of benefit. Similarly, the fact that such tumors are usually ER negative suggests that chemoprevention with ER modulators such as tamoxifen may not be effective. However, Narod et al.,⁴¹ in a case-control study of breast carcinoma patients, demonstrated that tamoxifen use significantly reduced the risk of contralateral breast carcinoma in BRCA1 and BRCA2 mutation carriers (as a combined group) by 50%. The risk reduction was also statistically significant for the group of BRCA1 mutation carriers when analyzed separately. Conversely, a subanalysis of the NSABP-P1 tamoxifen chemoprevention study failed to show a reduction in the risk of first breast carcinoma in BRCA1 carriers who took tamoxifen.⁴² However, the study lacked sufficient power to exclude such an effect. A non-statistically significant risk reduction of about 60% (similar to the risk reduction for tamoxifen users across the whole study) was seen in BRCA2 mutation carriers who took tamoxifen. The role of tamoxifen as a chemopreventive agent in BRCA1 mutation carriers remains controversial.

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