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Numerous high-risk epithelial lesions in familial breast cancer

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ABSTRACT

Purpose: To assess the occurrence of high-risk epithelial lesions in women of breast cancer families with and without a *BRCA* mutation.
Patients and methods: Prospective study of women at very high risk of breast cancer undergoing prophylactic mastectomy (68 *BRCA1* mutation carriers, 14 *BRCA2* mutation carriers and 24 non-BRCA mutation carriers).
Results: The prevalence of high-risk lesions is equal in women with a *BRCA1* or a *BRCA2* mutation, but is higher in non-BRCA mutation carriers: all lesions 43% *versus* 71% ($p = 0.02$), atypical lobular hyperplasia 26% *versus* 67% ($p = 0.001$), atypical ductal hyperplasia 17% *versus* 42% ($p = 0.01$), lobular carcinoma-*in situ* 15% *versus* 29% ($p = 0.10$) and ductal carcinoma-*in situ* 9% *versus* 17% ($p = 0.25$). The presence of high-risk lesions is related to absence of a *BRCA* mutation and to age over 40 years.
Conclusion: Women with an autosomal dominant family history for breast cancer, with and without a *BRCA* mutation are prone to develop high-risk epithelial lesions, especially over 40 years.

1. Introduction

Little is known about the early stages of breast cancer development in women with a strong family history. This applies equally to those testing negative for a *BRCA* mutation and to those carrying a *BRCA1* or a *BRCA2* mutation. There might be differences in breast cancer development between *BRCA1* and *BRCA2* mutation carriers because the features of fully developed invasive breast cancers from *BRCA1* and *BRCA2* mutation carriers are different.[1–3] Women with hereditary predisposition to breast cancer are prone to develop epithelial lesions that indicate a high risk of subsequent invasive breast cancer.[4–6] These high-risk lesions include atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH),

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lobular carcinoma-*in situ* (LCIS) and ductal carcinoma-*in situ* (DCIS).[4,7]

The options for women with a deleterious germline mutation in *BRCA1* or *BRCA2* to handle their high risk are either regular surveillance or prophylactic mastectomy. Bilateral prophylactic mastectomy in healthy women with a *BRCA* mutation is associated with a 90% reduction in breast cancer incidence.[8,9] When applied at young age, around or before the age of 40 years, this may lead to a significant survival advantage.[10] This procedure is much less accepted for women who appeared to be negative for a *BRCA* mutation even though they have an apparent autosomal dominant family history for breast cancer.[11–14] Especially women with breast cancer at young age and a strong family history but without a *BRCA* mutation may want to opt for contralateral prophylactic mastectomy. While cancer-free survival is the ultimate test of effectiveness, a first indication may be gleaned from examining mastectomy specimens.

Information is lacking on whether the prevalence of high-risk lesions differs between women with and without a *BRCA* mutation. In a previous study by our group, of women at high hereditary risk of breast cancer, the prevalence of a *BRCA* mutation was lower in the group with high-risk lesions compared to the group without high-risk lesions.[4] At that time the group that was tested negative for a mutation was not strictly defined and the groups with a *BRCA1* or a *BRCA2* mutation were too small to be studied separately. In the present study, we investigated the differences in prevalence of high-risk epithelial lesions in women with an exceptionally strong family history for breast cancer with and without a *BRCA* mutation, who chose for prophylactic mastectomy because of their high risk for breast cancer. These results may be relevant for breast cancer prevention in women with an autosomal dominant family history for breast cancer.

2. Patients and methods

2.1. Patient characteristics

Women at high hereditary risk of breast cancer, who underwent prophylactic mastectomy between 1989 and 2004 with and without previous breast cancer, were included. In case a woman had previous breast cancer, prophylactic mastectomy of the contralateral breast was performed. All women had extensive genetic counseling and were shown to have a strong family history for breast cancer, often in combination with ovarian cancer, suggestive for autosomal dominant transmission of the disease, occurring in consecutive generations and at young age. All women had been tested for germline *BRCA1* or *BRCA2* mutations associated with breast and/or ovarian cancer in their family. Analysis was done of the entire open reading frames and all exon boundaries by a combination of protein truncation testing (PTT) of the exons 11 and denaturing gradient gel electrophoresis (DGGE) of the boundary of the exons 11 and of all coding exons. Multiple ligation probe amplification (MLPA) was used to test for exon deletions. Whenever a *BRCA* mutation had been identified in the family, healthy relatives were tested for that specific mutation. The lifetime risk of breast cancer in *BRCA* mutation carriers is 55–85%,[15] and the estimated lifetime risk of breast cancer in the group without a *BRCA1* or *BRCA2* mutation in our study is more than 30%, based on the model of Claus *et al*.[16] Medical records of all patients were reviewed for family history and breast cancer related risk factors (such as age, menarche, parity, and duration of oral contraceptives, salpingo-oophorectomy, and previous breast cancer). Patients with a *BRCA*-unclassified variant were not included.

Inclusion of patients was limited to those who chose for prophylactic mastectomy because of their high lifetime risk for breast cancer. Prior to mastectomy all patients had physical breast examination and mammography (some in combination with an MRI), without suspicion for pathology.

The data from 59 out of the presented 106 patients were described previously.[4] From the previously described cohort of 67 women, 8 non-*BRCA* mutation carriers were excluded in this study because *BRCA* mutation detection was not performed or with the currently available techniques.

2.2. Specimens

The handling of the specimens was based on the correlated radiographic and pathology technique developed by Egan,[17] and which has been routinely performed in our pathology department for many years.[18] The specimens were cooled and sliced in serial sections with approximately 5-mm intervals. Radiographs were made from these tissue slices. Suspicious lesions and randomly selected areas from each quadrant and the nipple were sampled, with a mean number of 18 ± 5 samples per specimen (range 7–39). One pathologist (PB) conducted a review of the pathology report, the histological slides, and the simple mastectomy specimen radiographs. Atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH), and lobular carcinoma-*in situ* (LCIS) were classified according to the criteria of Page *et al*.[19,20] Ductal carcinoma-*in situ* (DCIS) was classified according to the criteria of Holland *et al*.[21]

Quality and consistency of the procedure over time were tested by comparison of the prevalence of high-risk lesions in the group with a mastectomy ($n = 59$) performed between 1989 and 2001 *versus* the group ($n = 47$) with a mastectomy performed between 2001 and 2004. The number of samples and the prevalence of the various high-risk lesions between the older and the latter group were not different (data not shown).

2.3. Statistical analysis

From every patient only one breast was evaluated. If bilateral prophylactic mastectomy was performed, the breast was selected having the highest frequency (in descending order) of: DCIS, LCIS, ADH, and ALH, respectively. This order is based on the related risk for a woman with two breasts to develop breast cancer. Descriptive data are reported as mean ± standard deviation for continuous variables and as percentages for categorical variables. Group comparisons were tested for statistical significance using *t*-tests for continuous variables, and cross tables with Pearson χ^2 tests for categorical variables. Independent values of predictors for high-risk lesions were calculated using a multivariate logistic regression model. The following factors were entered in the model: non-BRCA

versus BRCA mutation carrier, previous oophorectomy *versus* no previous oophorectomy, previous breast cancer *versus* no previous breast cancer, and age at mastectomy older than 40 years *versus* younger than 40 years. Because none of our patients in the non-BRCA-group had a previous oophorectomy, we combined these two variables into a categorical new variable with three groups: *BRCA* mutation carrier without previous oophorectomy (the reference group), *BRCA* mutation carrier with oophorectomy, and non-BRCA mutation carriers without previous oophorectomy. Odds ratios with corresponding 95% confidence intervals were calculated in order to estimate the association with high-risk lesions. Also, predicted probabilities for high-risk lesions for different combinations of predictors were calculated from the multivariable model results.

3. Results

3.1. Histological findings in women with a BRCA1 or a BRCA2 mutation

Eighty-two patients with a deleterious *BRCA* mutation underwent prophylactic mastectomy (68 *BRCA1 mutation* carriers and 14 *BRCA2* mutation carriers). The total prevalence of all high-risk lesions in *BRCA1* and *BRCA2* mutation carriers was 44% *versus* 36% ($p = 0.56$), with ALH in 26% *versus* 21% ($p = 0.69$), ADH in 18% *versus* 14% ($p = 0.70$), LCIS in 16% *versus* 7% ($p = 0.38$) and DCIS in 9% *versus* 7% ($p = 0.83$), respectively.

Risk factors for breast carcinoma were documented at the time of mastectomy. The youngest family member with breast cancer in the *BRCA1* families was approximately 9 years younger than in the *BRCA2* families (44 ± 9 years and 35 ± 9 years, respectively ($p = 0.02$)). The youngest family member with ovarian cancer was 11 years older in the *BRCA1* families; 52 ± 7 *versus* 41 ± 7 years for *BRCA2* ($p = 0.006$), and a comparable proportion of families with ovarian cancer (43% *versus* 36%, $p = 0.5$). No other differences in risk factors between the group with a *BRCA1* or a *BRCA2* mutation were found (data not shown).

In order to enable comparison between *BRCA* mutation carriers and the non-BRCA group, the data from *BRCA1* and *BRCA2* mutation carriers were combined. In these 82 *BRCA* mutation carriers, the prevalence of high-risk lesions was equal among women with and without a prophylactic oophorectomy, being 47% (9/19) and 41% (26/63) ($p = 0.64$), respectively.

3.2. Histological findings in women with and without BRCA mutation

The presence of high-risk lesions was positively correlated with age (correlation coefficient 0.28, $p = 0.004$). Comparison of all women with and without high-risk lesions showed that women with high-risk lesions were older 44 ± 9 years *versus* 39 ± 8 years ($p = 0.003$). Women over 40 years of age had a higher prevalence of high-risk lesions than younger women: 60% (33/55) *versus* 38% (20/52) ($p = 0.03$).

Table 1 summarises the histological lesions and other risk factors for breast cancer in women with and without a *BRCA* mutation. A higher prevalence of histological high-risk lesions was found among patients not carrying a *BRCA* mutation

Table 1 – Breast cancer related risk factors (percentages or mean with standard deviation) in patients undergoing prophylactic mastectomy with and without a BRCA mutation

	All, N = 106 (%)	BRCA, N = 82 (%)	Non-BRCA, N = 24 (%)	p-Value[a]
Histopathology				
Overall presence of high-risk lesions	49	43	71	0.015
ALH	35	26	67	0.000
ADH	23	17	42	0.011
LCIS	18	15	29	0.10
DCIS	10	9	17	0.25
Genetic risk factors				
Youngest patient with breast cancer in the family	38 ± 8	36 ± 9	41 ± 6	0.045
Youngest patient with ovarian cancer in the family	50 ± 8	50 ± 8	50 ± 1	0.9
Families with ovarian cancer	35	41	13	0.007
Non-Genetic risk factors				
Age at prophylactic mastectomy (years)	41 ± 9	40 ± 9	44 ± 8	0.06
Mastectomy years after breast cancer (years)	2.7 ± 4.6	3.3 ± 5.2	1.8 ± 3.4	
Previous breast cancer	45	35	79	0.000
Age at previous breast cancer (years)	43 ± 9	42 ± 9	44 ± 7	0.40
Hormonal risk factors				
Oophorectomy >1 year before mastectomy	18	23	–	
Age at oophorectomy	43 ± 8	43 ± 7	–	
Postmenopausal	43	46	30	0.17
Menarche	13.3 ± 1.6	13.2 ± 1.6	13.6 ± 1.6	0.40
Parity	1.9 ± 1.2	1.9 ± 1.2	1.8 ± 1.2	0.90
OAC years	10 ± 8	11 ± 8	7 ± 6	0.022

ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ.
a Difference between BRCA and non-BRCA group.

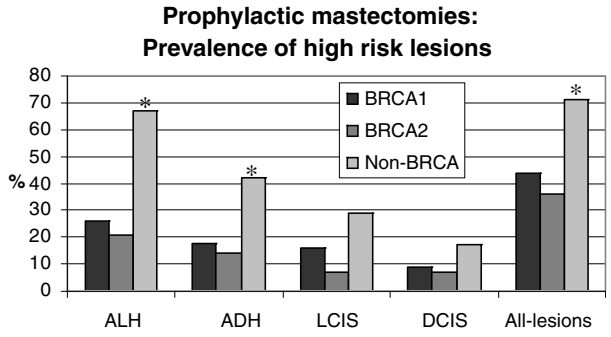

Fig. 1 – Prevalence of breast cancer-related risk lesions in patients with a *BRCA1* , a *BRCA2 mutation or non-BRCA* mutation carriers. ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma-*in situ*; DCIS, ductal carcinoma-*in situ*. * indicates significant difference from *BRCA* mutation carriers ($p < 0.05$).

(Fig. 1). The two groups appeared to be different in some aspects: women from the non-BRCA group had relatively more often previous breast cancer ($p < 0.0001$), never had a prophylactic oophorectomy, were slightly older ($p = 0.06$), and less often had a relative with ovarian cancer ($p = 0.007$) (Table 1).

When grouped according to their mutation carrier status, previous breast cancer and previous oophorectomy did not appear to play a significant role in the prevalence of high-risk lesions (Table 2). The prevalence of high-risk lesions was comparable in the groups with and without previous breast cancer, in *BRCA* mutation carriers 44% (13/29) and 41% (22/53), respectively ($p = 0.77$), and in the non-BRCA group 68% (13/19) and 80% (4/5), respectively. The average number of years between breast cancer diagnosis and preventive mastectomy was 2.7 ± 4.6 years.

Table 3 presents the results of the multivariate logistic regression analysis. Non-BRCA mutation carrier status and age over 40 years had significant independent predictive value for the presence of high-risk lesions in the mastectomy specimen. This analysis supports the previously drawn conclusion that preventive oophorectomy does not affect the presence of high-risk lesions in *BRCA* mutation carriers. Using the regression coefficients from the logistic regression analysis, we calculated the predicted probability for each woman to have histological abnormalities. This is shown in Table 4. Women at high familial risk for breast cancer not carrying a *BRCA* mutation over 40 years of age have the highest predicted probability of approximately 80% for the presence of high-risk lesions in their breast. For a woman over 40 years with a *BRCA* mutation this risk is approximately 55%.

Table 5 presents the data of 12 patients who appeared to have DCIS at, what was planned to be, a preventive mastectomy, the so-called occult DCIS. One of these patients also had an invasive ductal cancer. DCIS was moderate or high grade in 9 of 11 women, with a mean size of 10 mm [range

Table 3 – Risk factors for high-risk lesions in prophylactic mastectomy specimens: multivariable adjusted odds ratio's with 95% confidence intervals of various predictors

	Odds ratio 95%	CI	*p*
BRCA mutation without previous oophorectomy	Ref		
BRCA mutation with previous oophorectomy	0.80	0.25–2.55	0.71
Non-BRCA without previous oophorectomy	3.13	1.05–9.32	0.04
No previous breast cancer	Ref		
Previous breast cancer	0.78	0.32–1.89	0.58
Age at mastectomy under 40 year	Ref		
Age at mastectomy older than 40 year	2.44	0.96–5.88	0.06

Table 2 – Breast cancer-related risk factors (percentages or mean with standard deviation) in patients undergoing prophylactic mastectomy with and without high-risk lesions

	BRCA-positive			BRCA-negative		
	No high-risk lesions, N = 47 (%)	High-risk lesions, N = 35 (%)	*p*	No high-risk lesions, N = 7 (%)	High-risk lesions, N = 17 (%)	*p*
Genetic risk factors						
Youngest patient with breast cancer in the family	36 ± 8	36 ± 10	0.9	36 ± 5	43 ± 6	0.014
Youngest patient with ovarian cancer in the family	52 ± 8	47 ± 9	0.1	–	2 families	
Non-genetic risk factors						
Age at prophylactic mastectomy (years)	39 ± 8	43 ± 10	0.03	40 ± 6	46 ± 8	0.11
Age <40 year at prophylactic mastectomy	60	46	0.21	57	18	0.053
Previous breast cancer	34	37	0.77	86	76	0.61
Age at previous breast cancer (years)	38 ± 8	47 ± 9	0.01	40 ± 6	46 ± 7	0.087
Hormonal risk factors						
Oophorectomy >1 year before mastectomy	21	26	0.64	–	–	
Age at oophorectomy	41 ± 6	46 ± 8	0.02	31 jr	55 jr	
Postmenopausal	40	54	0.21	–	41	0.06
Menarche	13.0 ± 1.5	13.4 ± 1.8	0.6	14.2 ± 1.3	13.4 ± 1.6	0.31
Parity	1.8 ± 1.2	1.2 ± 1.3	0.7	1.7 ± 1.2	1.9 ± 1.3	0.8
Oral anti-conceptive use (years)	11 ± 8	11 ± 7	0.2	9 ± 9	5 ± 4	0.2

Table 4 – Predicted probability for the presence of high-risk lesions in prophylactic mastectomy specimen related to mutation status, breast cancer history, age and oophorectomy history

BRCA mutation	Previous breastcancer	Age under 40 years	Previous oophorectomy	Probability for high-risk lesions
+	–	+	–	0.36
+	+	+	–	0.30
+	–	–	–	0.58
+	+	–	–	0.51
+	–	+	+	0.31
+	+	+	+	0.26
+	–	–	+	0.52
+	+	–	+	0.46
–	–	+	–	0.64
–	+	+	–	0.58
–	–	–	–	0.81
–	+	–	–	0.78

Table 5 – Patient characteristics with occult DCIS in prophylactically removed breasts

ID nr	BRCA mutation	DCIS size (mm)	DCIS grade	ADH	ALH	LCIS	Invasive	Mastect age	Oophor.	BC age
8	*BRCA1*	2	3		Yes	Yes		35		35
76	*BRCA1*	6	2					43		
11	*BRCA1*	11	2					51		
98	*BRCA1*	15	3	Yes				39		39
64	*BRCA1*	40	2					29		
120	*BRCA2*	4	3		Yes	Yes		56		56
10	*BRCA2*	13	2	Yes	Yes		Yes	52	Yes	
40	Non-BRCA	2	3					51		
37	Non-BRCA	3	1	Yes	Yes	Yes		53		54
30	Non-BRCA	4	2	Yes	Yes	Yes		42		41
29	Non-BRCA	6	1	Yes	Yes			30		
3	Non-BRCA	10	3	Yes	Yes			48		48

DCIS, ductal carcinoma-*in situ*; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma-*in situ*; invasive, invasive ductal cancer; Mastect., mastectomy, Oophor., oophorectomy 1 year or more previous to mastectomy, BC, previous breast cancer.

2–40 mm]. The age of these patients was 44 ± 9 years, seven being over the age of 40 years. Five DCIS patients were *BRCA1* mutation carriers, two a *BRCA2* mutation carrier and five from the non-BRCA group. The large majority of DCIS cases had other high-risk lesions too: 6/12 (50%) ALH, 7/12 (58%) ADH, and 4/12 (33%) LCIS. Six patients (50%) with DCIS had previously been diagnosed with breast cancer in the contralateral breast.

4. Discussion

We here show that women with an autosomal dominant family history for breast cancer that is not caused by a *BRCA1* or *BRCA2* mutation have an even higher prevalence of epithelial high-risk lesions than mutation carriers. Furthermore, the presence of high-risk lesions is associated with age; especially at age over 40 years a large number of women with and without a *BRCA* mutation have epithelial high-risk lesions. These epithelial lesions may predict the occurrence of subsequent invasive breast cancer.[5,6,22–24]

After initial diagnosis of breast cancer in a *BRCA1* or *BRCA2* mutation carrier, the risk of developing cancer in the opposite breast is approximately 30% in 10 years,[26] increasing to 40% in 10 years when breast cancer occurred before the age of 40.[27] Data concerning the risk of cancer in the opposite breast of women with an autosomal dominant family history for breast cancer without a *BRCA* mutation are lacking. Most likely the risk of a second primary breast cancer in these women greatly depends on the age of breast cancer diagnosis, as well as on family history. The optimal management of patients with breast cancer and an autosomal dominant family history for breast cancer is still controversial. Simple mastectomy is an effective way to prevent breast cancer.[8,9] However, it is unknown whether contralateral prophylactic mastectomy leads to survival advantage.[13,14] The prognosis of the treated breast cancer may greatly influence survival of patients with contralateral prophylactic mastectomy. Especially young women who had breast cancer with characteristics indicating a good prognosis and a high genetic risk of a second primary breast cancer may benefit from prophylactic contralateral mastectomy.

Most women in the non-BRCA group have sought genetic counseling because of a combination of breast cancer at a relatively young age and an autosomal dominant family history, suggestive for autosomal dominant transmission of the disease. Most likely the non-BRCA group has a heterogeneous genetic origin, consisting of women carrying a yet unknown *BRCA* mutation, or a combination of several less potent susceptibility genes. They considered contralateral preventive mastectomy more acceptable than life long surveillance with

an expected high risk of a second primary breast cancer within 10–12 years.[25] Although prophylactic mastectomy can be an option for these women, it is not the only option. Improved surveillance with advanced technologies such as MRI may be able to detect cancers at an early stage.[11] In theory chemoprevention, for example with tamoxifen, may be an option, in spite of the fact that for hereditary cancer the preventive effect of tamoxifen is still uncertain.[11] Especially for women with a BRCA1 mutation, the effectiveness of chemoprevention is questioned, because breast cancers from most BRCA1 mutation carriers do not have ER/PR receptor activity. In the present study 36% of the BRCA mutation carriers were positive for ER/PR receptor activity, this percentage was higher, 70%, in the non-BRCA group. No statistical difference was found for the presence of high-risk lesions between the group with and without ER/PR receptor activity. However, this conclusion may be influenced by the small sample size.

It is important to realise that for women with an autosomal dominant family history but without a personal history of breast cancer and no detectable *BRCA* mutation, alternative options instead of preventive mastectomy should be considered, because risk status cannot adequately be measured and the ability to modify this risk by mastectomy is not sufficiently known.

The higher prevalence of high-risk lesions in the non-BRCA group cannot be explained by a lower incidence of previous oophorectomy as compared to *BRCA* mutation carriers. Previously it was shown that breast cancer risk, in premenopausal *BRCA1* mutation carriers, reduces after bilateral prophylactic oophorectomy.[28] The decreased production of sex hormones after oophorectomy may be responsible for this reduction in breast cancer risk. An earlier study by our group suggested that oophorectomy relates to a lower occurrence of high-risk histological lesions.[4] It was discussed that this relation might have been caused by selection as all women who underwent oophorectomy were *BRCA* mutation carriers, but at that time groups where too small to be analysed separately. In the present study, we did not find a relation between oophorectomy and prevalence of high-risk lesions in a large group of *BRCA* mutation carriers. Therefore, oophorectomy cannot explain the lower prevalence of high-risk lesions in *BRCA* mutation carries as compared to the non-BRCA group. This indicates that previous oophorectomy should not be taken to indicate low-risk of epithelial lesions in women at high risk of hereditary cancer.

Controversies exist regarding the role of ductal carcinoma-*in situ* (DCIS) in both *BRCA1* and *BRCA2* mutation carriers.[29,30] From our data we can conclude that *BRCA1* and *BRCA2* mutation carriers are equally prone to develop high-risk lesions in their breasts, with a considerable proportion having occult DCIS. The data from a recent study among DCIS patients show that the prevalence of *BRCA* mutations among DCIS patients is similar to that found in patients with invasive breast cancer,[31] and suggest that DCIS belongs to the spectrum of inherited breast cancer. As a consequence, in family-histories, DCIS can be considered as equal to the breast-cancer affected status, when considering familial at-risk status for *BRCA*.[32–34]

The prevalence of high-risk lesions in *BRCA* mutation carriers from our study is comparable to that reported by a study from the Memorial Sloan-Kettering Cancer Center in 24 *BRCA* mutation carriers.[7] This study also showed that the prevalence of high-risk lesions in *BRCA* mutation carriers is much higher than in women without a genetic predisposition.[7] In contrast to our data and those from Memorial Sloan-Kettering, the Mayo Clinic reported a low prevalence (2–2.5%) of high-risk lesions in prophylactically removed breasts from *BRCA* mutation carriers with no major difference in the prevalence of precursor lesions between 28 *BRCA* mutation carriers and their matched controls.[35] Apart from differences in ethnic background, the number of sampling slices between the three studies may explain some of this difference. A mean of seven slices was examined in the Mayo Clinic study compared to 14 in the Memorial Sloan-Kettering study and 18 in the present study. This may have added to the lower prevalence of high-risk lesions found in the Mayo Clinic study.

A limitation of our study is the lack of a control group of women without familial breast cancer risk. Irrespective of this, the comparisons between *BRCA1* and *BRCA2* mutation carriers are not affected by this, as are the comparisons between woman at high genetic risk due to *BRCA* mutations and the high genetic risk group without *BRCA* mutation. The reported prevalence of undiagnosed DCIS in a review of autopsy studies, using various techniques, of women with an age range between 15 and 80 years is approximately 9% (range 0–15%).[36] For LCIS this prevalence is less extensively studied and reported to range between approximately 1% and 3%.[6] On average, the prevalence of these lesions reported in our study is higher than that reported in the general population.

The data of this study indicate that women with an autosomal dominant family history of breast cancer should be considered prone to develop high-risk epithelial lesions in their breasts, especially at age over 40 years. Prophylactic mastectomy can prevent progression towards invasive carcinoma. It is unknown whether this may lead to survival advantage in the group without a *BRCA* mutation.

Conflict of interest statement

None declared.

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