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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