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Humoral immune responses to MUC1 in women with a *BRCA1* or *BRCA2* mutation

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ABSTRACT

Introduction: Breast cancer patients with early disease and a natural humoral response to MUC1 have a favourable prognosis, suggesting a possible role of MUC1 antibodies (ab) in controlling haematogenous tumour dissemination and outgrowth. The aim of the study was to evaluate humoral immune responses to MUC1 in women at hereditary high risk of breast cancer to investigate whether this immune response could play a role in the prevention of disease.

Materials and methods: CA15.3 (U/mL), and IgG and IgM ab to MUC1 (arbitrary units per mL, Arb-U/mL) were measured in serum samples obtained from 422 women at hereditary high risk of breast/ovarian cancer, of whom 127 *BRCA1/2* carriers, attending the Familial Cancer Clinic of the VU University Medical Centre, and from 370 age-matched healthy controls. Serum samples obtained from women who developed breast cancer ($N = 12$) or breast cancer recurrence ($N = 17$), and from women who underwent prophylactic mastectomy ($N = 12$) and had no breast lesions were also tested.

Results: CA15.3 ranked significantly higher in mutation carriers than in controls ($P = 0.03$). MUC1 IgG ab levels ranked significantly lower in *BRCA1/2* mutation carriers than in controls ($P = 0.003$). MUC1 IgG levels were not significantly different ($P = 0.53$) between women who developed primary breast cancer (median 0.72 Arb-U/ml, range 0.52–2.44 Arb-U/ml) and women who underwent prophylactic mastectomy and had no breast lesions (median 1.04 Arb-U/ml, range 0.43–2.88 Arb-U/ml).

Conclusion: Serum levels of natural IgG ab to MUC1 are lower in *BRCA1/2* mutation carriers than in healthy controls. Furthermore, in contrast to previous results in women with sporadic breast cancer, no elevated MUC1 IgG ab were seen in women at hereditary high risk who developed breast cancer. Prophylactic immunotherapy with MUC1 substrates may be a strategy to reduce the risk of breast cancer in *BRCA1/2* mutation carriers, strengthening tumour immune surveillance.

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1. Introduction

Interest in the detection of a germline mutation in the *BRCA1*[1] or *BRCA2*[2] gene is based on its potential to identify women with a substantial high risk of breast and ovarian cancer that would benefit from preventive measures. Estimates of breast and ovarian cancer risk in women carrying a *BRCA1/2* mutation by 70 years of age range from 56% to 80% for breast cancer, and from 16% to 40% for ovarian cancer.[3–5]

These women at high risk of breast and ovarian cancer are included in screening programmes directed towards early detection of disease[6–8] or they undergo prophylactic surgery. Due to the limitations of screening, the most effective preventive measure for women at high risk is prophylactic mastectomy (pM) and/or prophylactic bilateral salpingo-oophorectomy (pBSO). The latter has been shown to reduce not only the risk of ovarian cancer[9] but also that of breast cancer.[10,11]

These radical methods still suffer from some limitations as pBSO does not protect from primary peritoneal carcinomatosis,[12] and a 5% residual risk of breast cancer is still present after pM. This limited prevention efficacy should be looked at in the light of the mutilating effect of pM, and the hormonal deprivation and subsequent morbidity caused by pBSO.[13]

Other forms of preventive treatment are therefore warranted, such as prophylactic vaccination to create an adequate immune surveillance against adenocarcinomas.[14] Cancer vaccines are being developed for the treatment of cancer but also with an eye on prevention,[15] and some common tumours may be prevented by specific vaccines administered to patients with a preneoplastic lesion or with a genetic risk of developing cancer.[16] A strong immune response induced by active immunotherapy may provide a constant surveillance mechanism that would protect women with a genetically determined high cancer risk from developing breast and/or ovarian cancer.

MUC1, a cell surface antigen expressed in glandular epithelia, is overexpressed and aberrantly glycosylated in adenocarcinomas. The peptides and glycans of MUC1 are being studied as substrates for cancer vaccines.[17] A natural humoral immune response to MUC1 has been associated with a favourable disease outcome in patients with breast, lung and pancreatic cancer.[18–20] We observed that women with breast cancer with early disease and a natural humoral response to MUC1 have a relatively low chance of developing metastases and a favourable prognosis, suggesting a possible role of MUC1 antibodies in controlling haematogenous tumour dissemination and outgrowth.[18]

In the present study, we analysed serum levels of MUC1 (CA15.3) and natural antibodies to MUC1 in women at hereditary high risk of breast /ovarian cancer compared to controls. Secondly, we investigated within the group of women at hereditary high risk whether the levels of natural antibodies to MUC1 differed between women who developed breast cancer and healthy women who underwent pM.

2. Material and methods

2.1. Study population

The study population consisted of 422 women at hereditary high risk for breast and/or ovarian cancer undergoing gynaecological and surgical screening as part of the cancer preventive strategy at the Familial Cancer Clinic of the VU University Medical Centre, between 1993 and 2002. Table 1 lists the clinical characteristics of the women at first visit. Women who had had no menstrual period for 12 months or more were defined as post-menopausal; otherwise, they were classified as premenopausal.

Pedigree analysis was performed for each individual. A clinical diagnosis of hereditary breast/ovarian cancer syndrome (HBOC) was assigned to those individuals belonging to a family with three or more cases of breast and/or ovarian cancer present in two generations, and a clinical diagnosis of familial breast/ovarian cancer syndrome (FBOC) to those individuals belonging to a family with two cases of breast and/or ovarian cancer.

DNA assessment was performed after counselling and informed consent. One hundred and twenty five women (30%) declined DNA assessment, leaving 297 women (70%) in whom *BRCA1/2* mutations were detected by a combination of protein truncation test (PTT), denaturing gradient gel electrophoresis (DGGE) and direct DNA sequencing (DS).[21] The large exons 11 of *BRCA1* and 10 and 11 of *BRCA2* were screened by PTT; the remaining exons of both genes were screened by DGGE. If aberrations were detected, DNA sequencing was used to elucidate the exact mutation. Additionally, we performed multiplex ligation-dependent probe amplification (MLPA) to screen *BRCA1* or exon deletions or duplication.[22] *BRCA1/2* mutations were detected in 127 women (30%), results were inconclusive in 137 women (32%), and 33 women were proven non-mutation carriers (8%). The latter were excluded from further evaluation. The control population consisted of 370 healthy women with a median age of 43 years (range 20–70 years). Controls were age-matched to the hereditary high risk women out of a cohort of 938 healthy women abstracted from a cohort of women described earlier.[23,24] As no information on the menstrual history of these women was available, we defined women from 52 years and older as post-menopausal ($N = 68$), and otherwise as premenopausal ($N = 302$).

The research protocol was approved by the Scientific Committee of the VU University Medical Centre Research Institute for Cancer and Immunology.

2.2. Serum samples

Serum samples were collected serially at every visit to the Familial Cancer Clinic, aliquoted and stored at −70 °C until analysed. We tested serum samples obtained from 370 controls and from 389 women at hereditary high risk at first visit to the Familial Cancer Clinic. Furthermore, we analysed serum samples obtained from women who developed a primary breast cancer ($N = 12$) or a breast cancer recurrence ($N = 17$) during screening, and from healthy women who underwent prophylactic mastectomy and had no breast lesions ($N = 12$). All serum samples were obtained within 12 months of surgery. The median time between obtaining the serum samples and date of breast cancer diagnosis, date of recurrence and date of prophylactic mastectomy was 8 months (range 0–9 months), 4 months (range 0–10 months) and 5 months (range 0–12 months), respectively.

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