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Survival of breast cancer in BRCA1 and BRCA2 carriers versus non-carriers: mutation analysis and tumour characteristics

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Approximately two to three percent of the women who develop breast cancer carry a germ-line mutation in one of the breast cancer susceptibility genes BRCA1 or BRCA2 (200 patients per year in the Netherlands). To date, several small studies have suggested a worse outcome of survival in BRCA1 and BRCA2 carriers. However, the evidence is inconsistent and most studies were subject to different types of bias. Furthermore, current risk estimations for the development of contralateral breast, or ovarian cancer (as a second primary) in BRCA1/2 carriers are based on data from large selected families with many cases of breast cancer and are therefore strongly biased. In a retrospective cohort study, we will evaluate clinical outcome in a large and unselected, non-family based, sample of breast cancer patients diagnosed under age 50 (e.g. overall and disease-free survival, as well as the occurrence of ovarian and contralateral breast cancer). In addition we will investigate whether tumour stage and histopathological characteristics at diagnosis differ between BRCA1/2 carriers and non-BRCA1/2 carriers. The cohort to be evaluated will include approximately 6000 patients, treated in eight hospitals from 1970–1995. Tissue blocks from these patients are being obtained and after coding, forty-eight BRCA1/2 founder and recurrent mutations, representing approximately 72% of the Dutch BRCA1/2 mutations, are being determined. In addition, histological characteristics of the tumour are being assessed. So far, BRCA1 and BRCA2 mutation analysis for about 1000 patients has been performed, which reveals a prevalence of 5% BRCA1/2 mutations. An interim analysis shows that BRCA1 tumours seem to have less favorable prognostic characteristics while these patients have a higher risk for contralateral breast cancer.

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The presence of hereditary BRCA1 gene mutations in women with familial breast cancer or familial ovarian cancer and the frequency of the occurrence of these tumours in their relatives

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In 48 women with familial breast cancer as well as in 22 women with familial ovarian cancer, the presence of patogenic mutations in *BRCA1* gene were found in 35.4% or 54.6% of patients respectively. From the patients possessing mutations we created two groups: the CaM – probands with breast cancer and CaOv – probands with ovarian cancer. The probands with breast cancer were younger by a mean of 5 years, than the probands with ovarian cancer (p=0.048).

Methods: The PCR-SSCP procedure was used for seeking mutations in the *BRCA1* gene. Fragments suspected of mutation presence were subjected to nucleotide sequencing.

Results: In the CaM group, which consisted of 17 women with breast cancer the following mutations in the *BRCA1* gene were detected: 5382insC, T300G, 3819del5 and IVS20+60ins12. The probands of the CaM group, and their relatives, developed a total of 49 breast and ovarian cancers. Among all these tumours the breast cancers of probands made up 34.7%, the breast cancers of probands' relatives made up 57.1% and the ovarian cancers of probands and their relatives made up only 8.2%.

The CaOv group consisted of 12 probands with ovarian cancers in whom we detected only 2 kinds of mutations: 5382insC and 185delAG. The probands of the CaOv group, and their relatives, developed a total of 38 ovarian and breast cancers. Among all these tumours the ovarian cancers of the probands made up 31.6%, the ovarian cancers of their relatives made up 34.2% and the breast cancers of the relatives 34.2% of tumours.

In probands with breast or ovarian cancer the predominant mutation was the 5382insC – in the *BRCA1* gene detected in 76.5%, and in 91.7%, respectively. Despite the predominant presence of the same mutation in probands from both groups the ratio of the number of breast cancers to the number of ovarian cancers in their relatives differed significantly (p=0.0003).

Conclusion: This data shows, that the presence of the 5382insC mutation – in the *BRCA1* gene is not always associated with the development of ovarian cancer. It is very likely that the development of ovarian cancer requires some additional factor, which is common among the familial ovarian cancer patients, and is almost inexistent among the familial breast cancer group of patients. On the other hand the development of ovarian cancer at a later age than breast cancer in probands suggests that there exist some factors, which slow down the development of ovarian cancer, or which accelerate the development of breast cancer.

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Non-random transmission of mutant alleles to female offspring of BRCA1 carriers in Poland

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Constitutional mutations in BRCA1 gene predispose to an autosomal dominant syndrome of breast and ovarian cancer. The penetrance of BRCA1 gene mutations is high – approximately 50% of women with mutations will be affected by cancer by the age of 50 and over 80% of women with mutations will be affected by age of 75. At birth, it is expected that 50% of the children of a carrier parent will inherit a mutant allele. Under the assumption that a mutant allele is transmitted to 50% of offspring, it is therefore possible to estimate age-specific penetrance values of the BRCA1 gene by counting the relative of carriers and non-carrier in a sample of healthy offspring, of varying ages, of carrier parents.

Three founder mutations in BRCA1 are common in Poland (5382insC, C61G, 4153delA). In an attempt to estimate the age-specific penetrance of these three mutations, we systematically reviewed the genotypes of mothers and daughters in a selected group of 387 families from International Hereditary Cancer Center in Szczecin, Poland. To avoid the possibility of selection bias we included only unaffected daughters who were offered genetic testing after the mutation was identified in the mother. The 91 carrier mothers had 141 daughters, of whom 126 were tested. Four of the daughters had been affected by breast cancer and were excluded. In total, 75 of 122 unaffected daughters (61.5%) were carriers of the mutation versus 47 noncarriers (Table 1). The reason for the surprisingly high observed frequency of carriers is not known. If confirmed it would have a basic significance for: 1) inheritance pattern and penetrance in the most commonly counseled studies of genetic disorder – BRCA1 syndrome; 2) mechanisms of spreading of founder mutations; 3) possibility of regulation of frequency of mutated alleles among offspring by environmental factors.

Table 1. Mutation frequency by age among unaffected daughters of carriers mothers

Age group	Number of carriers	Number of non-carriers	Proportion of carriers	p-value
0–19	12	14	46%	0.69
20–29	38	18	68%	0.008
30–39	16	10	61.5%	0.24
40–50	9	5	64%	0.29
TOTAL	**75**	**47**	**61.5%**	**0.011**