Familial Cancers/Tumor Genetics

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Familial risk of cancer: Data for clinical counseling and cancer genetics

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Background: Familial risks for cancer are important for clinical counseling and understanding cancer etiology. Medically verified data on familial risks have not been available for all types of cancer.

Methods: The nationwide Swedish Family-Cancer Database includes all Swedes born in 1932 and later (0 to 68 year old offspring) with their parents, totaling over 10.2 million individuals. Cancer cases were retrieved from the Swedish Cancer Registry up to year 2000. Standardized incidence rations (SIR) and 95% confidence limits (CI) were calculated for age-specific familial risk in offspring by an exact proband status.

Results: The familial risks for offspring cancer were increased at 24/25 sites from the same cancer in only the parent, at 20/21 sites from a sibling proband and at 10/11 sites from a parent & sibling proband. The highest SIRs by parent were for Hodgkin's disease (5.07) and testicular (4.45), nonmedullary thyroid (3.63), esophageal (3.47) and ovarian (3.30) cancer and for multiple myeloma (3.43). By sibling history, even prostate, renal, squamous cell skin, endocrine and pancreatic cancer and leukemia showed an SIR in excess of 3.00. The highest familial risk of 149.81 was for prostate cancer in brothers diagnosed before age 50 years.

Conclusions: We identified reliable familial risks for 24 common neoplasms, most of which lack guidelines for clinical counseling or action level. If, for example, a familial SIR of 2.2 would be use as an action level, counseling would be needed for most cancers at some diagnostic age groups. The present data provide the basis for clinical counseling.

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BRCA-1 status, molecular markers, and clinical variables in breast cancer patients with high probability of having an inherited, cancer-predisposing genetic mutation

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Purpose: to evaluate the clinical features and outcomes of Breast Cancer (BC) patients with genetic susceptibility to this disease and to address the question of the contribution of BRCA-1 germline mutation to the phenotype of these tumors.

Patients and methods: we reviewed the clinical and pathological records of 144 women with autosomal dominant inheritance of breast (+/- ovarian) cancer risk, consecutively seen at the Genetic Oncology Service of the University Parma Hospital between June 1999 and September 2003. All women underwent full genetic counseling. Of these, 101 selected patients with high probability of having a germ-line, cancer-predisposing mutation (high risk group), were tested for BRCA-1 mutation analysis. Exon 11 was screened for BRCA1 mutations using Protein Truncation Test (PTT); mutations detected by PTT were confirmed by Direct Sequencing (DS). All the other exons were analyzed by DS.

Results: The two different risk groups had similar clinical outcomes. Of the 57 patients with completed mutation analysis, 44 (77%) patients had wild-type BRCA-1, 8 (14%) had variants of unclear significance, 5 (8%) had deleterious mutations in BRCA-1. With regard to entry criteria for BRCA-1 genetic testing, mutations were detected in 5% (1/20), 2,5% (1/41), 16% (2/12) and 16% (1/6) of women with family history, early-onset BC (<40 years), Breast-Ovarian Cancer (BOC) and early-onset plus Bilateral Breast Cancer, respectively. BRCA-1 Associated Breast Cancers (BABC) were more likely to have histological grade 3 and high proliferation rate than cases in women without mutations (40% v 27%; 60% v 45%). These differences were not statistically significant. BABC were significantly more likely to be estrogen receptor-negative (67% v 16%, P = 0.04). Though not significant, all valuable tumors with BRCA-1 mutations were HER-2/neu negative. In the entire cohort, there were no significant differences between BABC and non-BABC in 5-year relapse-free survival (60% v 78%, P = not significant [NS]), 5-year event-free survival (60% v 66%, P = NS), or 5-year overall survival.

Conclusion: BABC seem to present with adverse molecular and histopathologic features when compared with cases not associated with BRCA-1 mutations. However, the prognosis of BABC appears to be similar to that of non associated cancer. Further studies of incident cases are necessary to define the independent prognostic significance of germline BRCA-1 mutations.

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Prospective incidence rates of breast cancer and efficacy of a structured surveillance program in proven or suspected carriers of BRCA1/2 gene mutations

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Purpose: Current policies for clinical management in women at high risk for breast cancer include a multimodal surveillance program starting at an early age. The purpose of this study was to evaluate the acceptance and efficacy of surveillance for the detection of hereditary breast cancer.

Patients and Methods: A total of 413 women participated in the surveillance program for at least one year with a median follow up of 2 years: 49 women with a BRCA1 or BRCA2 mutation, 203 women at high and 161 women at moderate risk. The surveillance program include biannual clinical breast examinations (CBE) and ultrasound (US) and annual mammography (MG) and magnetic resonance imaging (MRI). Detection rates and tumor stages of breast carcinomas diagnosed within

the program were compared with breast carcinomas detected in 313 female relatives outside the program and with a standard population documented in the local tumor registry.

Results: The acceptance rate for the surveillance program was 85%. Overall, 41 primary or secondary breast carcinomas were detected. The average detection rates were 89.6/1000 for mutation carriers, 47/1000 for high risk and 24.7/1000 for moderate risk women compared to 1/1000 in the local tumor registry. In a retrospective analysis these tumors were compared with tumors detected in relatives of these women outside the program and tumors documented in the local registry. Overall, 83% of the screen detected tumors were node negative and 85.4% were pre-invasive or smaller than 2 cm. In comparison, of the tumors detected in female relatives outside the program only 48% (p=0,0003) were node negative and 44% (p<0,0001) were pre-invasive or smaller than 2 cm. Of tumors gathered in the local tumor registry 56% (p=0,003) were node negative and 42% (p<0,0001) were pre-invasive or smaller than 2 cm.

Discussion: Prospective cancer detection rates in proven or suspected carriers of mutations in the BRCA1 or BRCA2 gene were significantly greater than expected in the average-risk population. A structured screening program including CBE, US, MG and MRI is effective in the early detection of breast carcinomas in this risk group and should be offered to these women as a matter of routine.

P4

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 - with ovarian cancer. The probands with breast cancer were younger by a mean of 5 years, then 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%. 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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The analysis of genetic polymorphisms in CYP1B1 and COMT genes in breast and endometrial cancer patients

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Breast (BC) and endometrial (EC) cancer are known to be severe malignant diseases, characterized by unfavorable consequences for women's health. We focused our comparative study on the impact of genetic polymorphisms in CYP1B1 and COMT genes into the individual predisposition for the development BC or EC. CYP1B1 and COMT are two enzymes responsible for the synthesis and inactivation of catecholestrogens. Polymorphic forms of these enzymes were shown to differ in their enzymatic activities. Hence, inherited alterations in the activity of COMT and CYP1B1 hold the potential to define differences in cancer risk associated with estrogen-induced carcinogenesis. We analysed 3 polymorphisms in CYP1B1 gene: Arg48Gly, Ala119Ser, Val432Leu and Val158Met polymorphism in COMT gene. By using standard RFLP (restriction fragments length polymorphism) method we have analysed breast cancer patients (N=210), endometrial cancer patients (N=138) and control individuals (N=152). Neither for breast cancer nor for endometrial cancer we have found statistically significant association with COMT polymorphism. At the same time we have demonstrated that Arg48 CYP1B1 polymorphic form, characterised by Shimada et al., as a form with the highest activity for the 4-hydroxylation of the estrogens, is strongly