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