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LESSONS LEARNED FROM THE ANALYSIS OF P53 IN FAMILIAL AND CHILDHOOD CANCER

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The p53 gene is part of a physiological pathway frequently impaired in human cancer. Germline transmission of an altered p53 allele prediposes to cancer with predominantly early onset of the disease. Mutation screening in the blood and tumor samples of a family with three siblings one suffering from brain tumor and two from rhabdomyosarcoma revealed p53 mosaicism in the founder of the cancer prone pedigree. The mutation probably occured at an early embryonic stage of the maternal germ cell developement. The specific alteration affecting p53 codon 273 has previously been shown to retain some phenotypic characteristics of wild type p53. Moreover, studies on Ewing tumors revealed that this type of "weak" p53 mutations predominates also in a distinct group of sporadic tumors of childhood and adolescence in which alterations of p53 are generally rare.

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PROGRESS IN OUR UNDERSTANDING OF THE GENETICS OF BREAST CANCER.

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For over one hundred years, families with unequivocal evidence of hereditary breast cancer have been reported. Many of these families are characterized by apparently dominant transmission of risk of breast cancer and an early age of onset which is often premenopausal in female carriers of this gene. In some of these families, gene carriers are also at increased risk of ovarian cancer. Previous genetic linkage studies have established that in some such families disease occurrence is linked to markers on chromosome 17q. A recent analysis of a collaborative linkage study involving 214 breast cancer families, including 57 breast-ovarian cancer families was conducted to examine the types of families that were due to this gene and to estimate the precise risk of breast cancer (and ovarian cancer) in gene carriers [1]. The results of this analysis suggested that a gene (or genes) on chromosome 17q accounts for the majority of families in which both early onset breast cancer and ovarian cancer occur, but that other genes predisposing to breast cancer exist. By examining the fit of the linkage data to different penetrance functions, the cumulative risk associated with the 17q gene was estimated to be 59% by age 50 and 82% by age 70. The corresponding estimates for the breast-ovary families were 67% by age 50 and 76% by age 70, and for the families without ovarian cancer 49% by age 50 and 90% by age 70. The search for this gene is in progress; current estimates suggest that the gene lies in a region of perhaps 4,000,000 DNA basepairs. With this information, it is possible to offer genetic counselling within these high risk families.

A careful analysis of families suggests that other genes are also involved in susceptibility. The risk of breast cancer may be much lower with this other gene or genes, and it is also possible that other genes are associated more with postmenopausal breast cancer. The importance of the 17q gene as compared to the other genes is still in doubt.

[1]Easton et al. (1993) American Journal of Human Genetics 52:678-701.

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CANCER CONTROL BY FAMILY HISTORY

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Cancer of all sites show a tendency to aggregate in families. Evaluation of family histories of cancer patients in Basel revealed to following results:
1. There is an overrepresentation of breast, stomach, endometrium, nervous system, esophagus and soft tissue malignancies in 3725 first degree relatives of 600 female breast cancer patients.
2. There is an overrepresentation of colorectum, stomach, endometrium and liver malignancies in 1184 first degree relatives of 184 colorectal cancer patients.
Several families belong to classical hereditary syndromes predisposing to cancer. Blood and tissue samples are stored and used for DNA investigations.
Management options for persons at elevated cancer risks are: 1. Doing nothing 2. Screening 3. Chemoprevention 4. Lifestyle changes 5. Prophylactic surgery.

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MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

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Multiple endocrine neoplasia (MEN) syndromes constitute a family of disorders characterized by neoplastic hyperfunction of two or more endocrine tissues. In MEN type 1 (MEN1) hyperparathyroidism, pancreatic-duodenal and pituitary tumors are the most frequent endocrinopathies. MEN type 2 (MEN2) is characterized by medullary thyroid carcinoma and phaechromocytoma. The diseases are transmitted as autosomal dominant traits with high penetrance. The predisposing genetic defects for MEN1 and MEN2 syndromes have been assigned respectively to chromosomal regions 11q13 and 10q11.2. DNA markers tightly linked to and flanking the disease genes are currently used to follow the transmission of the abnormal allele of the disease locus through the family and determine an individual's genotype before the onset of symptoms. These topics will be discussed in detail during the presentation.

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FAMILIAL PREDISPOSITION TO COLORECTAL CANCER

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Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are the most frequent and best studied of the hereditary colorectal cancer (HCC) syndromes. The FAP gene, called APC, is on the long arm of chromosome 5. The APC gene has been cloned and characterized. A large number of lesions in the APC gene responsible for FAP have been identified. Also a number of APC-linked markers are available for preclinical prediction of FAP by linkage. The direct analysis of APC mutations in the relatives at risk has the power of readily classifying the FAP-family members into carriers and noncarriers with 100% certainty. A gene for HNPCC has been localized on the short arm of chromosome 2, opening the possibility of developing tests for presymptomatic diagnosis of colorectal cancer in the majority of families with HNPCC as well. Heterogeneity among the HCC families will continue to be of considerable concern to the genetic counsellers till the molecular complexity of these conditions in individual families is resolved.

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FAMILIAL CLUSTERING OF LUNG CANCER AND OTHER SMOKING RELATED CANCERS

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Several studies have demonstrated familial aggregation of lung cancer in families of lung cancer patients.In this study information about 1041 first degree relatives of 189 lung cancer patients and about 1041 first degree relatives of 212 controls,without cancer were gathered.Lung cancer patients were comparable with controls according gender,smoking history occupation,residental district.Mantel-Haenszel method was used to assess crude relativ risk relative risk adjusted for age and smoking. Relatives of lung cancer patients had 1,6 fold higher risk for all cancers.This increased risk was due to higher risk for smoking related cancers(2,6 for men and 2,3 for women) and for lung cancer (10,1 for men and 11,8 for women). This higher risk was particulary evident for smokers but also can be obseved in nonsmokers.