Symposia

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Genetic predisposition to breast cancer - what is known?

Abstract not received.

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Genetic predisposition to breast cancer: what can be done ?

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The management of women at increased risk for breast cancer presents a clinical dilemma both to health care professionals and these women themselves. New developments in the ability to predict breast cancer risk are of major importance due to the fact that these women might benefit from risk reduction strategies. Available tools for in-depth assessment to defining subjects at high risk encompasses accurate exploration of complete family history, evaluation of factors associated with increased risk i.e. hormonal and reproductive factors, breast density, benign breast diseases, and others. In addition, the application of existing breast cancer prediction models (GAIL, CLAUS, BRACPRO), and when appropriate genetic testing (investigation of BRCA 1 / 2 mutation status) are valuable measures. Nevertheless, despite refinements all tools still have their limitations and none of the risk predicting models provides an entirely comprehensive estimate of risk using genetic and non-genetic risk factors together. As a future perspective long-term risk assessment should / might be tissue and / or serum based strategies. The gathered information of above mentioned processes should result in appropriate counselling and management. Thorough discussion of pros and cons of available risk reduction strategies as well as clarification of potential complication (uncertainties of all procedures on the long-term) and psychosocial impact are required to guide women in choosing their preventative / risk reducing options. What presently can be advised / offered to these women is: a) life style changes (weight control, through diet and physical exercise, cessation of cigarette smoking and reduction of alcohol intake; b) accurate surveillance with mammography, ultrasound, breast magnetic resonance imaging and new tools that technology is developing (quantification of cell proliferation via measurement of electropotentials at the skin surface (depolarisation index) or measurement of neo-angiogenesis with dynamic optical imaging, c) participation in pharmacoprevention clinical trials and d) preventative surgery like prophylactic subcutaneous /simple mastectomy (PM) (bilateral or contra-lateral in patients with previous breast cancer) and bilateral laparoscopic oophorectomy. Recommendation should adapted according to the estimated individual life time risk (slightly increased risk 12-15%, moderately 15-29%, highly 30-80%) taking into consideration that the level of available evidence for most of the risk reducing measures until now is not very strong.

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Genetic predisposition to colon cancer: what is known?

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The hereditary colon cancer phenotypes can be divided into two, depending on the presence or absence of intestinal polyposis. While hereditary nonpolyposis colorectal cancer (HNPCC) has no pathognomonic clinical features, familial adenomatous polyposis (FAP) and the hamartomatous polyposis syndromes can often be diagnosed through the presence of numerous benign polyps in the bowel. The main genetic HNPCC predisposition loci, encoding DNA mismatch repair genes, were identified, and microsatellite instability (MSI) associated with HNPCC tumors in 1993. These results did not only reveal the gene for HNPCC and provide tools for diagnosis, but also demonstrated in a common cancer type the importance of genomic instability for malignant transformation. Colon tumors associated with HNPCC have no pathognomonic features that could robustly be used for diagnostics. MSI in tumor DNA is a sensitive but unspecific marker for HNPCC, and diagnosis can be established only through germline mutation detection; perhaps 2% of colon cancer patients have germline mutations in the mismatch repair genes. The hamartomatous polyposis syndromes include Cowden syndrome, Peutz-Jeghers syndrome (PJS), as well as juvenile polyposis (JP). Cowden syndrome patients carrying PTEN mutations do not appear to be predisposed to intestinal cancer. PJS, caused by germline mutations in serine/threonine kinase LKB1, is characterized by mucocutaneous melanin pigmentation, as well as hamartomatous polyposis with pathognomonic histological features. Increased risk of intestinal and extraintestinal cancer is evident. In JP, caused by germline mutations in SMAD4 and BMPRII genes, the hamartomatous intestinal lesions are histologically different from those in PJS, and the cancer predisposition is more focused and most prominent in the colon and the pancreas. The gene for FAP is APC. The presence of 100 or more intestinal adenomas has been considered to be diagnostic. The risk of colorectal cancer is typically close to 100% by the age of 40, and extraintestinal cancers such as thyroid carcinoma also occur. Desmoid tumors are common. The most recently discovered colon cancer syndrome is recessively inherited adenomatous polyposis caused by biallelic mutations in base excision repair gene MYH. The number of polyps varies from few (5) to more than 100, thus making distinction between attenuated FAP and MYH polyposis difficult. Multiple low penetrance colon cancer predisposition genes remain to be discovered.

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Genetic predisposition to colon cancer: what can be done?

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HNPCC is an autosomal dominant inherited syndrome characterized by the combined occurrence of colorectal cancer (CRC), endometrial cancer (EC) and various other cancers at an unusual young age. The syndrome is caused by mutations in mismatch repair (MMR) genes. Approximately 4% of all CRC is due to this syndrome.

Since about five years, genetic tests for the detection of MMR gene mutations are available for clinical practice. This is extremely important because genetic testing allows the discrimination between carriers of a MMR mutation (relatives that need intensive surveillance of the colon) and relatives without a mutation (individuals that can be reassured and refrain from surveillance). However testing is time consuming and expensive because three or more MMR genes should be investigated for the presence of a mutation. Fortunately, new screening tools (microsatellite instability (MSI) and immunohistochemical analysis (IHC) of the tumour) are available that can be used to select families eligible for mutation analysis.

Previous Finnish studies have shown that colonoscopic surveillance of HNPCC families led to a reduction of CRC by 60%. A longterm prospective Dutch cohort study revealed that endoscopic surveillance with intervals $\leq$ 2years led to the detection of early stages (TxN0M0) of CRC. When a new primary CRC is diagnosed in a MMR gene mutation carriers, there are two surgical options: segmental resection or total colectomy with ileorectal anastomose. We performed a decision analysis study to compare the outcome of both surgical procedures. The results showed that total colectomy compared to segmental resection led to a substantial increase in life expectancy. On the basis of the results we recommend to perform a total colectomy in patients <60 years. In older patients both options might be discussed. Another problem is whether chemotherapy is effective in CRC and other cancers associated with HNPCC. Reports in the literature on the effect of chemotherapy are contradictory. We conducted therefore a retrospective study to assess the value of adjuvant chemotherapy. The results might indicate that 5FU-based treatment is not effective as adjuvant treatment in CRC associated with HNPCC. Prospective studies are needed to confirm these findings.

Families suspected of HNPCC in which MSI- and/or IHC-analysis excluded the presence of a MMR defect, also need periodic examination of the colon. In order to evaluate which intervals between examinations should be recommended in such families, we recently started a nationwide screening program in which an interval of 3 years is compared with an interval of 6 years (The FACTS study: the familial colorectal cancer screening study).