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Hereditary and Cancer Biology Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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Key words: cancer; life; research; literature; cell; Hereditary; Cancer Biology

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Aarnio, M., et al. (1995). "Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome." Int J Cancer **64**(6): 430-433.

Identification of hereditary non-polyposis colorectal cancer (HNPCC) indicates theoretical life-time risks of 50% for the descendants of an affected family member and of 100% for the true gene carriers. However, besides colorectal cancer (CRC), many other cancer types and sites are also involved, which gives reason to evaluate the magnitude of risk for various other cancer types. A detailed pedigree analysis of 40 families with HNPCC identified 414 patients affected with cancer. A Kaplan-Meier life-table analysis for the cumulative risk of various cancers was performed on the basis of the 293 putative gene carriers who had adequate clinical and histological documentation of their tumors. Cumulative risks were highest for colorectal (78%) and endometrial cancers (43%, women only), followed by gastric, biliary tract, urinary tract and ovarian cancers (19-9%). For the other probably HNPCC-related cancer types, such as small bowel carcinoma and brain tumors, the life-time risk was only 1%. The risk of any metachronous cancer reached 90% after treatment of CRC and 75% after endometrial cancer; the second tumor was most often a new CRC or endometrial cancer. CRC remains the most important cancer type in the HNPCC syndrome but does not develop in all gene carriers. This makes the decision of possible prophylactic colectomy for test-detected gene carriers difficult. Of the many other cancer types involved, at least endometrial cancer is common enough to necessitate a specific surveillance program.

Adem, C., et al. (2003). "Microsatellite instability in hereditary and sporadic breast cancers." Int J Cancer **107**(4): 580-582.

Sporadic cancers and familial breast cancers are characterized by an increase in genetic instability. Little is known about whether mismatch repair defects accompany this genetic instability. We investigated invasive and/or in situ breast cancers from 30 women with deleterious BRCA1/2 mutations and unclassified variant BRCA1/2 alterations. Forty cases of sporadic breast cancers were also investigated, including 7 medullary carcinomas. Malignant and benign lesions were examined from all cases to better understand tumor progression. Automated immunohistochemistry, with antibodies directed against hMLH1 and hMSH2, was used to screen cases for possible mismatch repair defects. When loss of expression was noted, DNA ploidy was performed by cytomorphometry. DNA, after laser microdissection, was extracted from a majority of familial cases and their corresponding controls, and microsatellite instability analysis was

performed. None of the familial or sporadic cases had loss of hMSH2 expression. All but one lesion, a DCIS arising in a deleterious BRCA2 mutation carrier, had loss of hMLH1 expression and a tetraploid profile by image cytomorphometry. There was no MSI in any explored lesions (n = 34), as determined by molecular analysis, including the DCIS with loss of hMLH1 expression. We conclude that DNA mismatch repair defects involving hMLH1 and hMSH2 underexpression are extremely rare events in sporadic and familial breast cancer. Mismatch repair gene mutations may be secondary random events in breast cancer progression.

Akiyama, Y., et al. (2001). "Infrequent frameshift mutations in the simple repeat sequences of hMLH3 in hereditary nonpolyposis colorectal cancers." Jpn J Clin Oncol **31**(2): 61-64.

BACKGROUND: A recently identified mismatch repair gene, hMLH3, contains two simple repeat sequence regions, (A)9 and (A)8, in its coding region. To clarify the role of hMLH3 in hereditary nonpolyposis colorectal cancer (HNPCC), we searched for hMLH3 somatic and germline mutations, particularly in the repeat regions, in 41 HNPCC patient cells. METHODS: We analyzed the hMLH3 (A)9 and (A)8 repeats in 27 colorectal cancers with microsatellite instability (MSI) as well as in normal cells from 41 HNPCC patients by means of polymerase chain reaction-single-strand conformation polymorphism. hMSH3 (A)8 and hMSH6 (C)8 repeats were also examined in these cancers. RESULTS: Frameshift mutations in the hMLH3 (A)9 repeat were observed in 4/27 (14.8%) cancers with MSI, all of which showed the severe MSI phenotype. No mutations in the (A)8 repeat were found in any case. The mutation frequency of the hMLH3 (A)9 repeat was similar to that of the hMSH6 (C)8 repeat (5/26, 19.2%), but was significantly lower than that of the hMSH3 (A)8 repeat (16/27, 59.3%) ($P < 0.001$). All four cancers with hMLH3 mutations exhibited germline hMSH2 and/or somatic hMSH3 mutations. No germline mutation in the hMLH3 (A)9 or (A)8 repeat was detected in normal cells from the 41 HNPCC patients. CONCLUSION: hMLH3 mutations were infrequently observed in HNPCC cancers with MSI and they may be secondary to other mismatch repair gene mutations. Hence hMLH3 may only play a small role in HNPCC tumorigenesis.

Akiyama, Y., et al. (1997). "Frequent somatic mutations of hMSH3 with reference to microsatellite instability in hereditary nonpolyposis colorectal cancers." Biochem Biophys Res Commun **236**(2): 248-252.

hMSH3 is one of the human DNA mismatch repair genes but has not yet been reported to be associated with hereditary nonpolyposis colorectal cancer. Recently, somatic mutation at a polyadenine tract, i.e., (A)8, in hMSH3 was reported in cancers with microsatellite instability (MI). To clarify the tumorigenetic role of hMSH3, we screened for somatic mutations at the hMSH3 (A)8 repeat in 29 tumors from 23 hereditary nonpolyposis colorectal cancer patients. One or two A deletions in the (A)8 repeat were found in 11 (57.9%) of the 19 MI-positive tumors but not in 10 MI-negative ones, indicating secondary mutations after germline mutations of other mismatch repair genes. Moreover, the MI frequency of three or more nucleotide repeats was higher in hMSH3 (A)8-mutated tum; or cells than in nonmutated ones ($p<0.05$). These data suggest that a mutation of a mismatch repair gene enhances the frequency of another mismatch repair gene mutation, such as of hMSH3, resulting in severe MI.

Albright, L. A., et al. (2005). "Population-based risk assessment for other cancers in relatives of hereditary prostate cancer (HPC) cases." Prostate **64**(4): 347-355.

BACKGROUND: To identify associations of other cancers with hereditary prostate cancer (HPC) we estimated relative risks (RRs) of 36 different cancers in relatives of prostate cancer cases in the Utah Population Data Base (UPDB), which combines genealogical and cancer data for Utah. METHODS: We utilized known genetic relationships between prostate cancer cases and their relatives with cancer, combined with age- and sex-specific cancer rates calculated internally from the UPDB, to estimate RRs for cancer in relatives of prostate cancer cases. RESULTS: Multiple other cancers were observed in excess in both first- and second-degree relatives of HPC cases including colon cancer, non-Hodgkins lymphoma, multiple myeloma, rectal cancer, cancer of the gallbladder, and melanoma (skin). CONCLUSIONS: This analysis supports the existence of heritable prostate cancer syndromes that include other cancers. We hypothesize that the study of homogeneous pedigrees co-segregating prostate cancer and another cancer could allow more straightforward localization and identification of the gene(s) responsible.

Arnold, N., et al. (1999). "A highly sensitive, fast, and economical technique for mutation analysis in hereditary breast and ovarian cancers." Hum Mutat **14**(4): 333-339.

Mutation analysis of complex genes without hotspots for sequence variations, such as BRCA1, is time-consuming and expensive. Of all currently available methods, direct sequencing has the highest sensitivity, but also the highest costs. Other techniques, such as SSCP, DGGE, and PTT, are more economical but, depending on the experience of the investigator, have at best a sensitivity of 90%. We investigated in a prospective study the feasibility and accuracy of the DHPLC technique. We present the application of the

DHPLC protocol for BRCA1 mutation detection on a HPLC device from Bio-Tek Kontron Instruments (Neufahrn, Germany). DNA from 46 women with hereditary breast and ovarian cancer undergoing genetic testing for BRCA1 mutations were tested. Of 1,518 amplicons analyzed by DHPLC, corresponding to 33 fragments spanning the entire BRCA1 gene, 626 were also directly sequenced. The comparison demonstrated that DHPLC detected all alterations found by direct sequencing. No false-positive signals were seen in cases of homozygous sequences. Further, no false-negative results were ever obtained in women with mutations or polymorphisms, or both. In cases of known genetic variations, the nature of the alterations could be predicted by DHPLC. We also compared different separation matrices. Up to about 500 injections, no significant differences in sensitivity could be observed between poly(styrene divinylbenzene) and end-capped silica based columns. However, after more than 500 injections, the resolution of hetero- from homoduplex deteriorated rapidly on silica columns.

Bignon, Y. J., et al. (1994). "[Criteria of genetic predisposition to hereditary non polyposis colorectal cancers]." Bull Cancer **81**(1): 60-65.

Clinical and histological characteristics of non polypoid colorectal cancers with an hereditary predisposition are presented. The various known genetic syndromes (hereditary non polyposis colorectal cancers, Lynch syndrome type I and type II, Torre-Muir's syndrome, hereditary flat adenoma syndrome) are discussed to find a possible correlation between this nosological classification and their molecular substratum. The main problem today, is to correctly define the population of hereditary predisposed patients to colon cancer, in order to seek and identify the major responsible gene. Any physician, specialist or not, should be encouraged to give the details of the cancer familial context of his patients, in order to aid the oncologist geneticist in his task.

Boilesen, A. E., et al. (2008). "Risk of gynecologic cancers in Danish hereditary non-polyposis colorectal cancer families." Acta Obstet Gynecol Scand **87**(11): 1129-1135.

OBJECTIVE: Women in hereditary non-polyposis colorectal cancer (HNPCC) families have an elevated risk of endometrial and ovarian cancer. The risk in Lynch syndrome families with known mutations in mismatch repair genes (MMR genes) seems to be higher than in familial colorectal cancer (CRC) families. Data in the Danish HNPCC register on the frequency and lifetime risk of gynecologic cancers were analyzed and the actual surveillance strategy discussed in relation to the results. DESIGN: Register-based retrospective study. METHOD: A total of 1,780 at-risk women were identified and epidemiological, clinical and MMR gene mutation data were retrieved. RESULTS: In a total of 105 cases of endometrial cancer, there was no significant difference in MSH2, MSH6 and MLH1 mutation carrier frequency. Compared to the general population, mutation carriers had a 20 times increase in lifetime risk of endometrial cancer. Lifetime risk was elevated four times in familial CRC families. In these families, frequency was correlated to the pedigree phenotype, with significantly higher frequency demonstrated in Amsterdam II families compared to Amsterdam I families and families suspected of HNPCC. A total of 39 cases of ovarian cancer were identified with a lifetime risk of three to four times the general population. No significant correlation was found between the frequency of ovarian cancer and MMR gene mutation status in the families. CONCLUSION: The benefit of surveillance concerning gynecological cancers seems to be less well founded in familial CRC families than in Lynch syndrome families. Modifying the surveillance strategy may be relevant in the future, but before changing existing guidelines concerning surveillance, further research is recommended.

Casey, M. J., et al. (2013). "Phenotypic heterogeneity of hereditary gynecologic cancers: a report from the Creighton hereditary cancer registry." Fam Cancer **12**(4): 719-740.

To determine the validity of observations suggesting a significant dichotomy of gynecologic cancers determined by linkage to specific genetic defects associated with two major autosomal dominant hereditary cancer syndromes; the Creighton University Hereditary Cancer Registry was searched for female carriers of germ line mutations in BRCA1 and BRCA2, associated with the Hereditary Breast Ovarian Cancer syndrome, and in the mismatch repair (MMR) genes MLH1, MSH2 and MSH6, associated with Lynch syndrome, who were registered with invasive uterine, ovarian, fallopian tube or peritoneal cancers between January 1, 1959 and December 31, 2010. From 217 such cases, a total of 174 subjects, consisting of 95 BRCA1 and BRCA2 mutation carriers and 79 carriers of mutations in MMR genes, were identified who had current signed Health Insurance Portability and Accountability Act forms and complete primary diagnostic pathology reports and clinical records. Data meticulously extracted from these cases were categorized and statistically analyzed. There were highly significant differences between carriers of BRCA1 and BRCA2 mutations and carriers of MMR gene mutations in the proportion of serous carcinomas compared with endometrioid carcinomas of the uterus, including cervix and endometium ($p < 0.002$), ovaries ($p < 0.001$) and overall, including fallopian tube and peritoneum cancers ($p < 0.001$). Endometrioid carcinoma was found in one and transitional carcinoma

in another of the 14 BRCA1 mutation carriers with fallopian tube cancer, and endometrioid carcinoma was found in two of four MMR gene mutation carriers with fallopian tube cancers. All other fallopian tube cancers were serous carcinomas. Seven BRCA1 and one BRCA2 mutation carriers were diagnosed with primary peritoneal serous carcinoma; no peritoneal carcinomas were registered in MMR gene mutation carriers. Nine of 14 gynecologic cancers with associated endometriosis in mutation carriers were endometrioid or endometrioid mixed carcinomas compared with just three of other histologic types. Primary breast cancers, that characterize the HBOC syndrome, were much more frequent in BRCA1 and BRCA2 mutation carriers; while multiple gynecologic cancers and associated colorectal and urinary tract cancers, which are features of Lynch syndrome, were more common in MMR gene mutation carriers. Both serous and endometrioid carcinomas were diagnosed in MMR gene mutation carriers at significantly younger ages than in BRCA1 and BRCA2 mutation carriers ($p < 0.0006$). These findings confirm a clear dichotomy of uterine, ovarian and fallopian tube cancers associated with inheritance of mutations in BRCA1 and BRCA2 contrasted with inheritance of MMR gene mutations. This opens possibilities for new approaches to molecular genetic research into carcinogenic pathways and raises important new considerations regarding counseling, screening, prophylaxis and treatment of mutation carriers.

Coupier, I. and P. Pujol (2005). "[Hereditary predispositions to gynaecological cancers]." Gynecol Obstet Fertil **33**(11): 851-856.

The breast, ovary and endometrial cancers are hereditary in 5 to 10% of the cases. These genetic predisposition syndromes can be classified into two major classes: ovarian cancer and breast cancer predisposition family cases (genes BRCA1 and BRCA2) and family cases of colon cancer, endometrial cancer and ovarian cancer (Lynch syndrome or HNPCC) (genes hMLH1, hMSH2, hMLH6). The estimate of the family and individual risk can contribute in a determining manner to the management of these patients, by the practice of screening or an adapted prevention. Indeed, the risk of cancer of an individual having a positive test for a gene of predisposition to breast cancer (BRCA1, BRCA2) or to the colon cancer (hMLH1, hMSH2, hMLH6) lies between 50 and 70% at the age of 70 years. The indication of a genetic test must be discussed within the framework of an oncogenetic consultation. An individual and family medical management ranging from simple monitoring to prophylactic surgery is proposed to these predisposed people.

Courtillot, C. and P. Touraine (2008). "[Management of families at high risk for hereditary breast-ovarian cancers: the endocrinologist's point of view]." Ann Endocrinol (Paris) **69**(3): 193-200.

Most cancers have a sporadic physiopathology, but approximately 5 to 10% of breast cancers and 10% of ovarian cancers involve a genetic predisposition. Sometimes, the gene involved in these hereditary cancers can be identified (usually BRCA1 or 2), but most of the time it remains unknown. However, all women considered at high risk, because of their familial history, must be identified so they can be provided with the most adequate care, since the probability is very high that they develop such a cancer in the future. Fortunately, effective strategies have been developed to reduce this risk. Early detection of breast cancer is possible and prophylactic treatments (chemoprevention and prophylactic surgery) exist for both breast and ovarian cancers. Another reason why it is essential that these high risk women are identified is that treatment for hereditary cancers differs in some ways from that of sporadic cancers. It is best that counseling be given in an interdisciplinary cancer genetic clinic, where all practionners are aware of the latest data and guidelines.

Esteller, M., et al. (2001). "DNA methylation patterns in hereditary human cancers mimic sporadic tumorigenesis." Hum Mol Genet **10**(26): 3001-3007.

Cancer cells have aberrant patterns of DNA methylation including hypermethylation of gene promoter CpG islands and global demethylation of the genome. Genes that cause familial cancer, as well as other genes, can be silenced by promoter hypermethylation in sporadic tumors, but the methylation of these genes in tumors from kindreds with inherited cancer syndromes has not been well characterized. Here, we examine CpG island methylation of 10 genes (hMLH1, BRCA1, APC, LKB1, CDH1, p16(INK4a), p14(ARF), MGMT, GSTP1 and RARbeta2) and 5-methylcytosine DNA content, in inherited (n = 342) and non-inherited (n = 215) breast and colorectal cancers. Our results show that singly retained alleles of germline mutated genes are never hypermethylated in inherited tumors. However, this epigenetic change is a frequent second "hit", associated with the wild-type copy of these genes in inherited tumors where both alleles are retained. Global hypomethylation was similar between sporadic and hereditary cases, but distinct differences existed in patterns of methylation at non-familial genes. This study demonstrates that hereditary cancers "mimic" the DNA methylation patterns present in the sporadic tumors.

Framp, A. (2010). "Working toward an understanding of the impact of hereditary cancers." Gastroenterol Nurs **33**(6): 400-405; quiz 406-407.

Hereditary diffuse gastric cancer is a genetically inherited aggressive form of stomach

cancer. Once the person is diagnosed as having this gene, they have a 75%-80% chance of inheriting the cancer. People who are at risk of this genetic mutation have to meet many challenges relating to the implications of the disease. An understanding is required by nurses to guide them in the provision of care for those afflicted with this inherited form of gastric cancer. A review of literature has been undertaken relating to other genetically inherited cancers including hereditary nonpolyposis colon cancer, familial adenomatous polyposis, and hereditary lobular breast cancer. The findings from the literature assist nurses in understanding the physical and psychological implications of genetically inherited cancer; however, further study is required to gain a complete understanding of the implications of hereditary diffuse gastric cancer.

Gevensleben, H., et al. (2010). "[Hereditary breast and ovarian cancers]." Pathologe **31**(6): 438-444.

Hereditary factors are responsible for 5-10% of all breast cancers and 10% of all ovarian cancer cases and are predominantly caused by mutations in the high risk genes BRCA1 and BRCA2 (BRCA: breast cancer). Additional moderate and low penetrance gene variants are currently being analyzed via whole genome association studies. Interdisciplinary counseling, quality managed genetic testing and intensified prevention efforts in specialized medical centres are essential for members of high risk families considering the high prevalence of malignant tumors and the early age of onset. Furthermore, the identification of BRCA-deficient carcinomas is of particular clinical interest, especially regarding new specific therapeutic options, e.g. treatment with poly (ADP-ribose) polymerase (PARP) inhibitors. There are presently no valid surrogate markers verifying the association of BRCA1/BRC2 in tumors. However, breast cancers harboring pathogenic BRCA1 mutations in particular display specific histopathological features.

Gologan, A. and A. R. Sepulveda (2005). "Microsatellite instability and DNA mismatch repair deficiency testing in hereditary and sporadic gastrointestinal cancers." Clin Lab Med **25**(1): 179-196.

The reference cancers associated with DNA mismatch repair (MMR)deficiency are the adenocarcinomas of patients with hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome. Sporadic gastrointestinal (GI) carcinomas, most commonly colorectal and gastric carcinomas, may also be associated with deficiencies of DNA mismatch repair. Deficiency in cellular MMR leads to wide-spread mutagenesis and neoplastic development and progression. An important diagnostic feature of MMR-deficient tumors is the high rate of mutations that accumulate in repetitive nucleotide regions, and these mutations are known as microsatellite instability(MSI). A standard panel of markers to test for MSI in tumors has been recommended and efficiently separates tumors into those with high, low, or no microsatellite instability (MSI-H, MSI-L, or MSS). Tumors characterized by MSI-H characteristically show loss of one of the main DNA MMR proteins, mLH1 or MSH2, and rarely MSH6 and PMS2, detected by immunohistochemistry (IHC). The combination of MSI testing and IHC for MMR proteins in tumors tissues is used to identify underlying DNA MMR deficiency andis clinically relevant screen patients who might have hereditary non-polyposis colorectal cancer for DNA repair gene germline testing. Increasing evidence demonstrates that tumors with a positive MSI status have lower lymph node metastases burden, and these patients have an overall improved survival, suggesting that the MSI and MMR status may contribute to decision making regarding treatment approaches. Updated guidelines for MSI and IHC for DNAMMR testing, and the biological and potential clinical implications of MMR deficiency and microsatellite instability in GI polyps and cancers are reviewed.

Guirouilh-Barbat, J. K., et al. (2010). "AKT1/BRCA1 in the control of homologous recombination and genetic stability: the missing link between hereditary and sporadic breast cancers." Oncotarget **1**(8): 691-699.

Endogenous replicative stress could be one trigger leading to tumor initiation: indeed, activation of the DNA damage response (DDR), considered the result of replicative stress, is observed in pre-cancerous cells; moreover, in hereditary breast cancers, almost all of the genes affected relate to the DDR. The most frequently mutated gene in hereditary breast cancers, BRCA1, is essential for homologous recombination (HR), a fundamental process for maintaining genome stability that permits the reactivation of blocked replication forks . Recent studies have established links between DDR and the oncogenic kinase AKT1, which is upregulated in about 50% of sporadic breast cancers. More specifically, the activation of AKT1 shows a deficient phenotype in BRCA1 and HR, revealing molecular similarities between hereditary and sporadic breast cancers. However, these results reveal a paradox regarding the physiological role of AKT1: in non-tumor cells, AKT1 promotes cellular proliferation, but consequently endangers genome integrity during replication if HR is inhibited. Since HR could itself lead to genetic instability, we propose that, under physiological conditions, moderate activation of AKT1 does not inhibit but prevents an excess of HR. The regulation of AKT1 would represent a fine transitory system for controlling HR and maintaining genomic integrity.

Hadaczek, P., et al. (2001). "Fhit protein expression in hereditary and sporadic colorectal cancers." Pol J Pathol **52**(3): 125-132.

The majority of hereditary nonpolyposis colorectal cancer (HNPCC) is caused by mutations in DNA mismatch repair genes, especially in MLH1 and MSH2. Tumours in such patients also show microsatellite instability characteristic for DNA repair defects. The FHIT gene, a candidate tumour suppressor gene located at 3p14.2 has been shown to be involved in carcinogenesis of many human tissues, including digestive tract tissues. In our study, we characterized Fhit protein expression in hereditary and sporadic colorectal cancers (CRC). Our intention was to determine if cancers with mutations in the mismatch repair genes, MSH2 and MLH1, would show more frequent inactivation of the FHIT gene. Sixteen HNPCC and 28 sporadic CRC cases were examined by standard immunohistochemical analyses. Both study groups comprised carefully and selectively chosen cases. We have observed higher frequency of loss or reduction of Fhit protein expression in hereditary CRC than in sporadic cases (44% vs. 25%). Although this difference was not statistically significant (p = 0.17), possibly due to the small number of available tumour specimens, the tendency is interesting. More extensive studies on a larger number of cases should be done in the HNPCC group to confirm statistical significance. Our results suggest that the FHIT gene plays an important role in carcinogenesis of at least one fourth of all colorectal cancers.

Hadziavdic, V., et al. (2009). "Molecular analysis: microsatellity instability and loss of heterozygosity of tumor suppressor gene in hereditary non-polyposis colorectal cancers (HNPCC)." Bosn J Basic Med Sci **9**(1): 10-18.

HNPCC (Hereditary non-polyposis colorectal cancers) development is caused by mutation of genes included in system of mismatch repair genes. The mutation exists at 60% of patients in hMSH2 gene, 30% in hMLH1 and 10% both in hPMS1and hPMS2 genes. RER+ exists in about 90% in hereditary non-polyposis colorectal cancer and about 15-28% in sporadic cancers. The purpose of the study was to determine highly sensitive microsatellite markers which can be fast and efficient way of microsatellite screening for detection of HNPCC patients. Moreover, we have analysed the loss of heterozygosity of tumour suppressor genes which could have the diagnostic value in detection of HPNCC patients.

Huang, J., et al. (2003). "[Mutational studies of adenomatous polyposis coli gene in carcinomas from patients with hereditary non-polyposis colorectal cancers]." Zhonghua Yi Xue Yi Chuan Xue Za Zhi **20**(3): 196-199.

OBJECTIVE: To analyze the mutational features of adenomatous polyposis coli (APC) gene and to explore the effect of mismatch repair (MMR) deficiency on its mutations in hereditary non-polyposis colorectal cancers (HNPCC). METHODS: PCR-based in vitro synthesized protein test (IVSP) assay and sequencing analysis were used to confirm somatic mutations of whole APC gene in 19 HNPCC patients. RESULTS: Eleven cases with thirteen mutations were determined. The frequency of APC mutation was 58%(11/19). The exhibiting mutations consisted of 9 frameshift mutations and 4 nonsense ones, indicating the existence of more frameshift mutations (69%). All of frameshift mutations were deletion or insertion of 1-2 bp and most of them (7/9) happened at simple nucleotide repeat sequences, particularly within (A) n tracts (5/9). All of four nonsense mutations resulted from C to T transitions at CpG sites. CONCLUSION: Mutational inactivations of APC gene were detected in more than half of HNPCC patients in this study, indicating that APC mutation is a common molecular event in the tumorigenesis of HNPCC. According to the location of frameshift mutations at simple nucleotide repeat sequences and point mutations at CpG sites, it was suggested that endogenous mechanisms like MMR deficiency might exert an effect on the nature of APC mutations in most HNPCC.

Hutchison, J., et al. (2013). "How microRNAs influence both hereditary and inflammatory-mediated colon cancers." Cancer Genet **206**(9-10): 309-316.

MicroRNAs have emerged as important post-translational regulators of gene expression and are involved in several physiological and pathological states including the pathogenesis of human colon cancers. In regards to tumor development, microRNAs can act as oncogenes or tumor suppressors. Two hereditary predispositions (i.e., Lynch syndrome and familial adenomatous polyposis) contribute to the development of colon cancer. In addition, individuals who suffer from inflammatory bowel diseases such as Crohn's disease or ulcerative colitis have a higher risk of developing colon cancer. Here, we discuss the occurrence of the deregulated expression of microRNAs in colon cancer that arise as a result of hereditary predisposition and inflammatory bowel disease.

Huttelova, R., et al. (2009). "[Prerequisites for preimplantation genetic diagnosis (PGD in carriers of mutations responsible for hereditary cancers]." Klin Onkol **22 Suppl**: S69-74.

BACKGROUNDS: Carriers of hereditary mutations in cancer susceptibility genes represent a limited but high-risk population characterized by a high probability of cancer development, frequently with its manifestation in early age and with a 50% chance of pathogenic allele inheritance by offspring. In case of monogenic disorders, preimplantation genetic diagnosis (PGD) could be used for characterization of the DNA region affected by pathogenic mutation in the early stages of an embryo created by in vitro

fertilization (IVF). Therefore, the transfer of unaffected embryos could be performed based on the results of PGD genotyping, enabling the development of offspring not carrying the pathogenic alteration. AIM: Here we present the consensus of the collaborative group of the Society for Medical Genetics, the Czech Society for Oncology and other professionals for use of PGD in the Czech Republic for carriers of mutations in cancer susceptibility genes. We address the conditions, prerequisites, and limits of practical application of this method. We also point out specific issues of ovarian hyperstimulation in carriers of mutations in BRCA1, BRCA2, and p53, anticipating the increased risk of hormonally dependent breast and ovarian cancers development. CONCLUSIONS: We assume that a narrow but non-negligible subgroup of cancer susceptibility gene mutation carriers may benefit from PGD.They are mainly individuals deciding to undergo IVF and PGD recruited from mutation carriers with extreme concerns about transmitting the mutation to their children. The PGD in these individuals should be managed by a closely cooperating multidisciplinary team of professionals responsible for indication of PGD, giving complete information regarding the IVF and PGD procedures including their limits, evaluating individual risks and performing instrumental and laboratory procedures with respect to up-to-date good laboratory and clinical practice.

Jazaeri, A. A. (2009). "Molecular profiles of hereditary epithelial ovarian cancers and their implications for the biology of this disease." Mol Oncol **3**(2): 151-156.

BRCA1 and BRCA2 germline mutations account for the majority of hereditary ovarian cancers and comprise 10% of total cases. Ovarian cancers arising from these mutations exhibit both overlapping and distinct clinical and molecular features. The expression profiles of sporadic ovarian cancers show similarities to those of BRCA1 and BRCA2-related tumors suggesting that BRCA-related pathways may be involved in their development as well. The purpose of this review is to consider the available data on ovarian cancers in the context of other investigations of BRCA-related transcriptional alterations, and highlight areas for future research.

Kim, C. J., et al. (2007). "Chk1 frameshift mutation in sporadic and hereditary non-polyposis colorectal cancers with microsatellite instability." Eur J Surg Oncol **33**(5): 580-585.

AIM: Protein kinase Chk1 (hChk1) is essential in human cells for cell cycle arrest in response to DNA damage, and has been shown to play an important role in the G2/M checkpoint. The BRAF mutations have been suggested to be linked with defective mismatch repair in colorectal cancers. The aim of this study was to investigate whether a frameshift mutation within the Chk1 gene contribute to the development or progression of eastern sporadic and hereditary non-polyposis colorectal cancer (HNPCC) with microsatellite instability (MSI). METHODS: We analyzed MSI using the 6 microsatellite markers and a frameshift mutation in the BRAF gene and in poly(A)9 within the Chk1 gene in 51 sporadic colorectal cancer and 14 HNPCC specimens. RESULTS: Eleven of the 51 sporadic colorectal cancers and all of the 14 HNPCCs were MSI-positive. Chk1 frameshift mutations were observed in 2 and 3 sporadic colon cancers and HNPCC, respectively, whereas no BRAF mutations were detected in these samples. Interestingly, all cases with the Chk1 frameshift mutation had high-frequency MSI. CONCLUSION: These results suggest that the Chk1 gene is a target of genomic instability in MSI-positive colorectal cancers and that the Chk1 framshift mutations might be involved in colorectal tumourigenesis through a defect in response to DNA damage in a subset of sporadic colorectal cancers and HNPCCs.

Knudson, A. G., Jr. (1989). "The ninth Gordon Hamilton-Fairley memorial lecture. Hereditary cancers: clues to mechanisms of carcinogenesis." Br J Cancer **59**(5): 661-666.

The study of hereditary cancer in humans, notably retinoblastoma, has identified a category of cancer genes that is different from that of the oncogenes. Whereas the latter group of genes exerts its effect through expression, the former does so as a result of failure of normal expression. Primary oncogene abnormality seems to play a crucial initiating role in certain neoplasms, particularly leukaemias, lymphomas and some sarcomas. In contrast, anti-oncogenes (tumour suppressor genes) appear to be important in the initiation of several solid tumours of children, as well as some common carcinomas of adults. Both classes are apparently involved in tumour progression and metastasis. Virtually every kind of cancer can occur in hereditary form, so the role of anti-oncogenes in the origin of human cancers may be considerable. The prototypic anti-oncogene has been that for retinoblastoma. For this tumour the recessive mechanism has been demonstrated by molecular means, and the gene has been cloned. The possibility has been suggested that gene (or gene product) replacement therapy could be accomplished.

Knudson, A. G., Jr. (1995). "Hereditary cancers: from discovery to intervention." J Natl Cancer Inst Monogr(17): 5-7.

This conference concerned hereditary cancers of the breast, ovary, and colon, which are the common, often fatal, cancers with the greatest heritability in their causation. Four genes whose mutations impart dominantly heritable predisposition to one or more of these cancers have been cloned and one more has been mapped. The most molecular details are known for

colon cancer. The APC gene of familial polyposis coli leads to the accumulation of numerous polyps, but the probability of transformation of the latter to cancer is low. This provides the opportunity to monitor putative preventive measures with an intermediate end point. In hereditary nonpolyposis colon cancer, transformation of the polyp to cancer is accelerated by an inherited mutation in either of two DNA mismatch repair genes. The discovery of an intermediate end point could be very helpful for breast cancer. Testing persons at risk for predisposing mutations depends heavily on the availability of promising measures for prevention or treatment.

Kohda, M., et al. (2016). "Rapid detection of germline mutations for hereditary gastrointestinal polyposis/cancers using HaloPlex target enrichment and high-throughput sequencing technologies." Fam Cancer **15**(4): 553-562.

Genetic testing for hereditary colorectal polyposis/cancers has become increasingly important. Therefore, the development of a timesaving diagnostic platform is indispensable for clinical practice. We designed and validated target enrichment sequencing for 20 genes implicated in familial gastrointestinal polyposis/cancers in 32 cases with previously confirmed mutations using the HaloPlex enrichment system and MiSeq. We demonstrated that HaloPlex captured the targeted regions with a high efficiency (99.66 % for covered target regions, and 99.998 % for breadth of coverage), and MiSeq achieved a high sequencing accuracy (98.6 % for the concordant rate with SNP arrays). Using this approach, we correctly identified 33/33 (100 %) confirmed alterations including SNV, small INDELs and large deletions, and insertions in APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, PMS2, and SKT11. Our approach yielded the sequences of 20 target genes in a single experiment, and correctly identified all previously known mutations. Our results indicate that our approach successfully detected a wide range of genetic variations in a short turnaround time and with a small sample size for the rapid screening of known causative gene mutations of inherited colon cancer, such as familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, and Juvenile polyposis syndrome.

Kwong, A., et al. (2016). "A new paradigm of genetic testing for hereditary breast/ovarian cancers." Hong Kong Med J **22**(2): 171-177.

INTRODUCTION: Genetic risk factors and family history play an important role in breast cancer development. This review aimed to summarise the current genetic testing approach to hereditary breast/ovarian cancer. METHODS: A systematic literature review was performed by searching the PubMed database. Publications available online until January 2015 that addressed issues related to hereditary breast/ovarian cancer genetic counselling/testing were selected. The search terms used were "familial breast/ovarian cancer", "susceptibility genes", "genetic counselling", and "genetic testing". The data extracted for this review were analysed by the authors, with a focus on genetic testing for hereditary breast/ovarian cancer. RESULTS: Although a greater proportion of inherited breast/ovarian cancers are due to the BRCA1 and BRCA2 mutations, a number of new genes have emerged as susceptibility candidates, including rare germline mutations in high penetrance genes, such as TP53 and PTEN, and more frequent mutations in moderate/low penetrance genes, such as PALB2, CHEK2 and ATM. Multi-gene testing, if used appropriately, is generally a more cost- and time-effective method than single-gene testing, and may increase the number of patients who can be offered personal surveillance, risk-reduction options, and testing of high-risk family members. CONCLUSIONS: Recent advances in molecular genetics testing have identified a number of susceptibility genes related to hereditary breast and/or ovarian cancers other than BRCA1 and BRCA2. The introduction of multi-gene testing for hereditary cancer has revolutionised the clinical management of high-risk patients and their families. Individuals with hereditary breast/ovarian cancer will benefit from genetic counselling/testing.

Kwong, A., et al. (2016). "Detection of Germline Mutation in Hereditary Breast and/or Ovarian Cancers by Next-Generation Sequencing on a Four-Gene Panel." J Mol Diagn **18**(4): 580-594.

Mutation in BRCA1/BRCA2 genes accounts for 20% of familial breast cancers, 5% to 10% of which may be due to other less penetrant genes which are still incompletely studied. Herein, a four-gene panel was used to examine the prevalence of BRCA1, BRCA2, TP53, and PTEN in hereditary breast and ovarian cancers in Southern Chinese population. In this cohort, 948 high-risk breast and/or ovarian patients were recruited for genetic screening by next-generation sequencing (NGS). The performance of our NGS pipeline was evaluated with 80 Sanger-validated known mutations and eight negative cases. With appropriate bioinformatics analysis pipeline, the detection sensitivity of NGS is comparable with Sanger sequencing. The prevalence of BRCA1/BRCA2 germline mutations was 9.4% in our Chinese cohort, of which 48.8% of the mutations arose from hotspot mutations. With the use of a tailor-made algorithm, HomopolymerQZ, more mutations were detected compared with single mutation detection algorithm. The frequencies of PTEN and TP53 were 0.21% and 0.53%, respectively, in the Southern Chinese patients with breast and/or ovarian cancers. High-throughput NGS approach allows the incorporation of control cohort that provides an ethnicity-specific data for

polymorphic variants. Our data suggest that hotspot mutations screening such as SNaPshot could be an effective preliminary screening alternative adopted in a standard clinical laboratory without NGS setup.

Lakatos, P. L. and L. Lakatos (2006). "[Current concepts in the genetics of hereditary and sporadic colorectal cancer and the role of genetics in patient management. Hereditary colorectal cancers]." Orv Hetil **147**(8): 363-368.

Colorectal cancer (CRC) is the second leading cause of mortality of malignant diseases in Hungary and according to the incidence and prevalence of CRC Hungary is second among European countries. Hence, it is of outstanding interest to know the current concepts on pathogenesis and genetical background of CRC, as well as incorporate this knowledge in the everyday practice. In the first part of the review authors address the genetic background of hereditary colorectal cancer syndromes. In fact, a positive family history may be found in 20-30% and genetically defined trait (e.g. familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC) and Peutz-Jeghers-syndrome (PJS)) is responsible for 3-5% of all colon cancers. Germline mutations of tumor suppressor gene, APC (5q21) are found in 70-90% of the cases. Until now more than 300 mutations were identified. Though a typical mutation was not found, the location of the mutation is associated to the clinical phenotype and prognosis. Of note, beside APC mutations, biallelic mutations of the MYH gene may be found in a subset of individuals with FAP. The diagnosis of HNPCC is based on family history and the presence of Amsterdam I-Il or Bethesda criteria. The genetic background and clinical phenotype of the syndrome is heterogeneous. Mutations of different mismatch repair genes (mainly hMLH1 or hMSH2) may be identified in most cases. Genetic testing is advised in first degree relatives of FAP patients, if genetic testing is not available colonoscopic surveillance should be done starting at the age of 10-12 years. Due to the high number of mutation genetic testing is difficult in HNPCC families and colonoscopic screening should be advised to affected families.

Li, F. P. (1995). "Translational research on hereditary colon, breast, and ovarian cancers." J Natl Cancer Inst Monogr(17): 1-4.

Discoveries of inherited cancer susceptibility genes are creating new opportunities for translational cancer control research. Identification of these genes was facilitated by epidemiologic studies of mendelian patterns of cancers in families and advances in laboratory techniques to detect inherited mutations. Tumor suppressor genes were the first cancer-predisposing genes identified, primarily through studies of rare cancers such as hereditary retinoblastoma and Wilms' tumor. Recently, a second class of susceptibility genes, mismatch repair genes such as MSH2 and MLH1, has been shown to be defective in hereditary nonpolyposis colon cancers. Knowledge of these genes and the recently identified BRCA1 gene for hereditary breast/ovarian cancers raises the possibility of cancer-predisposition testing of substantial portions of the general population. Carriers are at high risk of cancer and are candidates for early detection and chemoprevention studies. However, large-scale cancer-predisposition testing poses questions about not only ethical, legal, and social issues, but also technological and logistical challenges. Cancer-predisposition testing is new, and research is needed to maximize benefits while minimizing risks.

Losi, L., et al. (1997). "K-ras and p53 mutations in hereditary non-polyposis colorectal cancers." Int J Cancer **74**(1): 94-96.

Genetic instability related to defective DNA mismatch repair genes may be involved in the pathogenesis of carcinoma in Hereditary Non-Polyposis Colorectal Cancer (HNPCC). To test that the targets of genetic instability could include critical transforming genes involved in colon tumor progression, we examined 23 colorectal carcinomas in patients with HNPCC in order to detect somatic mutations in K-ras and p53 genes. Using single strand conformation polymorphism followed by direct DNA sequencing, we detected 4 mutations in K-ras gene (17%) and 3 in p53 gene (13%) which change the amino acid sequence of the protein p53. This is significantly lower than in sporadic cancer. Our data suggest that colon cancer in HNPCC might partly involve a distinct pathogenetic mechanism that involves other genes than those altered in sporadic tumors.

Lu, S. L., et al. (1996). "Loss or somatic mutations of hMSH2 occur in hereditary nonpolyposis colorectal cancers with hMSH2 germline mutations." Jpn J Cancer Res **87**(3): 279-287.

Hereditary nonpolyposis colorectal cancer (HNPCC) is a major cancer susceptibility syndrome known to be caused by the inheritance of mutations in DNA mismatch repair genes, such as hMSH2, hMLH1, hPMS1 and hPMS2. To investigate the role of genetic alterations of hMSH2 in HNPCC tumorigenesis, we analyzed 36 Japanese HNPCC kindreds as to hMSH2 germline mutations. Moreover, we also examined somatic mutations of hMSH2 or loss of heterozygosity at or near the hMSH2 locus in the tumors from the hMSH2-related kindreds. Germline mutations were detected in five HNPCC kindreds (5/36, 14%). Among them, three were nonsense mutations, one was a frameshift mutation and the other was a mutation in an intron where the mutation affected splicing. Loss of heterozygosity in four and somatic mutations in one were detected among the eight tumors with hMSH2

germline mutations. All these alterations were only detected in genomic instability(+) tumors, i.e., not in genomic instability(-) ones, indicating that mutations of hMSH2 were responsible for at least some of the tumors with genomic instability. These data establish a basis for the presymptomatic diagnosis of HNPCC patients, and constitute further evidence that both DNA mismatch repair genes and tumor suppressor genes may share the same requirement, i.e., two hits are necessary to inactivate the gene function.

Lu, S. L., et al. (1996). "Genomic structure of the transforming growth factor beta type II receptor gene and its mutations in hereditary nonpolyposis colorectal cancers." Cancer Res **56**(20): 4595-4598.

To characterize the tumorigenetic role of the transforming growth factor beta type II receptor (RII) gene, we defined its genomic structure, which consists of seven exons. The sequences of exon-intron junctions were determined to facilitate mutation analysis of each exon. Twenty-five carcinomas and five adenomas from hereditary nonpolyposis colorectal cancer patients were analyzed for mutations in the entire coding region. Four missense mutations (two in adenomas and two in carcinomas) were found in the 10 cases carrying the polyadenine deletions in one allele. These results indicate that RII shares the two-hit inactivation mechanism with tumor suppressor genes and that mutations of it may occur in the early stage of tumorigenesis.

Mendes, A. F., et al. (2011). "Experiencing genetic counselling for hereditary cancers: the client's perspective." Eur J Cancer Care (Engl) **20**(2): 204-211.

As genetic health care expands and genetic testing becomes more widely available, it becomes relevant to understand how individuals involved in genetic counselling are integrating this new information in health management and into their lives. This article examines the client's experiences of genetic counselling for hereditary cancers, which definitely play a major role in the assessment of their needs and also lead to improvement of the psychosocial focus in genetic counselling protocols. Methods include a semi-structured interview, administered in two focus groups, comprising 10 (5 + 5) participants after attending genetic counselling for hereditary cancers at a Portuguese public hospital. Findings suggest an experience embedded in two dimensions: (1) instrumental (goals, needs and decision making); and (2) emotional (uncertainty regarding genetic risk screening and an emotional complex). Ambiguity plays a crucial role, especially in two moments: (1) the hiatus between genetic testing and the screening results; and (2) after being confirmed as carrying a cancer susceptibility gene mutation. The spectrum of genetic illness comprises an intensely complex emotional experience that challenges individuals and their families in terms of health management, and personal and family planning. Recommendations are included in order to enhance the services available by expanding psychosocial support.

Menkiszak, J., et al. (2004). "Ovarian cystadenoma as a characteristic feature of families with hereditary ovarian cancers unassociated with BRCA1 and BRCA2 mutations." J Appl Genet **45**(2): 255-263.

The study aimed to determine whether hereditary ovarian cancers that are not caused by BRCA1/BRCA2 constitutional mutations are associated with a predisposition to cystadenoma. The study consisted of two parts. Part one concerned the incidence of ovarian cystadenoma in females from families with hereditary ovarian cancer unassociated with BRCA1 mutations. The study group included 62 female patients from 29 families, without any previously diagnosed malignancy, with no proven constitutional mutation of the BRCA1 gene. The first control group was composed of 62 female patients from 53 families, without any previously diagnosed malignancy, with an identified constitutional mutation of the BRCA1 gene. The second control group comprised 124 female patients for whom the only reason for the examination was a prophylactic check-up. All studied women were subjected to intravaginal ultra- sonographic investigations. In 8 patients with benign and/or borderline ovarian cystadenoma, a complete sequencing of coding fragments of the BRCA2 gene from the peripheral blood DNA was performed. Part two of this study concerned the incidence and pattern of malignant tumors in the families of female patients with ovarian cystadenoma. The final study group included 117 patients who had 726 I0 relatives (359 females and 367 males). We concluded that cystadenoma is likely to be a characteristic feature of the subgroup of families with hereditary ovarian cancers unassociated with BRCA1/BRCA2 constitutional mutations.

Mitchell, G. and K. A. Schrader (2016). "Testing for Hereditary Predisposition in Patients with Gynecologic Cancers, Quo Vadis?" Surg Pathol Clin **9**(2): 301-306.

Genetic testing for a hereditary predisposition to gynecologic cancers has been available clinically since the 1990s. Since then, knowledge of the hereditary contribution to gynecologic cancers has dramatically increased, especially with respect to ovarian cancer. Although knowledge of the number of gynecologic cancer-predisposing genes has increased, the integration of genetic predisposition testing into routine clinical practice has been much slower. This article summarizes the technical and practical aspects of genetic testing in gynecologic cancers, the potential barriers to more widespread access and practice of genetic testing for hereditary predisposition to

gynecologic cancers, and the potential solutions to these barriers.

Miyaki, M., et al. (2007). "Mutations of the PIK3CA gene in hereditary colorectal cancers." Int J Cancer **121**(7): 1627-1630.

Somatic mutations of the PIK3CA gene have recently been detected in various human cancers, including sporadic colorectal cancer. However, mutations of the PIK3CA gene in hereditary colorectal cancers have not been clarified. To elucidate the mutation status in familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), which are the most common hereditary colorectal cancers, we investigated PIK3CA mutations in 163 colorectal tumors, including adenomas, intramucosal carcinomas and invasive carcinomas. For comparison, we also analyzed mutations of the same gene in 160 sporadic colorectal tumors at various histopathological stages. Analysis at exons 1, 7, 9 and 20 of the PIK3CA gene revealed somatic mutations in 21% (8 of 39) of FAP invasive carcinomas, 21% (7 of 34) of HNPCC invasive carcinomas, 15% (8 of 52) of sporadic invasive carcinomas, and 14% (7 of 50) of sporadic colorectal metastases in the liver. Mutations in FAP and HNPCC carcinomas predominantly occurred in the kinase domain (exon 20), while the majority of mutations in sporadic cases occurred in the helical domain (exon 9). Adenomas and intramucosal carcinomas from all patients exhibited no mutations (0 of 148). Our data suggest that PIK3CA mutations contribute to the invasion step from intramucosal carcinoma to invasive carcinoma in colorectal carcinogenesis in FAP and HNPCC patients at a similar extent to that seen in sporadic patients.

Muir, B. and L. Nunney (2015). "The expression of tumour suppressors and proto-oncogenes in tissues susceptible to their hereditary cancers." Br J Cancer **113**(2): 345-353.

BACKGROUND: Studies of familial cancers have found that only a small subset of tissues are affected by inherited mutations in a given tumour suppressor gene (TSG) or proto-oncogene (POG), even though the mutation is present in all tissues. Previous tests have shown that tissue specificity is not due to the presence vs absence of gene expression, as TSGs and POGs are expressed in nearly every type of normal human tissue. Using published microarray expression data we tested the related hypothesis that tissue-specific expression of a TSG or POG is highest in tissue where it is of oncogenic importance. METHODS: We tested this hypothesis by examining whether individual TSGs and POGs had higher expression in the normal (noncancerous) tissues where they are implicated in familial cancers relative to those tissues where they are not. We examined data for 15 TSGs and 8 POGs implicated in familial cancer across 12 human tissue types. RESULTS: We found a significant difference between expression levels in susceptible vs nonsusceptible tissues. It was found that 9 (60%, $P<0.001$) of the TSGs and 5 (63%, $P<0.001$) of the POGs had their highest expression level in the tissue type susceptible to their oncogenic effect. CONCLUSIONS: This highly significant association supports the hypothesis that mutation of a specific TSG or POG is likely to be most oncogenic in the tissue where the gene has its highest level of expression. This suggests that high expression in normal tissues is a potential marker for linking cancer-related genes with their susceptible tissues.

Pastrello, C., et al. (2005). "MUC gene abnormalities in sporadic and hereditary mucinous colon cancers with microsatellite instability." Dis Markers **21**(3): 121-126.

Aim of this study was verifying whether mucin producing colon cancers (CRCs) could develop through a molecular pathway involving microsatellite instability (MSI) and MUC gene alterations. Out of 49 CRCs expressing variable amounts of mucin, 22 (44.9%) were MSI-H and 5 (10.2%) were MSI-L. MUC genes were analyzed by Southern blotting and extra bands were evident in the Variable Number Tandem Repetition (VNTR) regions of MUC2 (5 cases) and MUC5AC (2 cases), but not MUC1 and MUC4 genes. Since the somatic VNTR abnormalities were detected in 6 MSI-H and in 1 MSI-L tumors, they seem to be peculiar of mismatch repair defective CRCs. Our finding suggests that alteration and/or loss of structurally normal MUC genes may be an important step in the neoplastic molecular pathway of a subset of CRCs and that mutations involving VNTR repetitive sequences may exist in MSI tumors as a direct and/or indirect consequence of an inefficient MMR system.

Perey, L. and D. F. Schorderet (1996). "[Hereditary breast cancers]." Praxis (Bern 1994) **85**(35): 1035-1039.

Recently, genetic analyses in high risk families with several members suffering of breast and/or ovarian carcinoma led to the discovery of two genes, called BRCA1 and BRCA2, clearly responsible for hereditary predisposition of breast carcinoma. Another gene, p53, was also shown to be involved in hereditary predisposition of breast and other tumors in the setting of Li-Fraumeni syndrome. It is very important that women at risk could be seen by a specialized team for genetic counselling and explanation of advances and limits of molecular genetics. Such a team should be multidisciplinary in order to cover genetic, oncological, social, psychological and economical aspects of hereditary cancer predisposition. Prevention interventions and early detection methods are still investigational and definitely need to be performed in the setting of protocols in order to better evaluate their long term efficacy.

Phillips, K. A. (2000). "Immunophenotypic and pathologic differences between BRCA1 and BRCA2 hereditary breast cancers." J Clin Oncol **18**(21 Suppl): 107S-112S.

Morphologically and clinically, breast cancer is a heterogeneous group of diseases. This heterogeneity may be a manifestation of differences in the molecular genetic events underlying distinct breast cancer pathogenesis pathways. Examination of hereditary breast cancers (HBC), which have in common an underlying germline mutation in BRCA1 or BRCA2, may provide further insight into this concept. Multiple studies have confirmed that BRCA1-associated HBC (BRCA1-HBC) generally exhibit a specific phenotype that is characterized by high tumor grade and estrogen receptor negativity. Conversely, discrepancies exist between the findings of studies that have examined BRCA2-HBC, and a specific phenotype has not been consistently described. The characteristic phenotype of BRCA1-associated tumors may prove a useful additional tool in selecting individuals with breast cancer who should be offered BRCA1 mutation testing, although further studies are required. Lastly, evidence is emerging to suggest that BRCA1 might be involved in the pathogenesis of a subgroup of non-HBC (by gene underexpression rather than mutation) and that these tumors may exhibit the same phenotype as their hereditary counterparts.

Rhei, E., et al. (1998). "Molecular genetic characterization of BRCA1- and BRCA2-linked hereditary ovarian cancers." Cancer Res **58**(15): 3193-3196.

Hereditary ovarian cancers associated with germline mutations in either BRCA1 or BRCA2 were studied to determine whether somatic mutation of the P53 gene is required for BRCA-linked ovarian tumorigenesis and further, whether the spectrum of additional somatic molecular genetic alterations present in these tumors differs from that known to exist in sporadic ovarian cancers. Forty tumors, 29 linked to BRCA1 and 11 linked to BRCA2, were examined for mutational alterations in P53, K-RAS, ERBB-2, C-MYC, and AKT2. The presence of a P53 mutation in 80% of these cancers indicates that P53 mutation is common but not required for BRCA-linked ovarian tumorigenesis; notably, a significantly higher proportion of the P53 mutations in BRCA2-linked cancers were deletions or insertions compared with the more typical spectrum of missense mutations seen in BRCA1-linked cancers. Additionally, BRCA-linked ovarian carcinomas seem to develop through a unique pathway of tumorigenesis that does not involve mutation of K-RAS or amplification of ERBB-2, C-MYC, or AKT2.

Sekine, M. and K. Tanaka (2000). "[Linkage analysis for identifying genes implicated in hereditary cancers]." Nihon Rinsho **58**(6): 1206-1210.

The genes responsible for hereditary cancers such as retinoblastoma, colorectal cancer and breast cancer have been identified through application of positional cloning from human molecular genetics. Linkage analysis is a powerful method to locate a disease gene, however a precise genetic model, detailing the mode of inheritance, gene frequencies and penetrance, is required for parametric methods, but not for nonparametric methods. The nonparametric methods ignores unaffected people, and looks for alleles that are shared by affected individuals within nuclear families as well as extended families. Hence the methods usually have been performed to identify disease genes in many hereditary diseases. In this paper, we describe the rationale and strategy of linkage analysis in detail for genetic mapping of hereditary cancers.

Sinicrope, F. A., et al. (1999). "Reduced expression of cyclooxygenase 2 proteins in hereditary nonpolyposis colorectal cancers relative to sporadic cancers." Gastroenterology **117**(2): 350-358.

BACKGROUND & AIMS: Cyclooxygenase (COX) enzymes catalyze the conversion of arachidonic acid to prostaglandins. Evidence suggests that nonsteroidal anti-inflammatory drugs reduce the risk of colorectal cancer (CRC) and that this effect is mediated through COX inhibition. We analyzed and compared expression of the inducible COX-2 isoform in colorectal neoplasms from patients with hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and sporadic CRC. Given that COX-2 is induced by transforming growth factor (TGF)-beta and that TGF-beta type II receptor (RII) mutations are found in HNPCCs, we determined the relationship between RII status and COX-2 expression. METHODS: COX-2 protein expression was determined in colorectal epithelia using immunohistochemistry and Western blotting. Patients with HNPCC had known mutations in hMLH1 or hMSH2 genes and/or met the Amsterdam criteria. In CRCs from HNPCC cases, mutations were sought in the coding region of the RII gene using the polymerase chain reaction. RESULTS: COX-2 was detected in adenomas from 2 of 3 HNPCC, 6 of 7 FAP, and 5 of 8 sporadic cases. In CRCs, COX-2 staining was found in 16 of 24 (67%) HNPCC vs. 24 of 26 (92%) sporadic cases (P = 0.035) and in 2 of 2 FAP cases. Staining intensity was reduced in HNPCCs compared with sporadic CRCs (P = 0.035). Staining localized to the cytoplasm of neoplastic cells; normal epithelial cells were negative for COX-2. Overexpression of COX-2 in CRCs relative to normal mucosa was confirmed by Western blotting. TGF-beta RII mutations were

detected in 12 of 14 HNPCCs examined, including 3 of 4 COX-2-negative and 9 of 10 COX-2-positive cancers. CONCLUSIONS: The frequency and intensity of COX-2 expression was significantly reduced in HNPCCs relative to sporadic CRCs, and was not a consequence of RII mutations. Given that many HNPCCs express COX-2, inhibition of this enzyme may be an important strategy to prevent CRC in these patients.

Smith, I. M., et al. (2010). "Inactivation of the tumor suppressor genes causing the hereditary syndromes predisposing to head and neck cancer via promoter hypermethylation in sporadic head and neck cancers." ORL J Otorhinolaryngol Relat Spec **72**(1): 44-50.

Fanconi anemia (FA) and dyskeratosis congenita (DC) are rare inherited syndromes that cause head and neck squamous cell cancer (HNSCC). Prior studies of inherited forms of cancer have been extremely important in elucidating tumor suppressor genes inactivated in sporadic tumors. Here, we studied whether sporadic tumors have epigenetic silencing of the genes causing the inherited forms of HNSCC. Using bisulfite sequencing, we investigated the incidence of promoter hypermethylation of the 17 Fanconi- and DC-associated genes in sporadic HNSCC. Genes that only showed methylation in the tumor patients were chosen for quantitative methylation-specific PCR (qMSP) in a set of 45 tumor and 16 normal patients. Three gene promoters showed differences in methylation: FancB (FAAP95, FA core complex), FancJ (BRIP1, DNA Helicase/ATPase), and DKC1 (dyskeratin). Bisulfite sequencing revealed that only FancB and DKC1 showed no methylation in normal patients, yet the presence of promoter hypermethylation in tumor patients. On qMSP, 1/16 (6.25%) of the normal mucosal samples from non-cancer patients and 14/45 (31.1%) of the tumor patients demonstrated hypermethylation of the FancB locus ($p < 0.05$). These results suggest that inactivation of FancB may play a role in the pathogenesis of sporadic HNSCC.

Sobol, H., et al. (1996). "Truncation at conserved terminal regions of BRCA1 protein is associated with highly proliferating hereditary breast cancers." Cancer Res **56**(14): 3216-3219.

The existence of two subgroups of BRCA1-associated breast cancer (BC) families has been recently posited: the first with highly proliferating tumors, and the second composed of cases with a low proliferation rate. Our aim was to test whether the proliferation rate of BRCA1-associated breast cancers was affected by the site of the germ line mutation in the BRCA1 gene. We analyzed the distribution of the mitotic index, a histoprognostic grade component shown to segregate in families, matching for germ line mutation location in a series of 28 breast cancers from 20 kindreds. We observed a prevalence of highly proliferating tumors when the mutation occurs in the two terminal conserved domains of the BRCA1 protein, ie., in the amino and carboxyl termini ($P = 0.0024$). Our data provide evidence for a genotype-phenotype correlation and along with their strong conservation during evolution argue for the importance of these two regions in the control of mammary cell growth.

South, S. A., et al. (2009). "Consideration of hereditary nonpolyposis colorectal cancer in BRCA mutation-negative familial ovarian cancers." Cancer **115**(2): 324-333.

BACKGROUND: Inherited mutations account for approximately 10% of all epithelial ovarian cancers. Breast cancer (BRCA1 and BRACA2) gene mutations are responsible for up to 85% of inherited breast and/or ovarian cancer. Another condition that has been associated with ovarian cancer is hereditary nonpolyposis colorectal cancer syndrome (HNPCC), which carries a lifetime risk of up to 13% for ovarian cancer. The objective of this study was to determine the incidence of HNPCC-related gene mutations in patients with familial ovarian cancer who previously tested negative for BRCA1 and BRCA2 gene mutations. METHODS: Seventy-seven probands were identified who had familial ovarian cancer and negative BRCA gene mutation testing. Their pedigrees were analyzed for HNPCC syndrome. DNA samples underwent gene sequencing and Southern blot analysis for mutations in the 3 most common HNPCC-associated genes: mutL homolog 1 (MLH1) and mutS homolog 2 (MSH2) with reflex testing for MSH6 if tests for the first 2 genes were negative. RESULTS: None of the probands met Amsterdam criteria for the clinical diagnosis of HNPCC. DNA testing revealed 2 patients (2.6%) with deleterious mutations in the MSH2 gene. An additional 8 patients (10.4%) had substitutions in either the MLH1 gene or the MSH2 gene that were classified as variants of uncertain significance. If Amsterdam criteria were expanded to include ovarian cancer, then 15 of 77 patients (19.5%) would have met these expanded criteria. One deleterious mutation was noted in this group, yielding a mutation incidence of 6.7%. This percentage may be even higher if any of the identified variants of uncertain significance are confirmed to be deleterious. CONCLUSIONS: HNPCC should be considered when evaluating patients with suspected hereditary ovarian cancer who have had negative BRCA mutation testing.

Turpin, A., et al. (2014). "[Hereditary predisposition to cancers of the digestive tract, breast, gynecological and gonadal: focus on the Peutz-Jeghers]." Bull Cancer **101**(9): 813-822.

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disease due to mutations in the

tumor suppressor gene STK11. PJS is characterized by periorificial hyperpigmented macules (lentiginosis) and hamartomatous polyposis. Polyps can be located anywhere in the gastrointestinal tract, but are preferably observed in the small bowel (70-90%), the colon (50%) and the stomach (25%). They tend to be cancerous in a particular sequence hamartoma-dysplasia-cancer. The diagnosis is often made in the first or second decade following the appearance of lentigines or upon the occurrence of complications due to polyps (obstruction, intussusception, occult bleeding responsible for anemia). Furthermore PJS is associated with a significant increase in cancer risk (relative risk of 89% over the life according to the most recent series). Digestive cancers are the more frequent with cumulative incidences of 55% for gastro-intestinal cancer (39% for colorectal cancer, 13% for small bowel cancer and between 11 and 36% for pancreatic cancer, respectively). There is also an increased risk of non digestive cancers. In particular the risk of breast cancer is similar to that of patients carrying deleterious BRCA1 or BRCA2 mutations (cumulative incidence of 45%). Gynecological and gonadal tumors are frequent as well and can be more (adenoma malignum) or less aggressive (ovarian sex cord tumors with annular tubules and testicular tumors with calcified Sertoli cells). Finally the frequency of lung cancer is moderately increased. Recommendations for screening and management based on retrospective series in the literature have led to various strategies. The aim of this paper is to summarize the clinical and molecular diagnostic criteria of PJS as well as recommendations on screening strategies, management and monitoring.

Vaklavas, C., et al. (2012). "By the pricking of my thumbs, something wicked this way comes: sporadic cancers versus eponymous hereditary cancer predisposition syndromes." J Natl Compr Canc Netw **10**(1): 7-13.

Advances in cancer genomics have led to the recognition of a growing number of high-penetrance single-gene cancer predisposition syndromes. Frequently, the suspicion for a hereditary syndrome is raised by a strongly positive family history. However, other features, such as younger-than-usual age at diagnosis and rare histology should also prompt consideration of a genetic syndrome. Common malignancies frequently show a positive family history without an eponymous syndrome being recognized. This article reports on a case with an unusual constellation of malignancies with distinctive pathologies, which raised suspicion for an eponymous cancer pre-disposition syndrome. Absent a positive family history, a de novo mutation-an alteration in a gene that is present for the first time in a family member as a result of a mutation in a germ cell of one of the parents or in the fertilized ovum-was suspected. The authors discuss indications for genetic counseling and testing, limitations, and the evidence that supports the recommendations as formulated by working groups and the NCCN. Most frequently, these recommendations are reasonable statements based on the natural history of the disease, but without population-based studies for many rare syndromes, the actual penetrance, variable expressivity, and actual associated cancer risk are unknown.

Yagi, O. K., et al. (1998). "Proapoptotic gene BAX is frequently mutated in hereditary nonpolyposis colorectal cancers but not in adenomas." Gastroenterology **114**(2): 268-274.

BACKGROUND & AIMS: The p53 and BAX genes have been linked to apoptosis. p53 was not frequently found to be mutated in colorectal carcinomas with a microsatellite mutator phenotype, but frame-shift mutations in a tract of eight guanines within BAX were frequently found in these carcinomas. To understand the roles of these genes in hereditary nonpolyposis colorectal cancer (HNPCC) tumorigenesis, we examined whether BAX mutations occur in adenoma and carcinoma specimens from patients with HNPCC and also determined the frequencies of p53 mutations. METHODS: Thirteen colorectal adenomas and 24 adenocarcinomas from patients with HNPCC showing a microsatellite instability phenotype were screened by polymerase chain reaction followed by denaturing polyacrylamide gel electrophoresis and direct sequencing. RESULTS: Two of the 13 adenomas (15.4%) and 13 of the 24 adenocarcinomas (54.2%) showed mutation patterns and were confirmed to have frame-shift mutations at the BAX repeat site by direct sequencing. For p53, only 1 of the 24 adenocarcinomas (4.2%) showed a missense mutation. CONCLUSIONS: In HNPCC colorectal carcinomas, BAX was significantly ($P = 0.024$) more mutated than in adenomas. p53 was not frequently found to be mutated in these carcinomas. These data suggest that mutations in BAX, rather than mutations in p53, may contribute to the adenoma-carcinoma transition in HNPCC tumorigenesis.

Yamasaki, Y., et al. (2010). "Patient with eight metachronous gastrointestinal cancers thought to be hereditary nonpolyposis colorectal cancer (HNPCC)." Intern Med **49**(3): 209-213.

An 81-year-old woman presented with a chief complaint of swelling of both lower legs. She had a history of surgery for cancers of the stomach, rectum and colon. Among her immediate family members, her son had colon and rectal cancers, and her sister had ovarian cancer. After close examination the patient was diagnosed with small intestine cancer and ascending colon cancer. Gene mutation analyses did not reveal any mutations in DNA mismatch repair genes, but MSH-2 protein expression was lost only in the cancer

lesions. Here, we report this rare case of eight metachronous gastrointestinal cancers thought to be HNPCC.

Zbar, B. (1992). "The biology and genetics of hereditary cancers." Semin Oncol Nurs **8**(4): 229-234.

Hereditary cancer syndromes are generally produced by the inheritance of a single mutant gene. New tools have been developed that enable research workers to locate the defective genes responsible for the inherited forms of cancer. Once a disease gene has been localized, it may be possible to identify individuals who have inherited the disease gene before cancer develops.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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