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GENETIC PREDISPOSITION TO CANCER

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Summary

Genetic factors are known to play a major role in the etiology of cancer. In hereditary cancers, germ line gene mutations have been identified which strongly predispose individuals to cancers. These gene mutations have a high penetrance conferring an elevated risk (>90%) of developing the disease. Although these cancers are rare they have been well studied. On the other hand, the more abundant sporadic cancers are caused due to interaction of low penetrance genes with the environment. There is a cumulative effect of several low penetrance genes which, in the presence of carcinogens, predispose the individual to cancer. As a consequence of the germ line gene mutations / polymorphisms there are further somatic mutations resulting in activation of oncogenes / loss of tumour suppressor genes leading to genetic instability which is the hallmark of cancer. Once initiated, the cancer accumulates further genetic lesions in the form of oncogenes and tumour suppressor genes which play a crucial role in the progression of the disease. Genetic predisposition to breast and colorectal cancers are discussed in the review.

Key words : low penetrance genes, mutations, polymorphisms, breast cancer, colorectal cancer

Introduction:

Cancer is a complex, multistep process involving changes in the genome. It was discovered in late 1980s that genes in their mutant forms were inherited in affected families (1). Gain of function mutations (oncogenes) or loss of function mutations (tumour suppressor genes) led

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to the initiation of cancer. This formed the genetic basis for cancer predisposition. Many cancers arise from germ line mutations in proto-oncogenes and tumour suppressor genes which regulate cell proliferation and apoptosis such as p53 associated with Li Fraumeni syndrome (2,3) and RB1 associated with childhood retinoblastoma (4). There can also be mutations in genes responsible for maintaining genetic stability which includes DNA repair genes such as BRCA1 (5) and BRCA2 (6,7) both associated with breast and ovarian cancers and Mismatch Repair (MMR) genes associated with hereditary non-polyposis colorectal cancer (8,9). Following these inherited or spontaneous mutations, there is a sequential accumulation of mutations in the oncogenes and tumour suppressor genes leading to genetic instability and cancer. However, individual susceptibility is determined by a complex interaction between the germ line genetic variation, which constitute low penetrance genes, and exposure to environmental carcinogens. Mutations disrupt several molecular pathways in the cell and lead to self-sufficiency in growth signals, insensitivity to growth-control signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, invasion and metastasis (10,11). Some of these genetic lesions, which are high penetrance genes, are present in the germ line and predispose individuals to cancer.

Low penetrance genes are associated with sporadic cancers and are more difficult to study than high penetrance genes. To gain sufficient evidence to prove that a gene is involved in cancer predisposition, it is probably necessary for multiple, adequately-powered studies to demonstrate an association with the disease, especially if the allelic variants have only a small differential effect on risk. It may also be possible to show how genes interact with each other and the environment, although this will be even more difficult (12). We and others have proposed that there is a cumulative effect of a number of low penetrance genes which together confer high risk for certain cancers (13).

Genetic predisposition to breast cancer by rare, high penetrance alleles:

Familial clustering of breast cancer has been known for decades although the genetic basis was proven only recently. Familial breast cancer constitutes only 5-10% of all breast cancers out of which only ~20% are due to the well studied, high penetrance, BRCA1/2 genes (11). Almost 25% of familial breast cancers are due to unknown familial predisposing genes. BRCA proteins function in damaged DNA repair. Inherited mutations in BRCA1/2 genes confer high risk of breast, ovarian, prostate and colorectal cancers. However, unlike BRCA1 although BRCA2 confers a high risk to breast cancer it does not confer a high risk to ovarian cancer (6). Germ line mutations of p53 gene strongly predispose individuals to Li Fraumeni Syndrome which includes breast cancer

and other neoplasms (14). Individuals carrying BRCA1 and BRCA2 gene mutations are at an increased risk of breast cancer if exposed to X-rays since BRCA protein plays a role in DNA repair (15). Selecting for breast cancer cases with a strong familial background not accounted for by BRCA1 or BRCA2 show a strong association with mutation in a cell cycle check point kinase CHEK2*1100delC (16).

Low penetrance genes in sporadic breast cancer

A large proportion of breast cancers have unknown polygenic predisposing genes along with varying environmental factors (11). The identification of susceptibility factors that predispose individuals to breast cancer could give further insight into the etiology of this malignancy and provide targets for the future development of therapeutics. The candidate low penetrance genes with a variety of functions including carcinogen metabolism, DNA repair, steroid hormone metabolism, signal transduction, and cell cycle control need to be studied (17).

Female breast cancers are known to be associated with prolonged exposure to estrogens. Estrogens are known to influence breast cancer risk by interacting with estrogen receptors. Inter-individual variability due to polymorphisms in DNA sequence, associated with prolonged exposure to increased levels of estrogen, may define a sub-set of women with breast cancer (18-20). Oxidative metabolites of estrogen are known to cause DNA damage (20). Polymorphisms in genes involved in estrogen biosynthesis, and the conversion of estrogen metabolites and their by products could be the low penetrance genes conferring risk in the etiology of sporadic breast cancers. $Leu^{84}Phe$ polymorphism affects the capacity of O-Methyl Guanine Methyl Transferase (MGMT) to inhibit estrogen receptor-mediated cell proliferation and is associated with breast cancer risk (21). All these low penetrance genes could play a role either alone or in combination on exposure to exogenous or endogenous estrogens, in predisposing women to cancer.

Increased expression of Transforming Growth Factor β (TGFβ) plays a role in breast cancer progression. A functional polymorphism in the promoter region of TGFβ gene has been shown to increase breast tumour progression and metastasis (22). aThere are reports that DNA repair gene polymorphisms are important biomarkers for sporadic as well as familial breast cancer susceptibility (23). It has also been reported that RAD51 polymorphism in carriers of BRCA2 mutations are at a significantly elevated risk for breast cancer (24). In addition to endogenous factors, life-style factors such as smoking and alcohol use could contribute greatly to sporadic breast cancers.

Genetic predisposition to colorectal cancer by rare, high penetrance alleles

The incidence of colorectal cancer (CRC) in India is low compared to western

countries (25), although there are a large number of patients seen. The lifetime risk of colorectal cancer (CRC) in the general population is ~5%. Of all the CRCs ~5% are hereditary cancers. Germ line mutations in the DNA mismatch repair genes are known to be associated with genetic instability leading to Hereditary Non-Polyposis Colorectal Cancer (HNPCC) also known as Lynch Syndrome (~2-4% of all CRC) (26). In individuals with HNPCC mutations the risk is greater than 70%. Similarly in individuals with mutation in the gene Adenomatous Polyposis Coli (APC, ~1% of all CRCs) the risk of developing Familial Adenomatous Polyposis (FAP) is greater than 70%. The risk of CRC increases if there are affected members in the family. Mutations in APC are not only responsible for FAP but also play a rate-limiting role in sporadic CRC (27). Genetic testing is routinely being used in the west to detect HNPCC and FAP. Microsatellite Instability (MSI) testing detects alterations in the genome and is characteristic of HNPCC although it is also seen in 10-15% of sporadic CRC. In families with a moderate history of cancer, the presence of MSI indicates the likelihood of HNPCC. There is also a commercially available test which determines whether or not a person has a mutation in the MMR genes MLH1 and MSH2 gene.

Low penetrance genes in CRC

A large number of studies have reported that common genetic variations in low penetrance genes confer risk of CRC. Inherited predisposition to CRC is in part mediated through polymorphic variation (28). Houlston and Tomilson (29) carried out a metaanalysis of 50 studies where polymorphisms in 13 genes had been studied and concluded that only 3 - APC-I1307K, HRAS1-VNTR and MTHFR variants represented the strongest candidates for low penetrance susceptibility alleles for CRC (29). APC-I1307K – a germ line missense mutation, is common in Jews from Eastern Europe and has been reported to confer a two-fold increased risk to CRC (30). So also, biallelic mutations in MYH gene are associated with an attenuated FAP phenotype (30). Low-penetrance genes such as TGFBR16A may account for a sizable proportion of familial colorectal cancer occurrences (31).

Diet in association with genetic variations, has been reported to play a major role in CRC. Polymorphism in the gene CD36 which plays a role in metabolism of oxidized low density lipoprotein and long chain fatty acids is positively associated with CRC in individuals with moderate-high meat consumption (32). Folate metabolism supports the synthesis of nucleotides as well as the transfer of methyl groups. Polymorphisms in folate-metabolizing enzymes have been shown to affect risk of colorectal neoplasia and other malignancies (33).

Hereditary breast and colorectal cancer (HBCC):

HBCC has been observed in a subset of breast cancer patients. The

1100delC variant in the cell cycle check point kinase gene CHEK2 was found to be present in 18% of 55 of HBCC patients as compared to 4% of 380 non-HBCC families (34). Although it is not the major predisposing factor for the HBCC phenotype, it appeared to act in synergy with other, as-yet-unknown susceptibility gene(s) (34,35). Another low penetrance gene, STK15 (Aurora-A) which is a serine/threonine kinase and involved in mitotic chromosomal segregation has been associated with breas and colon cancer. A genetic variant in STK15 T+91A (resulting in the amino acid substitution F31I) shows an increased risk of colon as well as breast cancer (36).

Conclusion:

A large number of tests are available for genetic screening and genetic screening has tremendous implications in patient management. Gene-environment interactions have a major role in susceptibility to majority of sporadic cancers. Our current understanding of these interactions is limited, and concerted research efforts in this area will be important for a full understanding of predisposition to cancer (26). When mutations are detected, specific cancer screening and follow up programs should be offered to mutation carriers, which could prove to be profitable in terms of cost-effectiveness when compared to standard care.

Individuals found to be carriers can be offered:

- counselling to avoid environmental exposures that further elevate risk,
- intensive medical surveillance for early detection,
- participation in chemoprevention trials, and
- prophylactic surgery to remove at-risk tissues.

Clinical cancer genetics should become an integral part of cancer management.

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