MINI REVIEW

Genetic predisposition to cancer

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ABSTRACT

A number of genes linked to cancer predisposition have been discovered in recent decades. Some of them create autosomal dominant monogenic cancer predisposition syndromes, which are extremely rare. The higher cancer incidence is attributable to a complex etiology in the majority of families, with a number of lower penetrance cancer predisposition genes interacting with environmental variables. Genetic testing, enhanced surveillance, preventive surgery, and chemoprophylaxis may be recommended for persons at elevated risk of cancer due to a family history of cancer. The difficulties underlying cancer genetic predisposition are examined in this article by looking at two common cancers: colorectal and breast cancer. Although the genetic nature of cancer has been known for over a century, the inherited features of cancer susceptibility have just recently become more fully defined. Compared to only a small minority twenty years ago, nearly half of all referrals to genetics centres are now for cancer susceptibility testing. Families with numerous individuals affected by a rare disease, sometimes accompanied by other phenotypic anomalies, have been the focus of studies on familial aspects of cancer.

Key Words: *Breast cancer; Colorectal; Genes; Hereditary*

INTRODUCTION

Typical familial cancer constellations or an overabundance of specific 'common malignancies,' especially in children and teenagers. According to epidemiological research, the presence of cancer in one family member increases the empirical risk of the same or related cancers in relatives, with the degree of risk varying depending on the age of diagnosis and the number of affected relatives on the same side of the family. The genes underlying some monogenic syndromes of cancer predisposition have been identified through linkage studies in families with several close relatives who have been diagnosed with the same cancer type. Some of them are cancer-specific predisposition syndromes, whereas others are rare inherited multisystem illnesses. A particular phenotype, such as facial dimorphism, neurological illness, or other traits, is associated with cancer propensity. Cancer predisposition syndromes caused by a single gene are uncommon, accounting for just a small percentage of familial clusters of prevalent malignancies. The impacts of numerous fewer penetrant genes combined with environmental conditions are more likely to cause familial predisposition. These higher frequency lesser penetrance candidate genes for prevalent malignancies are being sought. The distinction between inherited and sporadic malignancies will become a spectrum rather than a binary when the members of the orchestra of interacting propensity and protective genetic variables are identified. The advancement and broad availability of inexpensive microarray technology may one day make customized risk profiling for many cancer types available to the general public. The genetic and molecular processes of these cancer risk genes are becoming well understood. Genes linked to cancer susceptibility Germline mutations in tumour suppressor genes or oncogenes are the most common causes of inherited cancer predisposition. Tumour suppressor genes are genes that prevent tumours from growing. Tumour suppressor genes are engaged in preventing neoplastic processes and can act in a variety of ways: Gatekeeper genes (traditional tumour suppressors) regulate basic cell

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activities and control cell cycle, proliferation, differentiation, and apoptosis, limiting cell growth [1,2].

DNA mistakes are corrected and repaired by caretaker genes. Landscaper genes are involved in the regulation of the cellular microenvironment. Proto-oncogenes encode proteins such as growth factors, growth factor receptors, membrane-associated signalling proteins, or transcription factors, and they are activated during cell growth in response to the stimulation of growth promoters. Proto-oncogenes are transformed into oncogenes through retroviral activity, mutation, chromosome rearrangement, or amplification. The protective controlling 'brake' function of a tumour suppressor gene is lost when it is mutated. When an oncogene is turned on, the 'accelerator' function is turned on as well. In both cases, mutations in the gene result in an increased tendency for uncontrolled cell replication and, as a result, cancer. The classic two-hit hypothesis states that cancer predisposition syndromes are genetically 'dominant' at the family level but'recessive' at the cellular level. The propensity is inherited as a dominant trait since only one mutant allele is handed down. Tumor development, on the other hand, necessitates the presence of two mutated alleles. The second hit is a somatic mutation in the wild-type gene, which causes biallelic mutations in that cell, gene loss, and uncontrolled replication of a subsequent clone of tumour cells. . Somatic mutations in these genes are frequently found in tumour tissue from sporadic cancers, in addition to germline mutations that cause inherited syndromes. Breast cancer is a type of cancer that affects for women the lifetime population risk of BC is about 11% which is influenced by hormone-related factors like menarche age, menopause, parity, lactation, and the use of exogenous hormones. Over 50 epidemiological studies have found a higher risk of BC in a relative of someone who has been diagnosed with the disease. One of the largest case-control studies evaluating familial BC risk, the Cancer and Steroid Hormone (CASH) research, has generated the widely-used Claus model and related risk estimation. The number of cases in a family, the age at which the affected persons were diagnosed, and the proximity of the link all influence an individual's chance of developing BC. A positive family history increases the risk of cancer in BC. Monogenic cancer predisposition syndromes cause a minor percentage of BC. BRCA1 and BRCA2 are tumour suppressor genes that are found on the 17th and 13th chromosomes, respectively [3-5].

Extrapolating from current detection rates, mutations in BRCA1 and BRCA2 are thought to account for 1%-2% of all BC cases. In carriers of these mutations, the lifetime risk of BC is up to 80%, and the lifetime risk of Ovarian Cancer (OC) is up to 60% for BRCA1 and 40% for BRCA2. Surveillance and prophylactic measures are recommended due to the high risk of developing BC and OC, especially in children. From early adulthood, annual mammography is recommended, though the risks of radiation exposure must be considered. The MARIBS project is assessing Magnetic Resonance Imaging for Breast Screening in high-risk women. The UKFOCSS study is currently evaluating ovarian screening using transvaginal ultrasound and serum tumour marker (*CA-125*) estimations. Tamoxifen chemoprophylaxis may lessen the incidence of BC in BRCA mutation carriers however it is still being studied. The IBIS II research looks at the role of aromatase inhibitors as a prophylactic treatment for postmenopausal women with a family history of BC. Prophylactic mastectomy reduces the chance of mutation carriers significantly, although it may come with psychological and cosmetic consequences. In premenopausal women, oophorectomy reduces the odds of BC and OC by roughly 50% and 90%, respectively (although there is a residual risk of peritoneal cancer in the latter). *BRCA* mutation carriers are also at a higher risk of developing other malignancies. However, the absolute risks are so low that prostate cancer is the only other malignancy for which surveillance is commonly recommended the Impact trial is evaluating annual prostate screening in male mutation carriers. There are a few other uncommon factors of breast cancer susceptibility. Li-Fraumeni Syndrome (LFS) is a rare autosomal dominant cancer predisposition condition caused by germline mutations in *TP53*, a tumour suppressor gene known as "the guardian of the genome" that regulates the cell cycle checkpoints. In somatic tissue from sporadic tumours, *TP53* is usually mutated. Germline *TP53* mutations are uncommon, accounting for fewer than 1% of early-onset or familial BC cases. By the age of 60, a woman with LFS has a 90% chance of developing BC, and it can happen early, typically before the age of 30. 10 Childhood sarcomas, brain tumours, and adrenocortical carcinoma, as well as pancreatic cancer, are all linked to LFS. Many additional tumours have also been found to be more common in LFS than in the overall population, according to studies. Cowden Syndrome (CS) is an autosomal dominant disorder caused by germline mutations in the tumour suppressor gene *PTEN*. It is linked to benign and malignant breast, thyroid, and endometrial tumours. Women with CS have a 20%-50% lifetime risk of breast cancer. Multiple harmatomas, such as harmatomatous intestinal polyps and, less occasionally, skin, renal cell, and brain tumours, can form. Mucocutaneous lesions, such as facial trichilemmomas and papillomatous papules, acral keratoses, and the scrotal tongue, are common in CS. Thyroid pathology might be benign or cancerous in up to 75% of CS patients. Progressive macrocephaly and developmental delay are common in children with CS. Breast and endometrial screening, as well as skin and thyroid clinical surveillance, are all suggested. Mutations in the *ATM* gene cause ataxia telangectasia, a rare genetic disease. AT patients have a 100-fold increased risk of *BC* over their lifespan and a 100-fold increased risk of haematological malignancies. AT is linked to neurological problems such as developmental delay, truncal ataxia, extrapyramidal movement abnormalities, and oculomotor apraxia. Immunodeficiency and conjunctival and cutaneous telangectasiae are common symptoms. Carriers of a single germline mutation in the *ATM* gene appear to be 3 times-4 times more likely to develop *BC*. Only approximately 5% of BC is caused by these well-known cancer propensity genes. The presence of *BC* in other families could be attributable to the interaction of numerous less penetrant genes with environmental factors or to rarer, as yet unidentified, extremely penetrant monogenic predisposition genes. Heterozygosity for some *ATM* mutations, for example, may result in a significantly elevated risk of BC. *CHEK2* is a low penetrance *BC* predisposition gene that encodes a protein that interacts with *TP53* and *BRCA1*. It is thought to confer a two-fold greater risk in women. *HRAS1* is an oncogene found on the *11p15* chromosome, and specific mutations in this gene have been linked to an increased risk of breast cancer. There may be common environmental factors that contribute to susceptibility within families. Guidelines for the care of women with familial BC from the National Institute of Health and Clinical Excellence. Colorectal cancer is a type of cancer that affects the colon. Colorectal Cancer (CRC) is one in every 25 men and one in every 30 women in

the United Kingdom. Age, obesity, low socioeconomic position, and diet are all non-genetic risk factors for CRC. Relatives of CRC patients have an elevated empirical risk, according to epidemiological studies. The relative risk of colorectal cancer for a first-degree relative of an affected person is estimated to be between 1.9 and 7.5. Individuals with a monogenic colon cancer risk syndrome are considered to account for 5%-10% of colorectal malignancies. Cancer progression is aided by genes involved in DNA repair, cell cycle control, and cell death. Inherited mutations in the same genetic pathways that mutated somatically in cancer progression frequently increase cancer predisposition. Because novel mutations are rare and highly penetrant, early-onset mutations are frequently eliminated by natural selection, serious propensity to early-onset cancer is uncommon. The majority of hereditary cancer predisposition effects result from a mixture of several distinct mutations, with each mutation having only a minor impact on the likelihood of developing cancer. Families with a significant hereditary inclination for breast cancer get the disease at a younger age, but the disease has a lesser increase in incidence with age than families without the tendency. Families with a cancer propensity may begin the cancer progression earlier than other families, maybe because they inherit particular mutations that must be acquired somatically in other families. The normal mechanisms that control cell proliferation and death provide strong anti-cancer protection. This resilience also defends against harmful mutations while allowing cancer-predisposing alterations to become more common [6,7].

CONCLUSION

The recognition of a family history of cancer has been crucial to research and clinical care. The study of cancer families has discovered candidate genes whose roles illuminate mechanisms of oncogenesis and aid in the creation of therapeutic options, according to the research forum. In the clinical setting, families with a high cancer incidence can be found and genetic testing, surveillance, and preventative surgery can save lives. Surveillance is especially useful for detecting malignancies early in people who have been identified as having a significantly higher risk according to their family history. As a growing number of low penetrance cancer risk genes are identified, providing genetic testing, interpreting the results, and allocating appropriate surveillance will become a burden for individual clinicians and a complicated issue for healthcare providers. Within the United Kingdom, cancer surveillance protocols and services differ. With growing public awareness and the likely development of a wider range of genetic testing, less intrusive surveillance modalities, and possibly genetically-targeted chemoprophylaxis, the need for cancer predisposition evaluation is expected to skyrocket. On the public health agenda, service development should be a top priority.

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