Genetic predisposition to cancer

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Abstract

Over the last 28 years there has been a burgeoning development of genetic risk assessment and 'family history' clinics to deal with the ever-increasing demand from individuals at increased risk of cancer by virtue of their family history. Risk of inherited cancer can be divided into known syndromes, such as familial polyposis, and increased risk of common cancers due to family history alone. Risk of cancer can be assessed in three categories: average, moderate and high. Individuals at high risk or at risk of syndromes will generally be referred to a regional genetics centre. Moderate-risk individuals may benefit from early surveillance in secondary care, particularly for breast and colorectal cancer. Average-risk individuals can be reassured in primary care. Newer surveillance techniques such as magnetic resonance imaging are now being approved for high-risk categories. Genetic testing for a minority of high-risk individuals is now routine practice and surgical management options have gained validity. Much research is still necessary to improve early detection and develop non-surgical means of prevention.

Keywords *APC*; *BRCA1*; *BRCA2*; breast cancer; familial polyposis; oncogene; tumour suppressor gene

What's new?

- Licensing of gene-based treatments, such as poly (ADP-ribose) polymerase inhibitors
- The 100,000 Genomes Project to identify remaining inherited components by genome sequencing
- Better risk prediction, in common cancers such as breast, colorectal and prostate, using multiple validated common single-nucleotide polymorphisms and gene panel testing

Introduction

There has been increasing evidence of familial predisposition to cancer since the classic model of hereditary retinoblastoma was outlined.[1] The earliest reports of cancer families date back 200 years to a large cluster of breast cancer in the family of the French physician Broca, and a cluster of gastric cancer in Napoleon's family. Despite the pioneering work of clinicians and researchers such as Henry Lynch and Mary-Claire King in the 1960s–1980s, demonstrating the hereditary nature of at least a proportion of cancers (e.g. breast, colon), the hereditary element was not proven until the advent of molecular biology, when abnormalities were demonstrated in cancer-predisposing genes. Only in the last 28 years, therefore, has the hereditary nature of a small proportion of certain common cancers been proven. (See *The Biology of Cancer* on pages 1–5 of this issue for further reading.)

Molecular basis of cancer

That cancer is 'genetic' at the cellular level is now beyond dispute. All tumours result from mutations of either tumour suppressor genes (TSGs), which need to be inactivated to enable growth, or oncogenes, which require activation to promote growth. The majority of these genetic events are acquired, as a result of replication error (in simple copying of DNA during cell division), exposure to external agents (radiation, chemicals, viruses) or epigenetic factors such as ageing, which increase gene silencing through methylation. Nonetheless, recent evidence has confirmed that predisposition to cancer involves a polygenic pattern with multiple common gene variations associated with small elevations in risk.

Inherited cancer

Occasionally, mutations in TSGs can be inherited rather than acquired. Identifying the genes that cause hereditary disease has given insight into many cancers. The role of cancer-predisposing genes in the causation of sporadic cancer is still being widely researched, but much can be learnt from cancer-prone syndromes.

Broadly, predisposition can be subdivided into rare genetic syndromes, which have malignancy as a high-risk adverse effect, and a larger group that cannot be easily identified clinically, which have a strong family history of one or more common malignancies. Identifying patients with genetic predisposition to cancer is becoming important in treatment selection, as the genetic abnormality underlying their cancer may predispose them to enhanced treatment-related toxicity, especially if DNA damage and repair pathways are affected. Screening of other family members may also be relevant.

Retinoblastoma

Retinoblastoma is the model from which much of our current knowledge of TSGs has been gained. A familial tendency to this early childhood eye malignancy was recognized in the 19th century. About 50% of cases result from inheritance of a gene defect in one copy of the retinoblastoma gene (*RB* on chromosome 13), and over 90% of individuals who carry a mutation develop retinoblastoma, usually bilaterally. In 1971, Knudson proposed that tumour development requires mutational events in both copies of the gene.[1] Individuals who inherit a mutated copy need only one further mutation and are far more likely to develop the malignancy, which occurs at a younger age and is usually bilateral. Sporadic cases require two mutations ('hits') in a retinal cell rather than one (Figure 1), so bilateral tumours are unlikely to occur and the unilateral tumours present later. This hypothesis, which has since been validated in other conditions, now bears the originator's name.

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Ideagram of the 'two hit' hypothesis

The first hit is usually a mutation (represented by a cross) which causes disruption of the protein product. The second hit is often loss of the whole gene by deletion of part or all of the chromosome on which the gene resides.

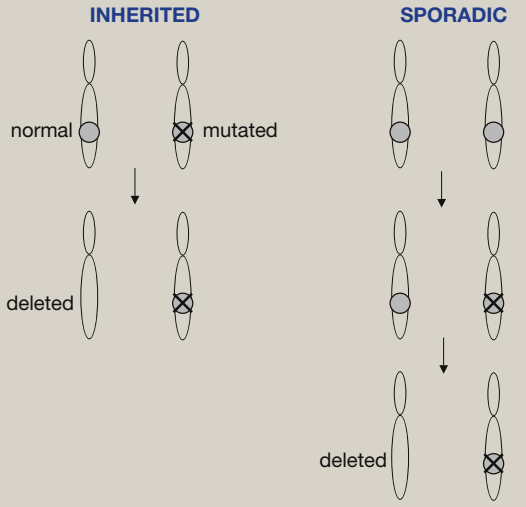

Figure 1

The route to discovering cancer genes

The discovery of retinoblastoma cases with constitutional deletions of chromosome 13 visible under the microscope concentrated research on that region. *Esterase D*, which was deleted, acted as a genetic marker for further studies. The gene for retinoblastoma was eventually localized and identified by gene linkage analysis in 1986. This same approach using chromosome studies of individuals, their tumours and genetic linkage have led to the discovery of nearly all high-risk genes that cause cancer predisposition (Table 1). Most of these genes and their products (proteins) were found in a heady 6-year period between 1989 and 1995. The last 20 years has seen progress towards understanding how these genes function through their protein products, and development of the first line of gene-based treatments, such as trastuzumab, imatinib and a new breed of synthetic lethal drugs, the poly (ADP-ribose) polymerase (PARP) inhibitors, to treat *BRCA1/2*-related cancers (see *Targeted Therapy in Cancer* on pages 34–38 of this issue). Much of the remaining inherited component has been unpicked in the last 8 years by genome-wide association studies to find lower risk genetic components.[2]

Genetic syndromes

These are usually readily identifiable by a clinical phenotype (group of associated clinical features) or laboratory tests. The syndromes may be autosomal dominant, recessive or X-linked (Tables 1 and 2). Although the conditions are generally uncommon, the TSGs involved also play a fundamental role in the genesis of sporadic tumours, which affect 35–40% of people in the developed world. The identification of genetic syndromes has led to genetic-based therapies, as well as earlier identification, monitoring and, most hopeful of all, prevention of common cancers.

Familial adenomatous polyposis (FAP)

FAP has been the model for transposing knowledge of a rare genetic disease to a commonly occurring cancer. FAP is an autosomal dominant condition characterized by development of hundreds to thousands of adenomatous polyps in the colon and rectum, usually by 30 years of age. Untreated, this leads to the almost inevitable development of a colorectal cancer by the age of 60 years. The condition is associated with osteomas, epidermal cysts and increased risks of other malignancies such as duodenal cancer, hepatoblastoma, glioma and thyroid cancer.

The gene for FAP (*APC*) was localized to 5q21–q22 and identified in 1991. FAP was one of the first conditions to show a clear-cut correlation between genotype (genetic changes in *APC*) and phenotype (clinical picture). Patients with mutations in the early part of the gene (5′, exons 2–5) had a mild clinical picture with late-onset polyps, whereas those with mutations from exon 9 through to codon 1450 of exon 15 had classical disease, with nearly all patients manifesting typical congenital retinal pigmentation. However, those with mutations beyond codon 1450 showed typical features of Gardner's syndrome (osteomas, cysts, desmoid disease) without retinal signs, and also mild polyp disease.[3] The *APC* gene is of fundamental importance in the majority of 'sporadic' colorectal cancers, although the acquired loss of both functioning copies of the gene is required. Use of genetic registers and genetic testing to target screening, along with appropriately timed removal of the colon, has led to an improved life expectancy in FAP of 15–30 years.[4]

Other dominant tumour syndromes

A number of other important dominantly inherited conditions are now well outlined clinically and genetically. von Hippel–Lindau (vHL) syndrome predisposes to retinal angioma, cerebellar haemangioblastoma, renal cell carcinoma and phaeochromocytoma. The neurofibromatoses, which consist of three subtypes, NF1, NF2 and schwannomatosis, carry an increased risk of mainly benign nervous system tumours. In the chief NF1 malignancy, the predominant tumour, the neurofibroma, is associated with at least a 10% lifetime risk of developing malignant peripheral nerve sheath tumours that are usually fatal. The second type, NF2, is largely associated with schwannomas and meningiomas, most individuals becoming deaf from bilateral VIIIth cranial nerve involvement. Gorlin's syndrome is characterized by multiple jaw keratocysts and basal cell carcinomas as well as a 2–5% risk of childhood medulloblastoma. In the multiple endocrine neoplasias, MEN1 affects the parathyroid glands, pituitary and pancreas, and in MEN2 patients develop thyroid medullary carcinoma and phaeochromocytoma.

All these conditions have benefited from gene identification and targeted screening that, in most cases, improves life expectancy.[4] This may mean intervention in childhood: in MEN2, the thyroid is removed preventively.

Common cancer predisposition

Most cancers require a number of genetic changes in a cell before an invasive tumour results. This number probably varies between four and 10, and few cancers are likely to be caused purely by the loss of two copies of a single TSG, as in retinoblastoma. A combination of loss of function of TSGs and oncogene activation is usually involved. The combination and order may alter the