

Review Article

Familial Cancers

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ABSTRACT

Although cancer is common in the general population, only a small proportion is thought to be due to highly penetrant cancer genes. Families with a highly penetrant cancer predisposing gene may be recognised by the presence of a high number of individuals within the family with a particular cancer type, or individuals with features associated with rare inherited cancers, such as

retinal changes or multiple colonic polyps. It is likely that there are many other less penetrant genes, which, in combination with environmental influences, will confer a greater lifetime predisposition to cancers. These genes are currently being identified through epidemiological studies.

KEY WORDS: BRCA1, BRCA2, cancer genes, screening, management

INTRODUCTION

Cancer is common in the general population, with one in three of the population in the Western world affected at some point in their lives. It has been noted that there are some families with a higher number of certain cancers than would be expected, and in some of these families these cancers have been found to segregate with mutations in particular genes.

COMMON FAMILIAL CANCER SYNDROMES

The following syndromes, although described as 'common familial cancer syndromes', are rare in the general population, accounting for only around 5 to 10% of all cancers. Families with a highly penetrant cancer predisposing gene may be recognised by the presence of a high number of individuals within the family with a particular cancer type, or individuals with features associated with rare inherited cancers, such as retinal changes or multiple colonic polyps. It is likely that there are many other less penetrant genes which, in combination with environmental influences, will confer on an individual a greater lifetime predisposition to cancers. These genes are currently being identified through epidemiological studies.

BREAST AND OVARIAN CANCER

It appears that around 5% of breast and ovarian cancers are related to highly penetrant mutations in the BRCA1 and BRCA2 genes. Other genetic disorders that may predispose to breast cancer are listed in Table 1.

Molecular aspects

About 35 per cent of breast cancers occurring in women under the age of 35 years may be due to highly penetrant dominant genes, falling to one per cent of those over 80 years. It has been recognised for many years that there is an association between breast and ovarian cancer. Two genes have so far been implicated in the pathogenesis of breast and ovarian cancer: BRCA1 localised to chromosome 17q21^[1] and BRCA2 localised to chromosome 13q12-13^[2,3], both of which appear to be tumour suppressor genes. Mutations in these genes result in a loss of function, allowing uncontrolled cellular proliferation.

Mutations in the BRCA1 gene have been linked to around half of all cases of autosomal dominant breast and ovarian cancer families. Information is now accumulating about the penetrance of the BRCA1 gene. In some families, the disease allele confers a breast cancer risk of 70 to 91% and an ovarian cancer risk of 32 to 84% by age 70 years. In addition, gene carriers have a six per cent risk for developing colon cancer by age 70 years, and male gene carriers also have an 8% risk of developing prostate cancer by the same age^[4]. A correlation has been noted between the position of the mutation within the gene and the ratio of breast cancer to ovarian cancer within a family, a lower proportion of ovarian cancer occurring with mutations in the 3' third of the gene^[5].

It is thought that less than half of hereditary site-specific breast cancer families are linked to mutations in the BRCA2 gene. Other cancers have

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Table 1

Genetic disorders associated with breast cancer susceptibility

1. Site-specific hereditary breast cancer
2. Breast/ovarian cancer
3. Li-Fraumeni syndrome
4. Cowden disease
5. Peutz-Jegher syndrome
6. Ruvalcaba-Myre-Smith syndrome
7. Klinefelter syndrome
8. Ataxia-telangiectasia syndrome

also been reported in BRCA2 families, especially male breast, ovarian, prostate and pancreatic cancers^[6]. There appears to be an ovarian cancer 'hot-spot', the ovarian cancer cluster region, in exon 11 of BRCA2^[7].

Four distinct recurrent mutations have been found in the Ashkenazi Jewish population (of Eastern European origin)^[8,9]. Three occur in BRCA1: 185delAG and 188del11 in exon 2, and 5382insC in exon 20. In BRCA2, there is a further common mutation 6174delT in exon 11. It is thought that the frequency of breast cancer susceptibility mutations in this population probably exceeds 2%.

BREAST CANCER

Calculation of risk for breast cancer is more difficult in families where there is not a clear-cut Mendelian genetic predisposition. Empirical risks for breast cancer can be calculated on the basis of the age at diagnosis of breast cancer in a first degree relative, based on studies carried out in the UK and USA^[10,11], and figures have also been produced for the relative risks to individuals with more than one affected relative.

Screening

At present, many centres throughout the UK and Europe are offering extra mammographic screening to those individuals thought to be at a high risk of developing breast cancer, although the minimum level of risk at which this is offered varies between centres (usually a lifetime risk of greater than 16% or twice the population risk). The frequency of screening also varies between centres, the majority offering mammograms once every one or two years. Most centres will not offer screening mammograms to women under the age of 35 years because mammograms performed on the denser breast tissue occurring in younger women are harder to interpret. There is also some indication that proliferating cells in the breasts of young women may retain damage due to exposure to radiation or are more susceptible to carcinogens^[12,13].

Prophylactic surgery

Prophylactic mastectomy in women who carry a

cancer causing mutation has been shown to produce a significant reduction in morbidity and mortality from breast cancer^[14,15]. However, women should be carefully counselled before taking this option. Referral to a plastic surgeon for reconstructive surgery should be offered.

OVARIAN CANCER

Screening

Currently, many European centres offer annual surveillance of the ovaries in women at higher risk of ovarian cancer. This usually entails annual blood testing for the serum tumour marker CA125, clinical examination and transvaginal ultrasonography, commencing either from age 25 years or from 5 years younger than the youngest age of onset of cancer in a relative. However, the effectiveness of this combination of screening has yet to be evaluated. For example, CA125 measurement detects only 50% of stage 1 ovarian cancers^[16].

Prophylactic surgery

Because the efficacy of screening has not yet been proven, women at a high risk of ovarian cancer are offered prophylactic oophorectomy once childbearing is complete. Although this reduces the lifetime risk for the development of ovarian cancer^[14], it does not guarantee complete protection. Intra-abdominal cancer indistinguishable from ovarian cancer has been reported in a small number of women who have had prophylactic oophorectomy, suggesting that cancer can develop in other tissues with the same embryological origin as ovarian tissue^[17]. However, other studies suggest that early metastatic events in ovarian cancer patients may have resulted in at least some of the apparent primary tumours in extra-ovarian sites^[18].

Hormonal factors

Many studies have been performed to look at the risk of breast cancer in relation to the use of the combined oral contraceptive pill. The consensus of opinion appears to be that there is a small increase in lifetime risk of breast cancer for users of the oral contraceptive pill, but that this risk declines with time after discontinuation of use^[19]. Use of the contraceptive pill can produce a substantial reduction in the risk of ovarian cancer^[20].

HEREDITARY NON-POLYPOSIS COLON CANCER

Hereditary non-polyposis colon cancer (HNPCC), also known as Lynch Syndrome, may account for 3-6% of all colorectal cancers^[21]. The tumours often occur before the age of 50 years, around half of these arising in the proximal (ascending) colon, and there may also be synchronous and metachronous cancers. Extra-

colonic cancers may occur, especially in the endometrium, stomach, small bowel, ovary, breast and uroepithelium^[22]. There is a higher incidence of villous and tubulovillous adenomas in the colon, which have a greater malignant potential.

HNPCC families are defined by the Amsterdam Criteria, laid down by the International Collaborative Group on Hereditary Nonpolyposis Colon Cancer (ICG-HNPCC), which state that there must be 3 cases of colorectal cancer in the family: one case being a first degree relative of the other two, affecting at least two generations, with at least one case under the age of 50 years^[23].

Molecular aspects

The majority of HNPCC families have a mutation in one of the four main mis-match repair genes: hMSH2^[24], hMLH1^[25], hPMS1^[26] and hPMS2^[27]. Defective mis-match repair leads to an accumulation of mutations and, therefore, an accelerated adenoma-carcinoma sequence^[28,29]. The commonest highly penetrant HNPCC mutations occur in hMSH2 and hMLH1, conferring a lifetime risk of colorectal cancer of 85-90% for males, but a lower risk for females. The lifetime risk for the development of cancers in females is around 69%, half of which are colorectal cancers, the other half endometrial cancers^[30]. In families with a mutation in hMSH2, there is a small difference in the number of endometrial cancers compared with hMLH1 (61% vs. 42%). There is also a significantly increased risk of uroepithelial cancers (kidney and ureter), stomach and ovarian cancer^[31].

Management and screening

Those individuals in an HNPCC family who develop colorectal cancer are either offered total colectomy with ileorectal anastomosis or biannual faecal occult blood testing (FOBs) along with biennial colonoscopy because of the increased risk of developing a second primary cancer. Affected females should also be offered surveillance for endometrial and ovarian cancers.

Surveillance of the colon is also recommended for unaffected carriers of the HNPCC mutation, or those at 50% risk because of a family history which conforms to the Amsterdam criteria. Some centres offer colonoscopy every 2-3 years and biannual FOBs from the age of 25. Others commence colonoscopy from 5-10 years before the youngest age at which cancer developed in the family, repeated 5 yearly if no polyps are found or 2-3 yearly if polyps are present.

Surveillance of the endometrium is also recommended for females at risk, usually undertaken by annual transvaginal ultrasound either from age 25 or from 5 years before the youngest age at which cancer developed in the family.

Prevention

Research is on-going in the area of cancer prevention. Dietary factors have been shown to alter the risk of developing colorectal cancer^[32]. There is also strong evidence that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have a protective effect against colorectal cancer, possibly by suppression of adenoma development^[33,34].

FAMILIAL ADENOMATOUS POLYPOSIS

Molecular aspects

This condition is inherited as an autosomal dominant condition. It is due to a mutation in the APC gene, a tumour suppressor gene mapping to 5q21. It has a high degree of penetrance and a high new mutation rate; around 24% of cases are thought to be due to new mutations^[35]. It is responsible for about 1% of all colorectal cancer in the UK. The main feature is the predisposition to the formation of several hundreds or thousands of tubular adenomatous polyps throughout the colon. These are usually detectable by the age of 35 years, although polyps have been reported in the first decade of life. Less than 0.1% of these polyps become malignant. However, malignant change can occur within 12 years of development. Polyps can also be found in the upper gastrointestinal tract, giving rise to cancers such as peri-ampullary adenocarcinoma.

Other features

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is present in 66 to 92% of FAP individuals^[36]. Desmoid tumours may be present in families where CHRPE is absent, and there may be an inverse relationship between these two features^[37]. They are histologically benign connective tissue tumours, but can cause problems due to local invasion. They affect around 10% of FAP patients and commonly arise in the abdomen^[38], induced or promoted by surgical procedures, pregnancy, and oral contraceptives. Other extra-colonic features are listed in Table 2.

Not all families with attenuated FAP are linked to the APC gene^[39]. However, those mutations in the APC gene identified within these families occur before codon 157 in exon 4. Other genotype-phenotype correlations have been noted. Mutations before exon 9 are rarely, if ever, associated with CHRPE. Mutations in exon 15 between codons 1444 and 1578 do not appear to be associated with CHRPE, but desmoid tumours are nearly always present. Mutations between codons 1250 and 1440 appear to have a more severe phenotype, with more polyps and a more aggressive course^[40,41].

Variations in severity have been noted within a family, as one individual may have as few as two polyps, whereas a first degree relative may have over 100.

Table 2

Variations in the FAP syndrome

FAP subgroup	Colonic polyps	Associated extracolonic features
Gardner syndrome	Multiple intestinal polyps	Multiple osteomas, epidermal cysts, desmoid tumours (especially small bowel mesentery), supernumary teeth and jaw cysts. Tumours of thyroid, brain, adrenal, biliary tree, liver.
Turcot syndrome	Colorectal polyps < 100	Brain tumours, eg medulloblastoma, glioblastoma. Skin lesions - pigmented spots sebaceous cysts, BCC.
Attenuated FAP/ Lynch's flat adenoma Syndrome	Colonic polyps < 100	Not common but incl. gastric polyps and mandibular osteomas.

Screening

With the identification of the gene associated with FAP and the recognition of the usefulness of CHRPE, it is now possible to identify high-risk asymptomatic individuals. Surveillance of the bowel is usually commenced around age 11 years. It has also been found that non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin may have some beneficial effect on the rate of growth of colonic adenomas^[42].

Prophylactic surgery

Those who have developed multiple polyps should be offered total colectomy with ileorectal anastomosis or panproctocolectomy with restorative ileoanal anastomosis. Thereafter, lifelong surveillance of the rectal stump, if preserved, is required. Upper gastrointestinal endoscopy is also recommended, usually from age 25 years, for the detection of duodenal adenomas.

Prophylactic surgery in itself has a significant morbidity, which is increased if the surgery is more extensive or if secondary surgery is required. Therefore, the site of the mutation within the gene may be an important factor to consider in the type of surgery to be recommended in individual cases^[40,41].

OTHER CANCER SYNDROMES

The genes for a number of other rare cancer syndromes have now been identified (Table 3).

Retinoblastoma

Retinoblastoma is a rare, highly malignant

Table 3

Inherited cancer genes

Chromosome region	Gene/locus symbol	Familial cancer syndrome
2p15-16	*hMSH2	Hereditary non-polyposis colon cancer
2q31-33	*hPMS1	Hereditary non-polyposis colon cancer
3p14	RCC1	Inherited renal cell carcinoma
3p21	*hMLH1	Hereditary non-polyposis colon cancer
3p25	*VHL	von Hippel-Lindau disease
5q21	*APC	Familial adenomatous polyposis coli
7p22	*hPMS2	Hereditary non-polyposis colon cancer
9q22.3	*NBCCS	Gorlin syndrome
9q34	*TSC1	Tuberous sclerosis
10q11.2	*RET	Multiple endocrine neoplasia 2
11p13	*WT1	WAGR syndrome (Wilm's tumour, aniridia, mental retardation)
11q13	MEN1	Multiple endocrine neoplasia 1
11q22-23	*ATM	Ataxia-telangiectasia
13q14	*RB1	Retinoblastoma
13q12-13	*BRCA2	Familial breast cancer, including males
16p13.3	*TSC2	Tuberous sclerosis
17p13	*p53	Li-Fraumeni syndrome
17q21	*BRCA1	Familial breast/ovarian cancer syndrome
17q11	*NF1	Neurofibromatosis type 1
22q	*NF2	Neurofibromatosis type 2

*Sequence known and disease specific mutations identified.

cancer of the developing retinal cells. It usually presents before the age of 5 years, but, if treated at an early stage, has a good prognosis. It can occur sporadically (non-hereditary) or as an autosomal dominant condition, although a significant number can occur as new mutations^[43]. Hereditary retinoblastomas often present at an earlier age and can be bilateral or multifocal. Knudson proposed a 'two-hit' hypothesis to explain these observations^[44]. Individuals with a family history of retinoblastomas are thought to inherit one non-functional gene, with the second gene at the same locus being inactivated somatically in a developing retinal cell. Survivors of hereditary retinoblastoma are at an increased risk of developing a non-ocular malignancy, the commonest being osteosarcoma^[45].

Multiple endocrine neoplasia syndromes

This rare group of disorders is characterised by tumours involving two or more endocrine glands within a single patient. There are two main disorders: MEN-1 (Wermer's syndrome) and the MEN-2 group, including familial medullary thyroid carcinoma (FMTC), MEN-2A (Sipple's syndrome) and MEN-2B (previously known as MEN111). They are inherited as autosomal dominant traits, although a significant number are new mutations^[46].

MEN-1 has been mapped to 11q13 (thought to be a tumour suppressor gene). It is characterised by hyperplasia or neoplasia of the parathyroid

glands (> 95%), the pancreatic endocrine system (gastrinoma, insulinoma, glucagonoma and VIPoma) and the anterior pituitary. There may be associated tumours, including carcinoid tumours and adrenal gland tumours. Hyperparathyroidism is a feature in > 95% of cases. Penetrance is high, with 80% of patients developing clinical manifestations by age 80^[47]. Screening should commence in childhood and continue for life, with annual clinical assessment and biochemical surveillance.

FMTC, MEN-2A and MEN-2B are thought to be due to activation of the ret proto-oncogene on chromosome 10q11.2^[48]. The features are listed in Table 4. Hirschprung's disease has been reported in some families, and is due to a loss of function mutation in the ret proto-oncogene. Other features associated with MEN-2B include musculoskeletal abnormalities (kyphosis, scoliosis, talipes equinovarus, slipped femoral epiphyses), Marfanoid habitus, neuromas of lips, tongue, and conjunctiva, mega-colon and mega-ureter. It is thought that approximately 25% of all medullary thyroid cancers are familial.

Table 4
Features of MEN-2

	MTC	Phaeo	HPT	Other
MEN-2A	+	+	+	Commonest
MEN-2B	+	+	-	Early onset, Neuromas
FMTC	+	-	-	Later onset, Indolent

Von Hippel-Lindau syndrome (VHL)

The VHL gene has been located to 3p25-26. It is inherited as an autosomal dominant condition, with almost 100% penetrance by age 65 years^[49]. Associated cancers include retinal angioma, central nervous system (CNS) haemangioblastoma, renal malignancies and pheochromocytoma. Recommended screening includes annual retinal examination from age 5 years, computerised tomography (CT) or magnetic resonance imaging (MRI) of the renal system 3 yearly from age 15, annual renal ultrasound and annual urinary VMA measurements. Most centres will perform a CT or MRI brain scan only when the patient becomes symptomatic^[50].

Li Fraumeni syndrome (p53)

This is a rare syndrome in which mutations in Tp53 are inherited as an autosomal dominant condition. Malignancies occur at an early age and include sarcomas, adreno-cortical tumours, breast cancers, brain cancers and leukaemias^[51,52]. Breast

screening is usually offered to women at risk in these families, although there is concern about the effects of radiation on Tp53 mutation carriers.

CONCLUSIONS

- Only a minority of cancers are due to highly penetrant gene mutations (around 5 to 10%).
- The majority of cancers are likely to be due to adverse environmental influences, although there may be genetic susceptibilities to these influences.
- Recent developments in the understanding of the genetic basis of some predispositions to cancer have led to a rapid expansion in the ability to predict those who are at a high lifetime risk of developing cancer.
- Clinical geneticists have an important role in identifying individuals in families with an increased disposition to cancer due to a highly penetrant gene.
- High risk individuals require support and counselling. Appropriate screening and management need to be available, including prophylactic surgery in some cases.
- Genetic testing is possible for some conditions. Support and counselling is required for the patient before and after such testing.
- It is important to remember that the incidence of sporadic cancer is very high. Therefore, even if an individual is tested and found not to carry the gene mutation segregating with the family's cancers, there is still a residual risk of this individual developing a similar cancer.

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