Information sheet 3: genes and cancer

Overview

In any living organism – whether it is a tree, a mushroom, a fish or a human - cells grow and divide, either to make the organism grow larger or to replace worn-out cells. This cell growth and division carefully controlled by a large set of genes known as 'cell cycle control genes'.

Cancer is ultimately caused by mutation of these genes (see Information sheet 2), which results in uncontrolled cell growth and division: this ultimately leads to development of tumours. Additional mutations allow the tumour to spread within the body, a process known as 'metastasis'.

Much of the time, mutations in cell cycle control genes are acquired throughout life and accumulate slowly in cells. These mutations are often random spelling mistakes that happen without a specific cause, or they may be caused by exposure to harmful factors in our environment – radiation or the toxins in tobacco smoke, for example – or other disease processes – such as diabetes and obesity. A cell needs to accumulate a critical number of mutations in different genes ('mutation load') in order for its growth to become destabilised and for a tumour to develop. A tumour will usually have a number of 'driver mutations' that are especially important in driving the disordered growth. It is also usual to see 'passenger mutations' that arise as a result of that disordered growth. It usually takes many years to get to this stage, which is why cancer is generally a disease of later life. Sometimes, either by chance or as the result of hereditary diseases (see below), the critical mutation load will be reached earlier in life, which is why we sometimes see common tumours affecting younger people.

There are some people in the population who are born with a major mutation in a cell cycle control gene. They may have inherited this from one of their parents or, on occasion, it may have arisen as a spelling mistake during the formation of the egg or sperm used to conceive them (a so-called 'new mutation'). This mutation is present in every cell of their body and is said to affect their *germ line*[1]. In such people, a cell still has to reach the critical mutation load in order to trigger the growth of a tumour but, since that person started their life with such a mutation in every cell of their body, it takes less time to reach the point of tumour growth. In such people it is usual to see tumours developing earlier in life: breast cancer at 35 years of age, for example, rather than 65. Such people are said to 'predisposed' to develop cancer,

[1] Eggs and sperm are referred to as *germ cells* – so the DNA we start our lives with as a single cell formed by fusion of a single egg and sperm is called our *germ line* DNA.

and these rare hereditary diseases are usually known as 'hereditary cancer predisposition syndromes'.

Table 1: examples of hereditary cancer predisposition genes.

Gene	Syndrome name	Common associated tumours	Other associated tumours
BRCA1	Hereditary breast/ovarian cancer syndrome	Breast cancer Ovarian cancer Prostate cancer	
BRCA2	Hereditary breast/ovarian cancer syndrome	Breast cancer Ovarian cancer	Melanoma Pancreatic cancer
MLH1, MSH2, MSH6, PMS2	Lynch syndrome	Colon cancer Endometrial cancer Renal / ureteric cancer	Ovarian cancer Stomach cancer Pancreatic cancer Bile duct cancer
RET	Familial medullary thyroid cancer / Multiple endocrine neoplasia type 2	Thyroid cancer	Parathyroid tumours Phaeochromocytoma

What suggests that someone has a major germ line gene mutation?

The most important predictors are:

Family history

As we have seen above, germ line mutations in cell cycle control genes are often associated with different types of cancer. These may either develop in the same person, or may affect different members of the same family.

Age at diagnosis

Cancers triggered by germ line gene mutations tend to develop at an earlier age than in the general population.

These two sets of data create a family 'fingerprint' that can be used to identify families who might benefit from more detailed assessment, including genetic testing. Indeed, the NICE clinical guidelines for the assessment and management of familial breast cancer[2] recommend that both family history and age at diagnosis (as well as the specific type of breast cancer) are taken into account when deciding if someone should be offered genetic testing of the *BRCA1* and *BRCA2* genes. Even if someone has no family history, but has developed cancer at a young age, he/she may still have a germ line gene mutation.

[2] https://www.nice.org.uk/guidance/cg164 accessed 6th July 2018

Table 2: common patterns of cancer in hereditary cancer syndromes

Cancers in family history	Possible responsible gene
Breast Ovarian Prostate	BRCA1
Breast Ovarian Melanoma Bile duct	BRCA2
Breast Adrenal gland Sarcoma Brain	TP53
Colon Endometrium Stomach Brain Skin	MLH1/MSH2/MLH6/PMS2
Colon Multiple colon polyps Liver	APC

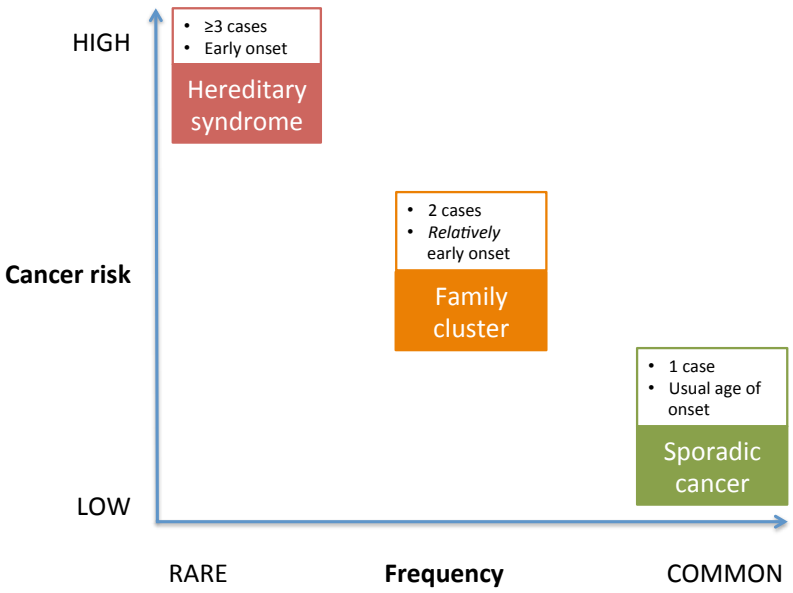
What if I have a family history of cancer but it doesn't look like a rare inherited syndrome?

Ii is important to distinguish between clustering of cancer in a family – which should be referred to as 'familial cancer' – and proven inherited disease – which should be referred to as 'hereditary cancer'. Unfortunately, medicine is filled with historical examples in which care to distinguish between these two has not been taken, often for perfectly understandable reasons. For example, familial adenomatous polyposis (FAP) is the term used to describe an hereditary disease in which a germ line mutation in a gene called *APC* (often inherited) leads to the development of multiple colon polyps and, if not treated, colon cancer. However, we often see families in which a number of close relatives have the same type of colon polyps as FAP but they don't have the condition. Ideally, the term familial adenomatous polyposis should be used in *those* families, and the disease known as FAP should really be called *hereditary* adenomatous polyposis (HAP). Life is never that simple, however.

Why is this important?

The following graph helps us to understand the real difference between hereditary disease and family clusters. Inevitably, this is a generalisation but it holds true for many different types of common cancers, for example breast, bowel, pancreatic, melanoma, kidney etc., as well as many types of non-cancer diseases like diabetes.

Figure 1: genes, hereditary disease and family clusters



Hereditary cancer predisposition syndromes are the result of rare, 'high risk', gene mutations. In families affected by such conditions we usually – but not always – see multiple affected relatives who have developed cancer many years before the normal age for that cancer (e.g. breast cancer at 30, compared with >60 in the general population).

Within any population there are some more common genetic alterations that, individually, have little effect, but in some families a number of these have become concentrated over time. In such families we see the same cancer occurring more than once (usually twice) in closely related people (a 'familial cluster'), but the age at diagnosis is neither as low as in hereditary disease, nor as high as the general population. The close relatives of affected people in such families have a moderately increased risk of developing the same cancer.

There are also many common genetic variants that have very little effect on their own, even when combined in the same individual. In these people, non-genetic factors are likely to be a more important trigger for the development of their cancer.

This model also works for common non-cancer diseases like high blood pressure, diabetes, heart failure and high cholesterol levels.

Acquired (non-inherited) mutations in cell cycle control genes

Most cancer – 95% or so – is triggered by *acquired* mutations in someone who does not have a rare germ line gene mutation. These are also referred to as driver and passenger mutations.

It is becoming increasingly popular – and in many situations increasingly necessary – to test DNA extracted from a cancer tumour for driver mutations in specific genes. The reason for this is that specific genetic subtypes of tumour, characterised by the presence or absence of specific driver mutations, respond differently to a range of different treatments. This is starting to allow personalisation of cancer care. Over the next decade it is likely that this will revolutionise cancer care.

In the future we are also likely to see DNA analysis of different areas of the same tumour, detection of tumour DNA in blood samples (which will be useful in early diagnosis / screening and monitoring response to treatment) and the routine use of whole genome sequence analysis to provide a comprehensive overview of the myriad of genetic changes in a tumour (the 'mutation load').