Cancer Genetics - The Jewish Perspective

The Genetic Predisposition to Cancer

One in three of us will develop a cancer at some time. Hopefully later in life and now often curable, but it is always a shock when the diagnosis is made. After initial questions about treatment options and prognosis, people may go on to ask, '*Why me? Why now? How did this happen?*'

Answers are starting to come from studies of the genes that control cell growth and those genes that repair errors in other genes. This is particularly for breast, ovarian and bowel cancers that occur at a younger age and that cluster in some families. Some families particularly those of eastern European Ashkenazi origin are at greater risk of inheriting an alteration in one of these cancer predisposition genes.

Important as genes are, they are not the whole story. Environmental factors - what we eat, our lifestyle and what we are exposed to, for example smoking can also cause cancers. It is the interplay between a genetic predisposition and these environmental triggers, ***nature and nurture*** that determines who may develop cancer, where in the body this might be and at what age. We all have a risk of cancer, but some of us are at greater risk than others.

Genes and Mutations

It is the sequence of the four genetic bases (**A**denine, **G**uanine, **C**ytosine, **T**hymine) in the long double-stranded DNA molecule that determines what function that gene has. Genes fall into three groups

i. structural genes coding for a body protein such as muscle
ii. regulatory genes known as oncogenes or tumour suppressor genes that control the cell or other genes in that cell
iii. repair genes that correct mistakes in the DNA of cells

Our complete set of 30,000 genes is carried within the 23 pairs of chromosomes inside the nucleus of every body cell. We inherit two copies of

each gene, one in each pair from our parents in the egg and sperm cell that made us. Mistakes in the copying of our DNA are called **mutations**. They occur spontaneously and accumulate in our DNA as we age. Mutations can also be inherited and passed down through families. The random spelling change of A to C or G to T, or the loss of a run of letters C-G-A-T-T-C-T-G-A from a gene will lead to a change in the message or inactivate the function of that gene (see Figure 1).

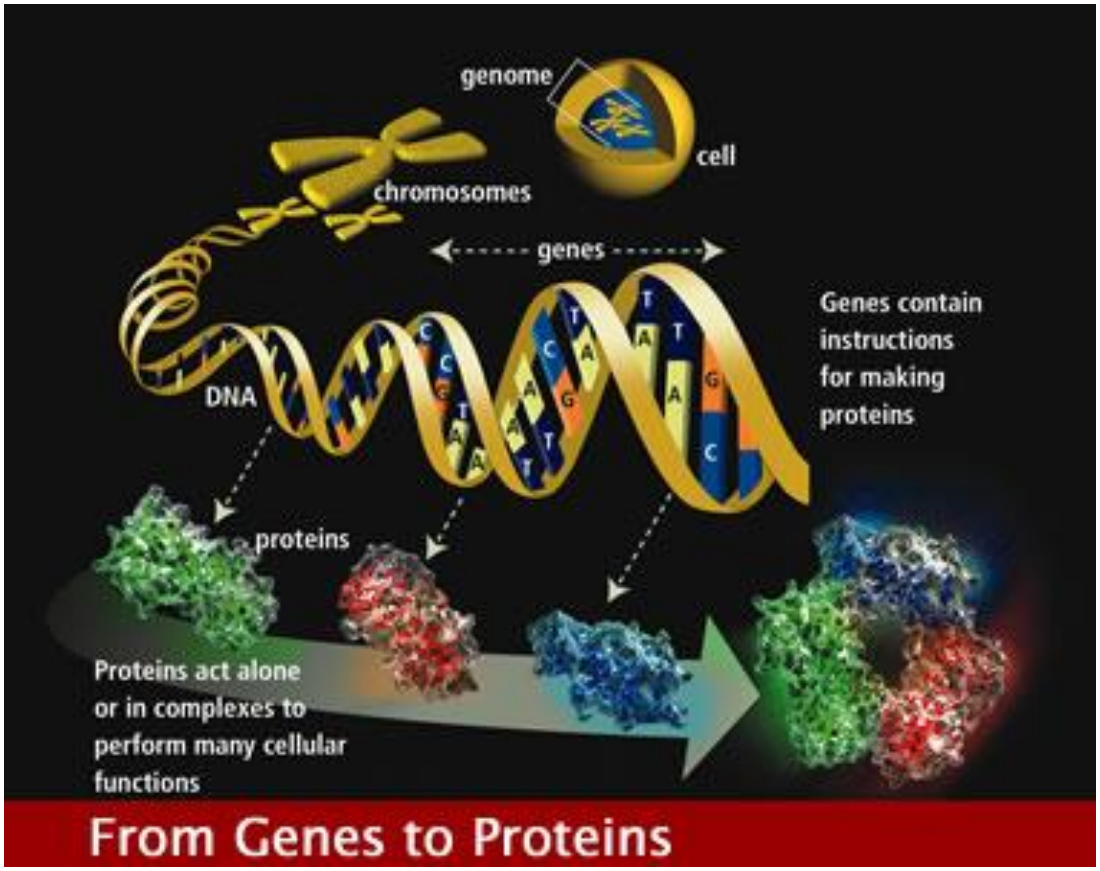

Figure 1 - The Structure of Genes Formed from DNA and Packaged into Chromosomes

Regulatory and Repair Genes

Apart from the structural genes that code for the proteins of the body; other genes have important roles as regulatory genes, controlling cells directly and by switching other genes on and off, like a co-ordinated orchestra. Genes also direct the differentiation of cells into the different organs and specialised tissues of the body. For example, primitive bone marrow cells will become the

mature red blood cells and white blood cells that we need. As we reach adult life these regulatory genes shut down cell division unless replacement cells are needed.

Errors in can creep into the DNA sequence over time and a set of repair genes are essential to maintain our library of genes in good working order. These DNA repair genes (they have also been called *'caretaker genes'*) can themselves mutate and fail to correct mis-matches in the sequence of the DNA strands. This explains why cancers tend to occur at an older age. As regulatory and repair genes become mutated, cells become increasingly uncoordinated until an invasive cancer develops (see Figure 2). There are now DNA based genetic tests that can identify these stepwise changes in specific genes (such as p53 and K-ras) as cells change from normal through a hyperplastic (overgrowth) cells and then into an invasive cancer.

Figure 2 - Gene Mutations that Progress in the Development of a Cancer

Cancer Predisposition Genes and their Mutations

Family members inheriting a cancer gene mutation are already a step further along the pathway that leads to cancer developing and have a higher risk of developing specific cancers at a younger than expected age. Tumour suppressor genes control cell division, acting like the brakes on cell growth. Mutations in tumour suppressor genes can occur spontaneously during your lifetime (**acquired**), or they may have been passed on (**inherited**), from one parent. Tumour suppressor genes come in pairs, one inherited from each parent in the egg and sperm cell that made you. If there is a change or a mutation in one copy of the tumour suppressor gene, this may not cause a problem as there is a second normal copy that is functioning and acts like a

back-up copy. The risk of cancer only occurs where there is a second mutation, (known as **Knudson's two-hit cancer hypothesis**) that inactivates the second of the pair of tumour suppressor genes. Cancer will only occur when the second copy has been affected. This occurs with a higher risk and at a younger age, if you have inherited a mutation in one of the pair of tumour suppressor genes. It is then really just a matter of time before they sustain a spontaneous mutation (second-hit) in the other copy of that gene pair. When both copies of the pair of genes have been inactivated or mutated, that tumour suppressor gene or DNA mismatch repair gene can no longer function and a cascading process of abnormal genetic changes occurs, (see Figure 3).

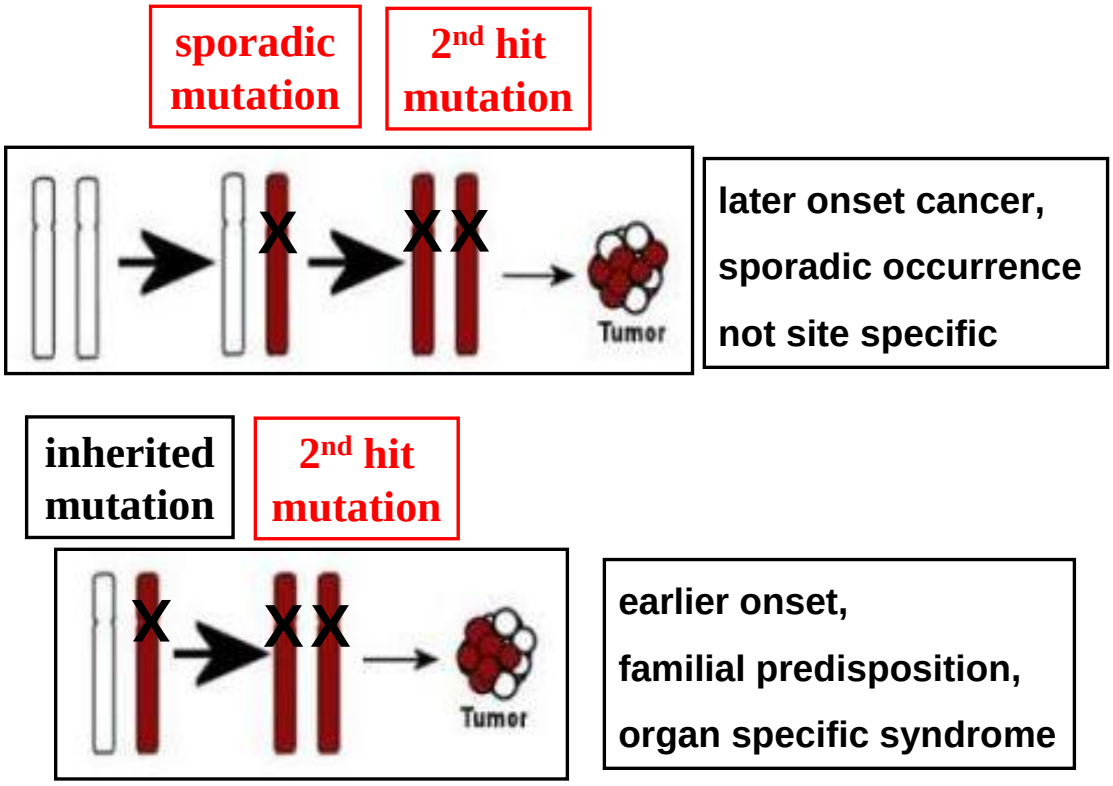

Figure 3 - Knudson's Two-Hit Hypothesis for Mutations in Tumour Suppressor Genes Cancer Causing Cancer

Your Family History

Some families have seen more than the expected number of relatives with a cancer. There may have been a clustering of the same types of cancer occurring at a younger than usual age, or one person may have unfortunately developed several primary cancers. These are pointers that there could be

an increased genetic risk for that family. Cancers such as lung and cervical cancer have other risk factors (such as smoking and lifestyle) that are not inherited and not genetic. About 5-10% of breast, ovarian, bowel and less so for prostate, uterus (womb), pancreas, bladder and kidney cancer may have an inherited tendency. A number of genes including BRCA1, BRCA2, the DNA Mismatch Repair Genes (MLH1, MSH2, MSH6, PMS2), APC, p53, p16, PTEN) have been identified with inherited that predispose families to a higher risk of cancer. There is on-going research into finding familial prostate and pancreatic cancer genes. Some genes will be commoner than others, with variable effects on the risks of developing cancer.

Why Are There Cancer Genes in the Jewish Community?

About 1 person in 50 (2%) in the Jewish community carries one of these cancer predisposition genes. These are particularly the hereditary breast and ovarian cancer (and less so for prostate and pancreatic cancer) predisposition gene mutations: BRCA1 5382insG; BRCA1 185delAG; BRCA2 6174delT and the bowel cancer predisposition gene APC I1307K. There are several ideas of why these mutations may be more common in the Jewish community. This may be due to a ***selective advantage*** that in the past allowed someone carrying this gene mutation to be somehow fitter and survive adverse environments. Or it may the ***founder effect*** that groups in the population are descended from a common ancestor who carried that gene mutation gene. Their descendents will then be more likely to inherit and pass on that gene and a mutation if this has been present. This is the case for other genes in the Jewish community, for example Tay-Sachs and Gaucher's disease. Mutations in other genes may become more common in a population by a random process known as ***genetic drift***. This is simply the chance that over generations some genes become more frequent whilst other genes are lost from that population. The strong religious tradition of Jews to marry in and remain isolated from their neighbours will tend to preserve these genetic traits. This has favoured a number of gene mutations to appear more frequent, particularly for Ashkenazi Jews from the shtetl communities of eastern Europe. This is why it is important to have bone marrow donors from

within the Jewish community that share a common genetic background and increase the chances of finding a compatible match[1,2].

Cancer in the Family - What Should I Do?

All of us may know of someone in our family with cancer. But if you have more than the expected number of cancers, particularly breast, ovarian or bowel cancer you may want to look into this further. Ask your GP or contact CHAI[3], but the following may be pointers to an increased risk in your family history:

- breast cancer at 40 or younger in a mother, sister or daughter
- breast cancer at 50 or younger in two close relatives (including mother, aunt, grandmother, sister, daughter or cousin
- breast cancer at any age in there close relatives
- ovarian cancer at any age
- bowel cancer under the age of 45
- bowel cancer at any age in two close relatives

You cannot change your family!, but you can change your lifestyle and diet to reduce your risk. Stop smoking, avoid too much saturated fat, increase fibre in your diet, exercise and lose weight. If there is a moderate family history additional screening (mammography breast checks and colonoscopy to check the bowel for polyps), may be suggested. Inherited cancers include breast, ovarian, bowel and less so prostate, pancreas, uterus (womb) and renal (kidney) cancers.

If you are concerned that your family may be at higher risk of cancer, your GP can refer you to one of a national network of cancer genetics clinics[4]. A detailed family history will be taken and the types of cancers in your family confirmed from hospital records. You will be invited to discuss your family history and given information about your risk and the options open to you. A family member who has had a 'genetic cancer' maybe asked if they are prepared to give a blood sample to test their DNA for alterations in one of the cancer genes. There are many considerations to be made before considering genetic testing, particularly the implications for you and your family and for

insurance. This will be discussed in a genetic counselling session before the test is taken. Full genetic analysis can take two to three months or longer if extra genes are tested.

Testing For a Cancer Predisposition Gene

Knowing that you carry a cancer predisposition gene makes the development of some form of cancer more likely, but not inevitable. A woman who carries the BRCA1 or BRCA2 mutation may have up to a 70% risk of developing breast cancer and a 40% risk of ovarian cancer in their lifetime. At first this can be difficult to come to terms with. You may feel worried about your health, concerned for your family, or even feel responsible even though it's no one's fault. This is quite understandable. Genetic counselling and time spent discussing your options with experts together with the support of family and friends' helps people to come to terms with this and make decisions that are best for them[5]. There are no right or wrong things to do. Everyone is different in how they react.

You may be worried about you risk of cancer if a relative carries a cancer predisposition gene or just knowing that there is an the increased risk in the Jewish community. If you have not had a cancer yourself, then a detailed discussion may be needed to discuss what is called '**predictive testing**'. After careful discussion, weighing up the pros and con you may be offered a genetic test. If your test shows that you have inherited the cancer predisposition gene mutation, additional screening will be suggested. Women carrying one of the BRCA1 or BRCA2 gene mutations may ask to have their ovaries removed if they have completed their family or to consider a prophylactic mastectomy. Everyone is different and everyone needs an individual discussion with a genetic counsellor. Your test result can affect how you feel about your health in the future and it can affect health and life insurance.

The Future

It is a lot of information and a lot to think about, but there is also optimism that increasing understanding of the genetic basis of cancer will allow better

advice about cancer prevention, the development of more effective drugs and treatments[6]. There are families who carry these genes, but who have never developed a cancer. Their lifestyle and studies on their other genes (known as **modifier genes**) may tell us how we can better advise at-risk people in the population from ever developing cancer. We already have new drug treatments such as Herceptin™ and PARP inhibitors that target the genetic changes in cancer cells with increasing effectiveness and less toxicity.

Research programmes are under way to identify who might be carrying such genes and what their level of risk is. Testing for the specific Jewish BRCA1 and BRCA2 gene mutations is being offered to selected families even when a cancer has not developed in the family. This offers many opportunities, but also raises questions; '*Do you want to know?, What will you do if you find you are carrying a cancer gene mutation? Will you tell your family?*' These questions require a lot of discussion and careful thought. Widespread screening across the population will identify people who carry a cancer predisposition gene mutation, but who may never actually go on to develop a cancer. CHAI, genetic counsellors and cancer experts are there to provide information, discuss your options and offer support.

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Further Reading and Sources

[1] **Sue Harris Bone Marrow Campaign**, Tel: 020 8342 8733

[2] **The Anthony Nolan Trust**, Units 2 - 3, Heathgate Place, 75 - 87 Agincourt Road, London, NW3 2NU. Tel: 0303 303 0303, http://www.anthonynolan.org.uk/ E-mail:info@anthonynolan.org.uk

[3] **Chai Cancer Care,** 44-146 Great North Way London NW4 1PN Tel. 020 8202 2211. http://www.chaicancercare.org/

[4] **Genetic Alliance UK**, Directory of Genetic Centres and Services, http://www.geneticalliance.org.uk/services.htm

[5] **Macmillan Cancer Support**, 89 Albert Embankment, London, SE1 7UQ. Tel: 0808 808 00 00 or 020 7840 7840. Lots of information avaialable on their website. *Cancer genetics - how cancer sometimes runs in families,* **http://www.macmillan.org.uk/Cancerinformation/Causesriskfactors/Genetics/Cancergenetics/Cancergenetics.aspx**

[6] **Cancer Research UK**, 61 Lincoln's Inn Fields, London, WC2A 3PX. Updates on the science and research into cancer genetics. ***Our research into finding cancer genes***. http://info.cancerresearchuk.org/cancerandresearch/ourcurrentresearch/topic/findingcancergenes/index.htm

Further Reading and Sources

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Table of Figures

Figure 1 - The Structure of Genes Formed from DNA and Packaged into Chromosomes.....3
Figure 2 - Gene Mutations that Progress in the Development of a Cancer.....4
Figure 3 - Knudson's Two-Hit Hypothesis for Mutations in Tumour Suppressor Genes Cancer Causing Cancer.....6