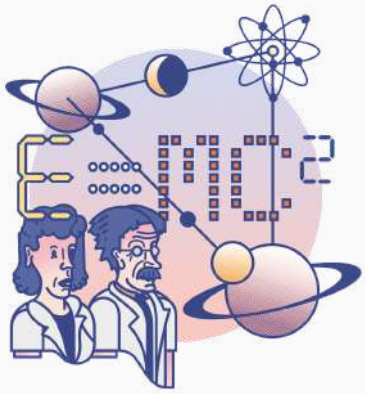
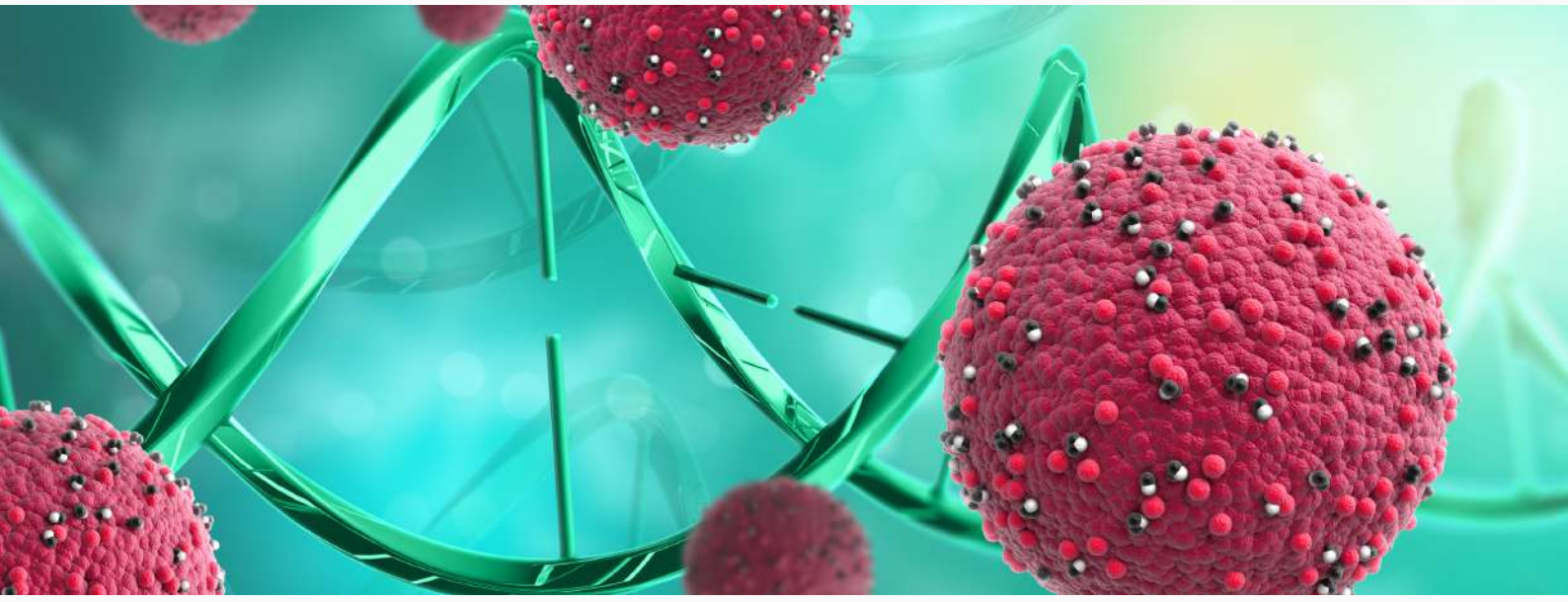


Cancer Genetics Project

Isabel McMeeking



SUPERVISED BY KATE (PHD GENETICS RESEARCHER ON THE UCL-BIRKBECK MRC DTP, UNIVERSITY COLLEGE LONDON PROGRAMME)

Are some cancers more genetic than others?

Cancer is defined as a disease caused by an uncontrolled division of abnormal cells in a part of the body. Cancer is a genetic disease that is brought about when changes occur to genes that affect their function. DNA consists of nucleotides and these are read as codons, which are three DNA bases that code for a specific amino acid to make a protein. When a mutation occurs, the sequences of these nucleotides change, so different codons are read and therefore a different protein may be coded for. Some cancers are more genetic than others due to the way that they have arisen. A cancer is more genetic when it has been inherited from parents or induced by a random mutation. The cancer is less genetic when it is acquired during someone's lifetime due to environmental factors. This can be as a result of exposure to substances or UV light that damages the DNA and can lead to somatic changes. The mutations within DNA that lead to cancer also vary as they may affect just one nucleotide, for example swapping nucleotides, it being missing entirely or there may be larger changes to the DNA such as rearrangements, deletions or duplications. Additionally, epigenetic modifications can alter how the DNA is expressed as it removes or adds chemical marks and affects the amount of mRNA that is produced. Therefore there are also different alterations that affect how some cancers are more genetic than others. This review will also discuss the treatments available in order to understand why this topic is important and relevant when researching cancer.

A gene is a basic unit of heredity and a sequence of nucleotides in DNA or RNA that encodes for either RNA or a protein. There are certain changes to the genome which allow for increased cell growth and these are changes to oncogenes and tumour suppressor genes. Oncogenes promote cell growth and reproduction, so if a mutation were to occur on this gene, its function may be altered and cell growth may be over promoted, leading to a tumour. Tumour suppressor genes act against oncogenes so if a mutation were to occur on these, the inhibition of cell growth would be disabled which could lead to cancer development. For example, TP53 is a tumour suppressor gene that protects the genome against cancer as it can detect DNA damage and stop cells from replicating. Therefore if a mutation occurred that rendered its function, it cannot detect the damage and the cells are allowed to proliferate. An example of an oncogene is EGFR. This is an epidermal growth factor receptor that receives signals that tell the cell to grow. If a mutation occurred that caused it to always be switched on, there may be more signals than there should be which may cause cancer development, so therefore over action is bad. Oncogenes do not only affect cell growth, but also DNA repair and other properties such as the Hallmarks of Cancer which determined different principles for understanding neoplastic diseases and included factors such as resisting cell death and sustaining proliferating signalling. Factors such as epigenetics or chromosomal abnormalities can affect these genes and lead to cancer. Epigenetics is how genes work and the modification of gene expression to turn certain genes on and off. Epigenetics is important within cancer due to the effects that changing the gene expression can have. For example, when DNA methylation occurs on the promoter region, it alters how transcription factors bind, so if it is methylated, factors do not bind as effectively and protein production decreases. Similarly, this can happen to nucleosomes which consist of histone proteins and DNA. Histone acetylation causes the DNA to loosen around the histones as it diminishes the electrostatic affinity between histone proteins and DNA, and thereby promotes a chromatin structure that is more susceptible to gene transcription. This change in transcription and gene expression has been linked to tumour development as it affects key genes regulating cellular functions such as cell proliferation, cell-cycle regulation and apoptosis. The epigenetic changes make the cancer less genetic than random mutations to TP53 for example, so therefore how genetic a cancer is can be determined through the way that it has been brought about. Another way that a cancer inducing mutation can occur is through large chromosomal abnormalities, and these make the cancer more genetic as they occur through random mutations. However, these are more rare as they are easier for the body to detect as they are larger than other mutations. It may be the loss of an arm of a chromosome, known as chromosomal deletions or the addition of chromosomes or chromosomal translocation. It was interesting to look at the Philadelphia chromosome which is a reciprocal translocation involving chromosomes 9 and 22 that is commonly identified in chronic myelogenous leukaemia (CML). The fusion gene encodes a tyrosine kinase signalling protein that leads to uncontrollable cell division. Therefore, these fundamental genetic principles demonstrate how different factors can contribute and cause cancer.

There are different factors that affect the development of cancer and therefore how genetic the cancer may be. When external factors such as the sun and UV light cause cancer, this will mean that the cancer will be less genetic than if the cancer is due to a random mutation or a cancer syndrome. UV radiation causes mutations and physical changes to the DNA through wrong nucleotide pairings which can cause the DNA to break or even cause dimers. When your skin is unprotected from the sun, UV radiation can damage your DNA and if this cannot be repaired, the cell can begin to divide and grow in an uncontrolled way. This growth can eventually lead to cancer. In the paper 'The Repertoire of Mutational Signatures in Human Cancer', it is interesting to look at the number of mutations contributed by each mutational signature for different tumours. For example, in skin-melanomas it is predominantly the signature related to UV light exposure that caused the development of that cancer. Therefore it has been identified that UV light and external factors do have a large role in causing cancer, showing how this cancer is less genetic than others through the way that it is brought about. Additionally, smoking can also cause cancer and is brought about by lifestyle choices. Cigarettes contain carcinogens that cause DNA damage through different mechanisms. This involves the alterations of oncogenes, inactivation of tumour suppressors, evasion of apoptosis genes, and defective DNA repair genes. For example, they may cause cells to divide at a faster than normal rate, which could increase the chances that DNA changes will occur. Therefore it can be seen that the factors that cause cancer and the way that it is brought about determine how genetic the cancer is and there are also many different mechanisms and elements which may stimulate cancer development.

On the other hand, cancers can be more genetic than others as they can occur through random mutations. A cancer syndrome is a genetic disorder in which inherited genetic mutations in one or more genes predispose the affected individuals to the development of cancers and may also cause the early onset of these cancers. This is a Mendelian disorder and an example includes Li-Fraumeni syndrome. This mutation occurs in the tumour suppressor gene TP53 and it greatly increases the patients chance of developing several types of cancer. It is interesting to see that of 200 Li-Fraumeni syndrome family members diagnosed with cancer, 15% developed a second cancer[1]. This can also be seen in *BRCA1*. This is a tumour suppressor gene that produces proteins that help repair damaged DNA. The loss of *BRCA1* function renders the tumour hypersensitive to chemotherapeutic agents that include DNA double-strand breaks. The paper 'Hypermethylation of *BRCA1* gene: implication for prognostic biomarker and therapeutic target in sporadic primary triple-negative breast cancer' showed that *BRCA1* methylation significantly correlates with basal-like breast cancer therefore showing the effects that genetic cancer can have and how this is a more genetic cancer than others that have been previously discussed.

Although there are many factors that cause cancer and affect how genetic it is, there are also different treatments that can either cure a patient or increase their life expectancy. One option is to undergo surgery to remove the mutated cells. Although this can be hard if metastasis has occurred and the cancer has spread or if the cancer is hard to reach. A different treatment includes radiation therapy where ionising radiation is sent out in a small beam to the cells. This can reach all cancers and it minimises the damage to healthy cells. On the other hand, chemotherapy can also be used which is where drugs are given to the patient to target the cancerous cells. As the cancer cells are constantly undergoing the cell cycle, the drugs target these cells and can induce apoptosis. These are important to minimise the number of cancer deaths and research is key in order to discover the mechanisms of inactivation of some cancers to provide novel therapeutic strategies targeting. Additionally, transplants are also an option such as a bone marrow transplant where the mutated blood cells are removed and new ones are created. Overall, it is often the case that combination therapy is used to treat cancer in order to prevent the resistance of the cancer cells to any treatment and to spread out the treatments in order to minimise the damage to healthy cells. Additionally, there are new chemotherapy options available such as antimetabolites that prevent the formation of new DNA and RNA by using 'fake' nucleotide bases that are incorporated but do not work which leads to DNA damage and apoptosis as well as topoisomerase which inhibits the unwinding enzymes of DNA so it cannot unsupercoil which causes stress to build up so there is no replication or transcription. Therefore the understanding of these novel treatment is important to create new ones that could potentially defeat some cancers. This demonstrates how there are many different treatments available but also how these treatments and research are extremely relevant and important in order to fully understand the disease and its effects.

---

[1] https://academic.oup.com/jnci/article/90/8/606/987603

To conclude, there are many different mutations that can occur and bring about cancer and these can affect oncogenes or tumour suppressor genes. These are very small changes to the genes, but there may also be larger changes including large chromosomal abnormalities. These abnormalities make the cancer more genetic as it has occurred through a random mutation whereas epigenetic changes mean that the cancer is less genetic. Cancer development can also occur through DNA methylation where transcription factors don't bind as effectively which deceases protein production or through histone acetylation where the DNA losens around histones so the DNA can be transcribed, increasing gene expression. How genetic a cancer is can also be determined through the external environments and lifestyle choices. When a cancerous mutation arises through a lifestyle choice such as smoking or exposure to UV light, the cancer is considered to be less genetic than if it is through a random mutation or due to a cancer syndrome. Although cancer brought about through inheritance or UV light both affect genes, it is the way that it is brought about that determines how genetic it is. Finally, the different treatments are interesting to look at through the way that each option targets the cancer and it is through the tumour microenvironment that the correct treatment is decided and undertaken, making these treatments very relevant in this review to understand and cure many cancers and to be able to aid research and cancer treatments. It in interesting to see that new cancer treatments are constantly being developed with different technologies currently under trial and 'nano medicine is contributing to the development of biocompatible materials both for diagnostic and therapeutic purposes'[2]. Therefore these novel technologies and treatments will help to fight cancer and hence why it is so important to understand how the disease works in order to treat it.

References:

1. 'The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia', C L Arteaga, September 2001
2. Multiple Primary Cancers in Families With Li-Fraumeni Syndrome, Michie Hisada, Judy E. Garber, Frederick P. Li, Claire Y. Fung, Joseph F. Fraumeni, April 1998
3. Innovative approaches for cancer treatment: current perspectives and new challenges, Carlotta Pucci, Chiara Martinelli, Gianni Ciofani, September 2019
4. Hallmarks of Cancer: The Next Generation, Douglas Hanahan, Robert A. Weinberg, March 2011
5. Hypermethylation of BRCA1 gene: implication for prognostic biomarker and therapeutic target in sporadic primary triple-negative breast cancer, X.Zhu, L.Shan, F.Wang, J.Wang, F.Wang, G.Shen, X.Liu, B. Wang, Y. Yuan, J. Ying, H. Yang, December 2014
6. Mutational landscape and significance across 12 major cancer types, Cyriac Kandoth, Michael D. McLellan, Fabio Vandin, Kai Ye, Beifang Niu, Charles Lu, Mingchao Xie, Qunyuan Zhang, Joshua F. McMichael, Matthew A. Wyczalkowski, Mark D. M. Leiserson, Christopher A. Miller, John S. Welch, Matthew J. Walter, Michael C. Wendl, Timothy J. Ley, Richard K. Wilson, Benjamin J. Raphael, Li Ding, October 2013
7. Historical review of the causes of cancer, Clarke Brian Blackadar, February 2016
8. A brief history of human disease genetics, Melina Claussnitzer, Judy H. Cho, Rory Collins, Nancy J. Cox, Emmanouil T. Dermitzakis, Matthew E. Hurles, Sekar Kathiresan, Eimear E. Kenny, Cecilia M. Lindgren, Daniel G. MacArthur, Kathryn N. North, Sharon E. Plon, Heidi L. Rehm, Neil Risch, Charles N. Rotimi, Jay Shendure, Nicole Soranzo, Mark I. McCarthy, January 2020

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6753017/