GRESHAM COLLEGE

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# INFECTION, IMMUNITY AND CANCER

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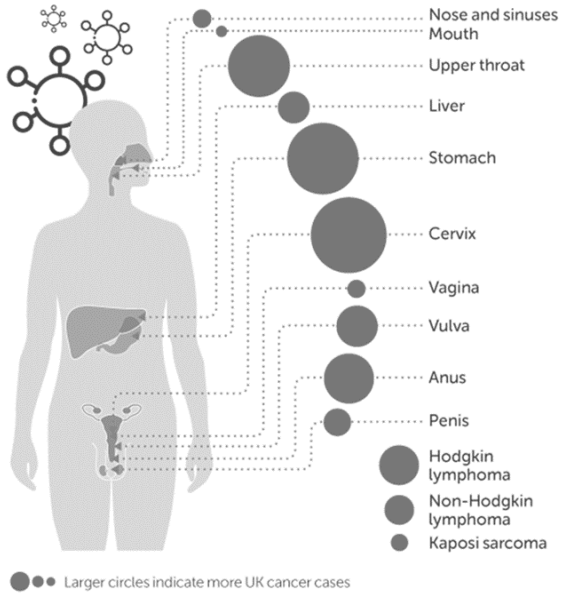
This is the first talk in a series on cancer, a battle we are slowly winning. The talk will cover two rapidly developing areas of cancer. The first is that some cancers have a strong infectious driver, a link to the previous series of lectures on infections. If these infections can be identified and then prevented or treated cancer may not occur. The second half is that the immune system protects against infection but also cancer. Using the immune system, or components of the immune system, to treat cancer is one of the fastest advancing areas in the fight against cancer.

Cancer and infection

Cancers with a strong infectious driver include cervical cancer in women (human papillomavirus), liver cancer (hepatitis B and C), some lymphomas caused by viruses, stomach and duodenal cancer caused by the bacteria *H. pylori* and rarer cancers caused by specific parasitic infections. HIV/AIDS enables several cancers including lymphoma and Kaposi's sarcoma. Figure 1, from Cancer Research UK shows some of the important cancers caused by infections in the UK.




Globally around 15% of cancers are estimated to be caused by infections. This is up to 1/3rd in Africa, and around 7% in Europe. In the UK and USA it is around 4%.

**Cervical cancer** is one of the of cancers with the clearest infection risk. Globally around half a million women are affected, with around 3000 cases a year in the UK. Put another way currently around 1/140 UK females will be diagnosed with cervical cancer in their lifetime, often at a young age. Survival has improved by over 70% since the 1970s, but there are still many early tragic deaths. Almost all of the cases are caused by a limited number of the human papilloma virus (HPV), which is very common. Screening has led to a 30 to 40% reduction in cervical cancer. The most important viruses causing cervical cancer are HPV 16 and 18. Vaccine effectiveness for these viruses is around 80%. The high coverage of HPV vaccine in girls in the UK will lead to a significant reduction in cervical cancer over the next four decades. The field continues to advance; vaccines covering a wider range of viruses being developed and deployed, and in the UK vaccination is now extending vaccination to boys. In addition to helping to protect women against cervical cancer this also should also reduce penile, vulval and anal cancers and some mouth and throat cancers caused by HPV.

Around 10% of **primary liver cancer, hepatoma**, in the UK is due to Hepatitis B and C (alcohol is a major driver here). However up to 90% of liver cancer in developing countries can be due to these viruses. In some countries hepatoma is probably the most common fatal cancer. Hepatitis B is common and easy to catch. It can be transmitted vertically from mother to child, horizontally between children and sexually. There are drugs to suppress but not cure Hepatitis B. There is however a highly effective vaccine against Hepatitis B and this is now being deployed globally. In Taiwan Hepatitis B vaccination reduced cancer incidence by 80% and mortality by over 90%. We therefore expect to see a significant fall in liver cancer globally in our lifetime. Hepatitis C is mainly acquired in adults predominantly through unsafe medical practice and intravenous drug use. There is no vaccine

currently but in the last 10 years several highly effective oral drugs have been developed with up to 90% cure rate. If treated early people should not progress to cancer.

The bacteria *H. pylori* is best known as a major cause of peptic ulcer (stomach ulcer, duodenal ulcer) disease. However, it also increases the risk 6 to 8 times for non-cardia **gastric (stomach) cancer**. It is also a major risk for a rare gut lymphoma. Treating (or preventing) *H. pylori* almost certainly reduces the risk of stomach cancer. Stomach cancer incidence has reduced by over 60% since the 1970s and continues to fall. The combination of early treatment of *H. pylori* and reductions in smoking, and possibly some changes in diet are likely to be major drivers of this improvement.

Several flukes, parasites which tend to have a life cycle depending on water snails are associated with increased risk of cancer. *Schistosomiasis haematobium*, a parasite (also known as Bilharzia) caught by bathing in infected water in Africa, can in heavy infections be associated with **bladder cancer**. Liver flukes caught by eating undercooked fish and shrimps, particularly in Asia, can cause the bile duct cancer **cholangiocarcinoma**. Control measures (schistosomiasis) and cooking or freezing fish (liver flukes) can substantially reduce the risk.

Other viruses can be associated with some significant cancers, in particular lymphomas. Epstein-Barr virus is very common is associated with about 40% of **Hodgkin lymphoma**. It is also associated with some **non-Hodgkin lymphomas** and the childhood disease **Burkitt's lymphoma,** also associated with malaria. A rare aggressive **adult T-cell leukaemia** is associated with the retrovirus HTLV-1. Probably the most important virus however is HIV. Its principal effect on cancer is to reduce substantially the effectiveness of the immune system if people progress to AIDS. This increases the risk of several of the infection-associated cancers outlined above including cervical cancer, liver cancer and lymphoma. A cancer which is extremely rare in people who do not have HIV, **Kaposi's sarcoma** (KS), is common in those with AIDS. If antiretroviral treatment is started early in HIV disease KS will not occur. KS is therefore much less common than it was 15 years ago in most countries.
*Cancer and the immune system.*

In addition to HIV several medical treatments suppress the immune system. For some this is temporary including some cancer chemotherapy and for some is relatively limited including for many inflammatory diseases. However, organ transplant requires significant immune suppression for a prolonged period to prevent organ rejection. There is clear evidence that following transplant the risk of several cancers increases. Cancer may also progress faster. Some of these are cancers with a known infectious trigger such as cervical cancer but also some non-infectious cancers are also much more likely in those who have significant immunosuppression from drugs. This is at least in part because the immune system in addition to protecting us against infections plays a major part in protecting us against cancers.

Increasingly tools from the immune system or the immune system itself are being used as treatment for cancer. Although some newspaper reports of breakthroughs maybe overly optimistic, there is no doubt this field, **immunotherapy**, will over time change the way much cancer is managed very substantially.

As listeners will know the immune system is extremely complex and multi-layered. Many elements of it are involved both in natural protection against cancer and in immunotherapy. This talk will highlight just a small number of the elements which are central to the fight against cancer. Broadly the immune system can be divided into the innate immune system, and the adaptive immune system. Within the innate system an important component is natural killer cells. These recognise missing self, that a cell surface marker (MHC) which signals that the cell belongs to you is missing and kill these cells. Some cancer cells lose this essential password and are therefore killed. Two components of the adaptive immune system are worth being reminded of. B-cells produce antibodies which lock very precisely onto particular receptors on a cell or another antigen. This ability to lock onto an extremely specific receptors is very important for immunotherapy. T-cells have multiple functions in cancer as well as infection but include killer T-cells which identify cell with a specific antigen and kill that. By definition cancer is in cells which have evaded the immune system.

The oldest immunotherapy still in wide use is probably BCG infection for **bladder cancer**. Bladder cancer is declining largely due to reductions in cigarette smoking but remains an important cancer with around 10,000 cases a year in the UK. Initial therapy for early disease is to cauterise off the cancer from the bladder wall. In many cases BCG, a modified mycobacterium like tuberculosis most commonly used as a vaccine, can be infused into the bladder. This causes inflammation and widespread immune activation and reduces progression by about 27%.

Several groups of drugs depend on using the very precise properties of **antibodies**. Like a key in a lock they have a variable and a constant end. They can now be manufactured very precisely to a cancer receptor. This has multiple potential uses. The simplest (although still complicated) is to manufacture antibodies which flag a cancer cell by locking onto receptors that are unique to that cell or are much more common in the cancer cell than other normal cells. One role for antibodies in nature is to flag a cell to the innate immune system for it to destroy. Some drugs work in this way, flagging cancer cells for destruction.

A second group of uses for antibodies is by binding with receptors on cancer cells which block or interfere with essential processes for cancer cell function. Two quite well-known examples are trastuzumab (Herceptin) which binds to HER-2 positive **breast cancer** cells and bevacizumab (Avastin) which interferes with the ability of solid cancers to grow blood vessels.

A third use of antibodies is to deliver toxic chemotherapy or radiotherapy very precisely to a cancer cell, reducing the toxicity for the rest of the body.

Immunotherapy can also use the **cellular immune system**. An important example is **melanoma**. There are around 16,000 cases a year in the UK. Survival is now around 90%, up from less than 50% in the 1970s and this is mainly due to better detection and early surgery to remove it. Once it has spread however it was until recently very difficult to treat. One drug class which has been in use for some time but is only slightly effective in cancer are the interferons, a group of proteins that activate the immune system. A major advance in the last few years however are drugs which cause immune checkpoint blockade. The immune system has several brakes to avoid over-activating. Several antibodies have been produced to block these and remove the brakes and the result is the immune system is much more vigorously activated. Advanced melanoma is one of the diseases which have been significantly improved by this technique. In the last month 5-year data of a trial of immune checkpoint drugs has shown over 50% survival at five years in advanced disease when given in combination. This area of science is still in its infancy. Removing the brakes on the immune system can lead to very dangerous reactions or intolerable side effects so (like most chemotherapy) it is not without risk.

The most personalised current immunotherapy is probably CAR-T therapy. T-cells are harvested from a patient with cancer. The gene for the receptor common in the cancer is inserted cells are grown and infused into the patient again. They hunt down and kill the cells with the receptor. Currently this method is only used in some lymphomas but in time may have wider use. It is very expensive and likely to remain so.

Vaccinations which prime the immune system to attack specific infections have proved one of the most powerful, versatile and durable tools in medicine. Vaccinations to stimulate the immune system for cancers are a biologically reasonable and attractive target. These might be therapeutic vaccines to stimulate the immune system against particular cancers during treatment, or theoretically to vaccinate against cancers before they occur. To date they have however proved difficult to get to work but may well be an avenue for the future.

This talk has considered several aspects of cancer and infection. Some cancers have a strong infectious driver, which can be prevented or treated and therefore significantly reducing the risk of getting the cancer. When the immune system is suppressed or damaged the risk of several cancers increases. Several elements of the immune system, including antibodies and cellular immunity can be used to fight cancer. This is a very encouraging area for the prevention and treatment of several cancers, to which we will return in subsequent lectures.

**Further reading**.

For comprehensive data on cancer in the UK, including up-to-date statistics on all the major cancers, the most readable source is the Cancer Research UK website.

https://www.cancerresearchuk.org/about-cancer/type

Immunotherapy is a fast-moving field, but a recent review on immune checkpoint blockade is a good if technical summary.

Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science.* 2018;359:1350-1355. https://science.sciencemag.org/content/359/6382/1350.full