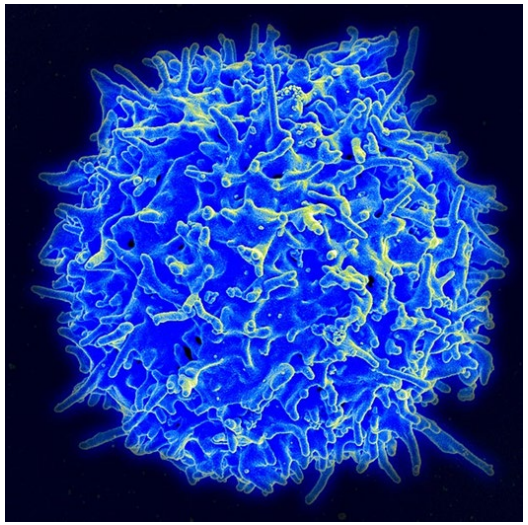
Infection, immunity and cancer.



Christopher Whitty

Gresham College 2019

Infection, immunity and cancer.

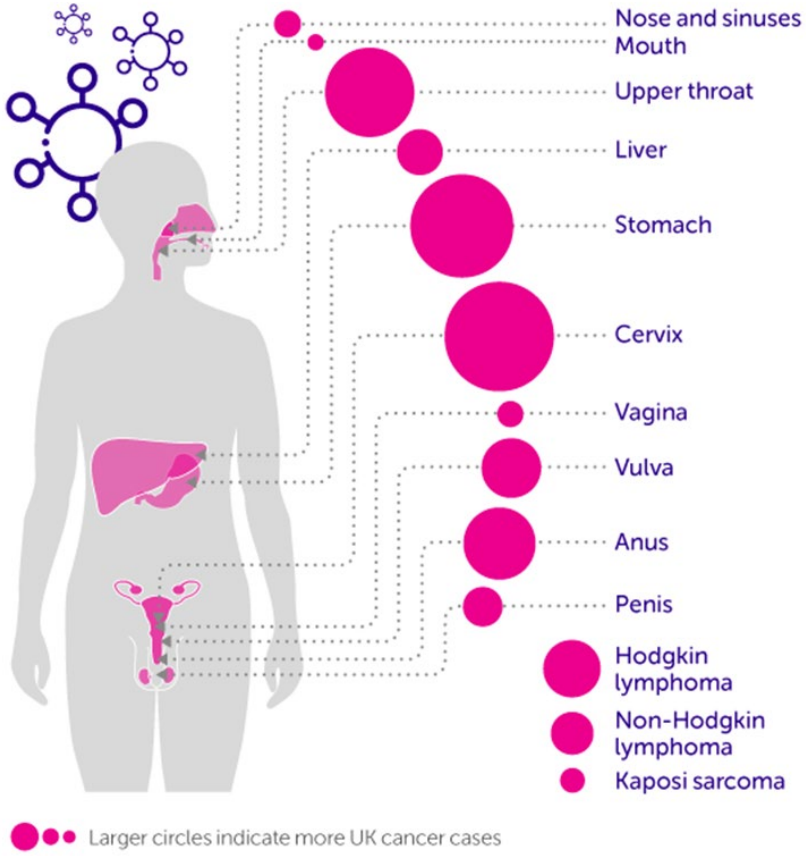
- Dr. Tulp said cancer is contagious in the 1600s; he was partially right.
- Some cancers have a strong infectious driver.
- If these can be identified, and then prevented or treated cancer may not occur.
- The immune system protects against infection and cancer.
- Using the immune system an increasingly important area of cancer treatment.

Rembrandt. *The anatomy lesson of Dr. Nicolaes Tulp*. 1632.

Cancers with strong infectious drivers include:

- Cervical cancer – human papilloma virus (HPV).
- Liver cancer- Hepatitis B and C.
- Some lymphomas caused by viruses.
- Some stomach and duodenal cancer- the bacteria *H. pylori*.
- Rarer cancers caused by specific parasitic infections.

- HIV enables several cancers including lymphoma and Kaposi's sarcoma.

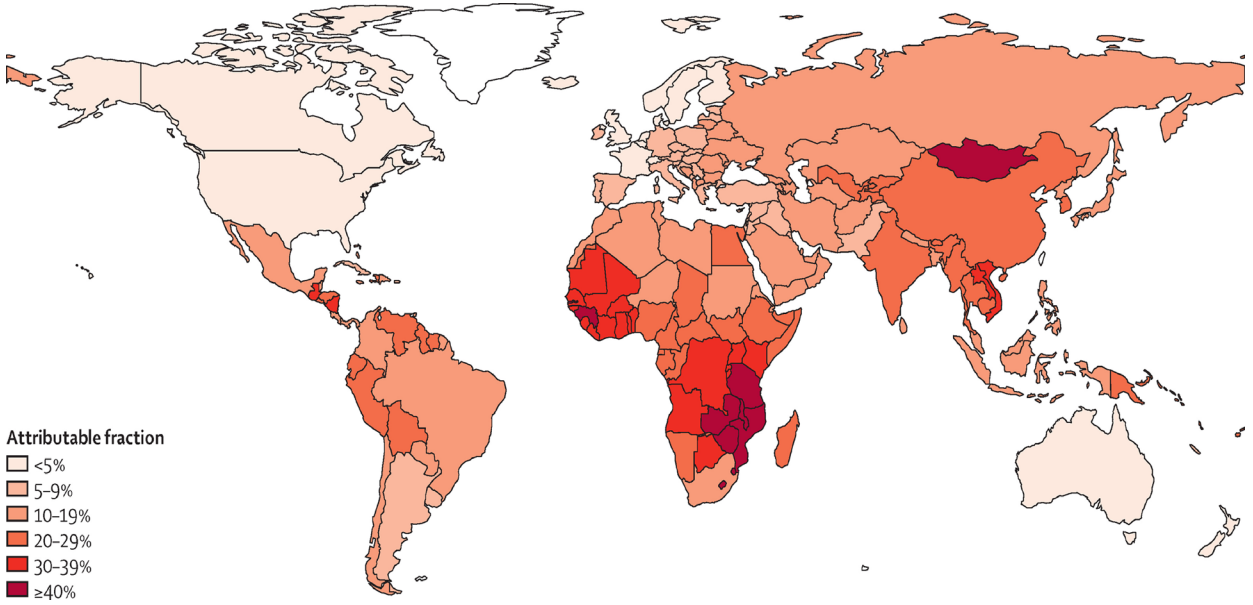


UK infection-driven cancer.
CRUK

Epidemiology of cancer caused by infection.

- Globally around 15% of cancers estimated to be caused by infections. 2.2 million a year.
- Up to a third in Africa. In Europe around 7%. UK, USA around 4%.

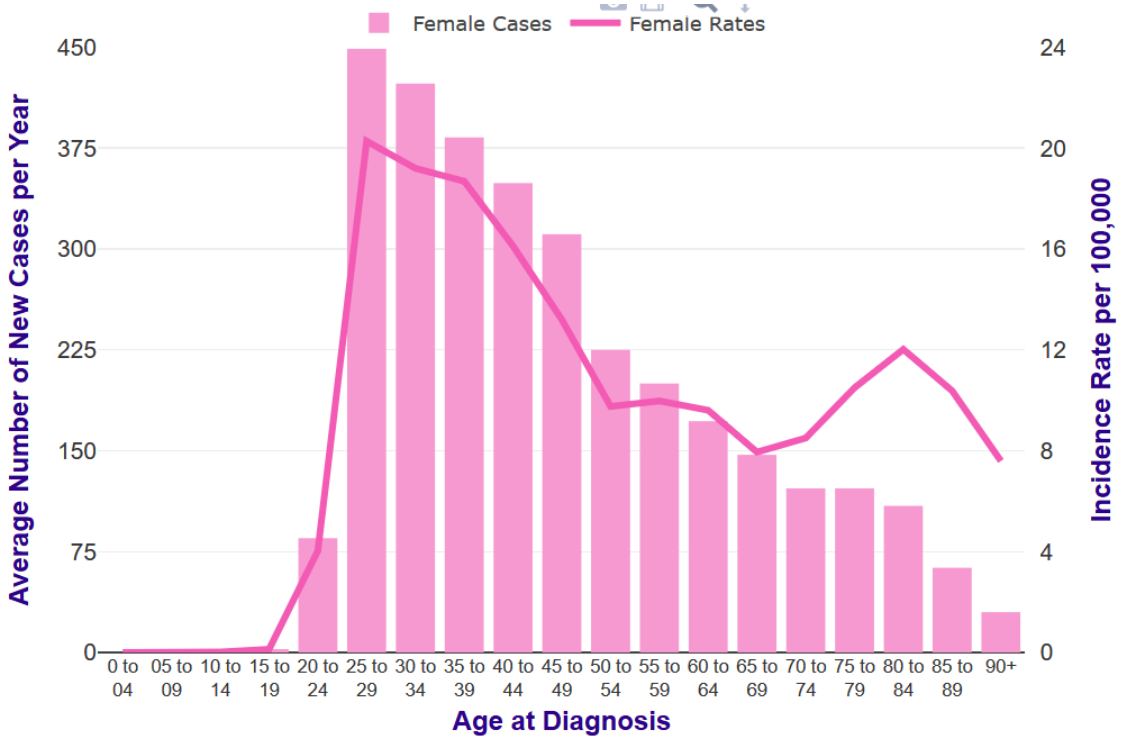
- 730,000 non-cardia gastric (stomach) cancers (89% total).
- 570,000 liver cancers (73% total).
- 530,000 cervical cancers (almost 100% total).



Plummer M et al 2016.

Cervical cancer.

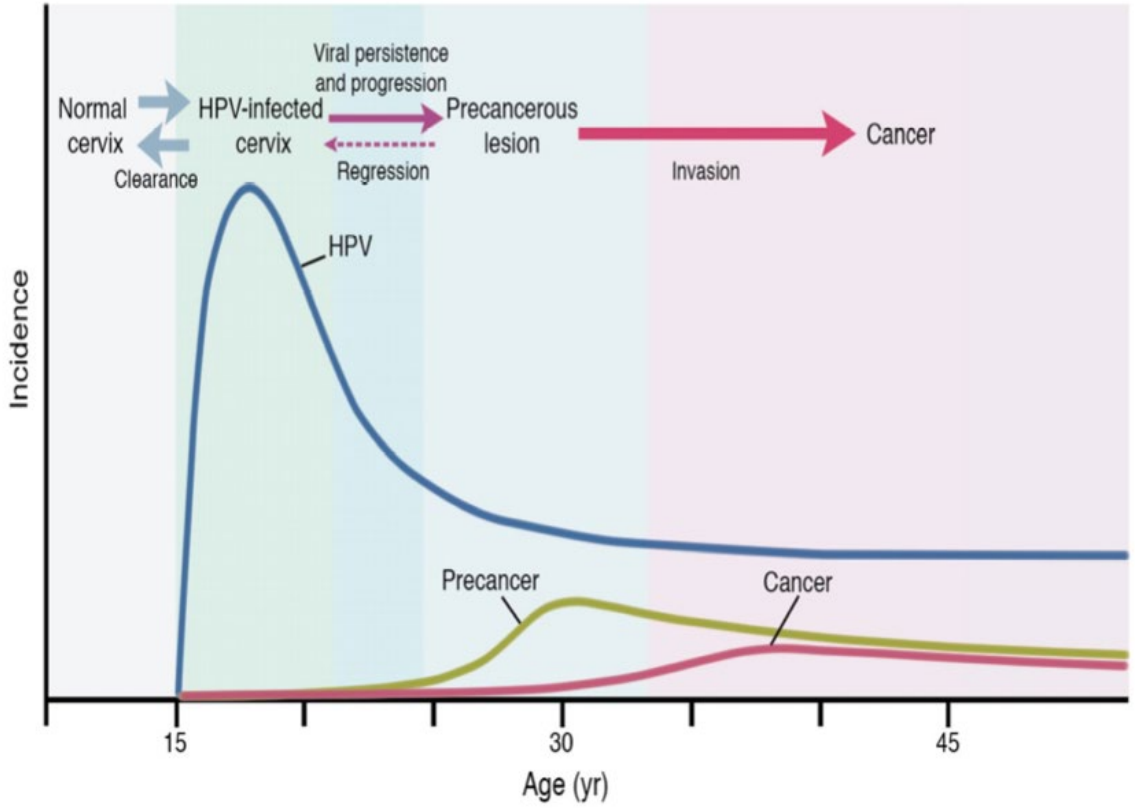
- Globally around half a million women affected.
- Around 3000 cases a year in UK.
- 1 in 142 UK females will be diagnosed with cervical cancer in their lifetime.
- 850 deaths a year. Often young.
- 10 year survival 63%. Survival has improved by 74% since 1970s.
- Almost 100% preventable.



CRUK

Almost all (>99%) cervical cancer caused by papillomaviruses (HPV).

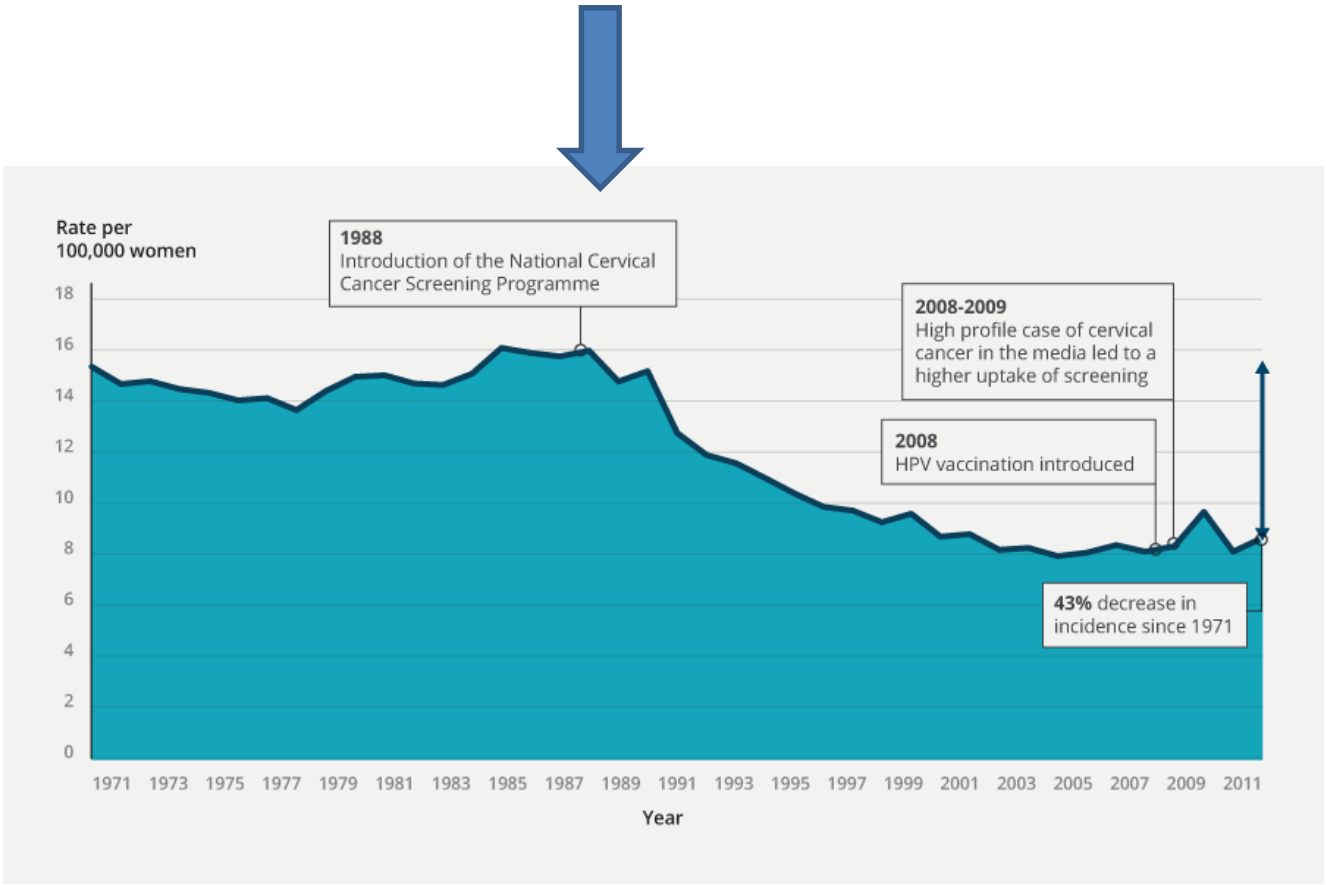
- Over 40 genital HPV viruses. Extremely common. Some cause warts (but not cancer). Many harmless.
- Generally acquired early after sexual debut. Most cleared.
- HPV16 and 18 responsible for 50-70% cervical cancer.
- Around 12 more can cause cancers.
- Smoking and HIV increase risk but HPV needed.



Schematic of HPV and cervical cancer. *U. Wisconsin.*

Screening of women 25-64 for pre-cancerous cells ('smear' or PAP test). Introduced in UK 1988.

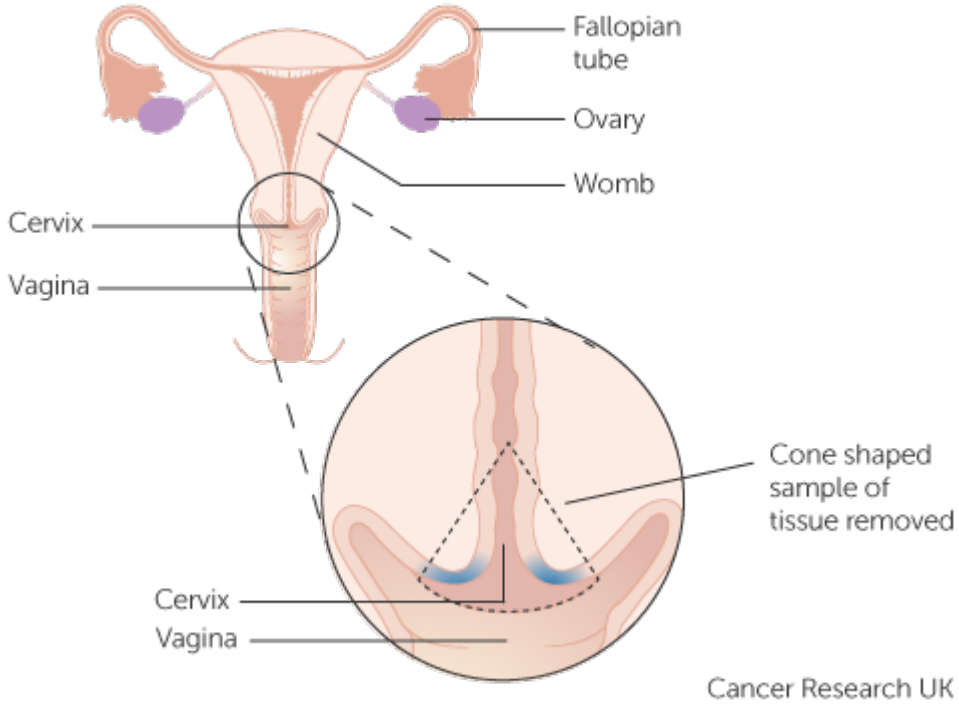
- Has led to a substantial reduction in cervical cancer- 30-40% in UK (ONS).
- Saves around 5000 lives a year in the UK.
- New primary HPV DNA tests from this year (UK) improve accuracy. Around 20% less cancer possible.



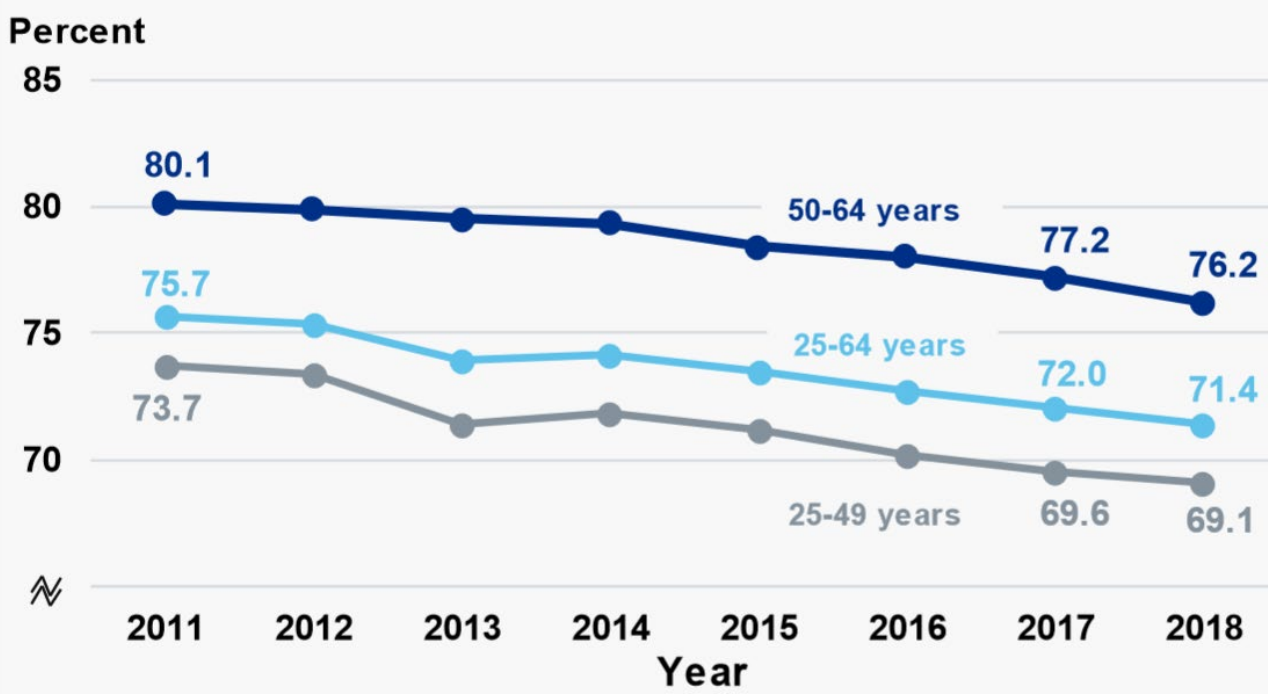
Rate/100,000 women since 1970

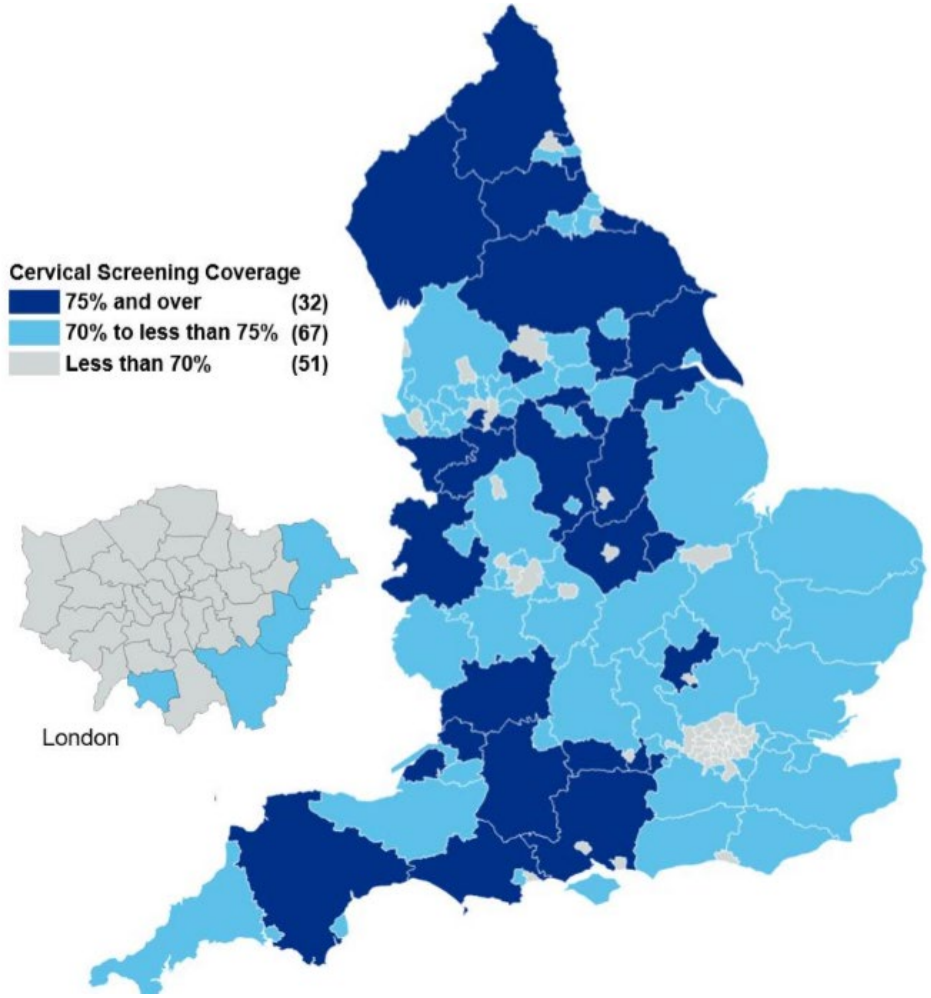
What are the downsides? It's a balance of risk and benefit.

- The earlier the identification the less invasive the treatment.
- Early identification leads to some over-treatment with relatively low-risk procedures.
- Later identification higher risk procedures but more will progress.
- Late identification- surgery- eg hysterectomy.
- Very late- it has spread. Major treatment.



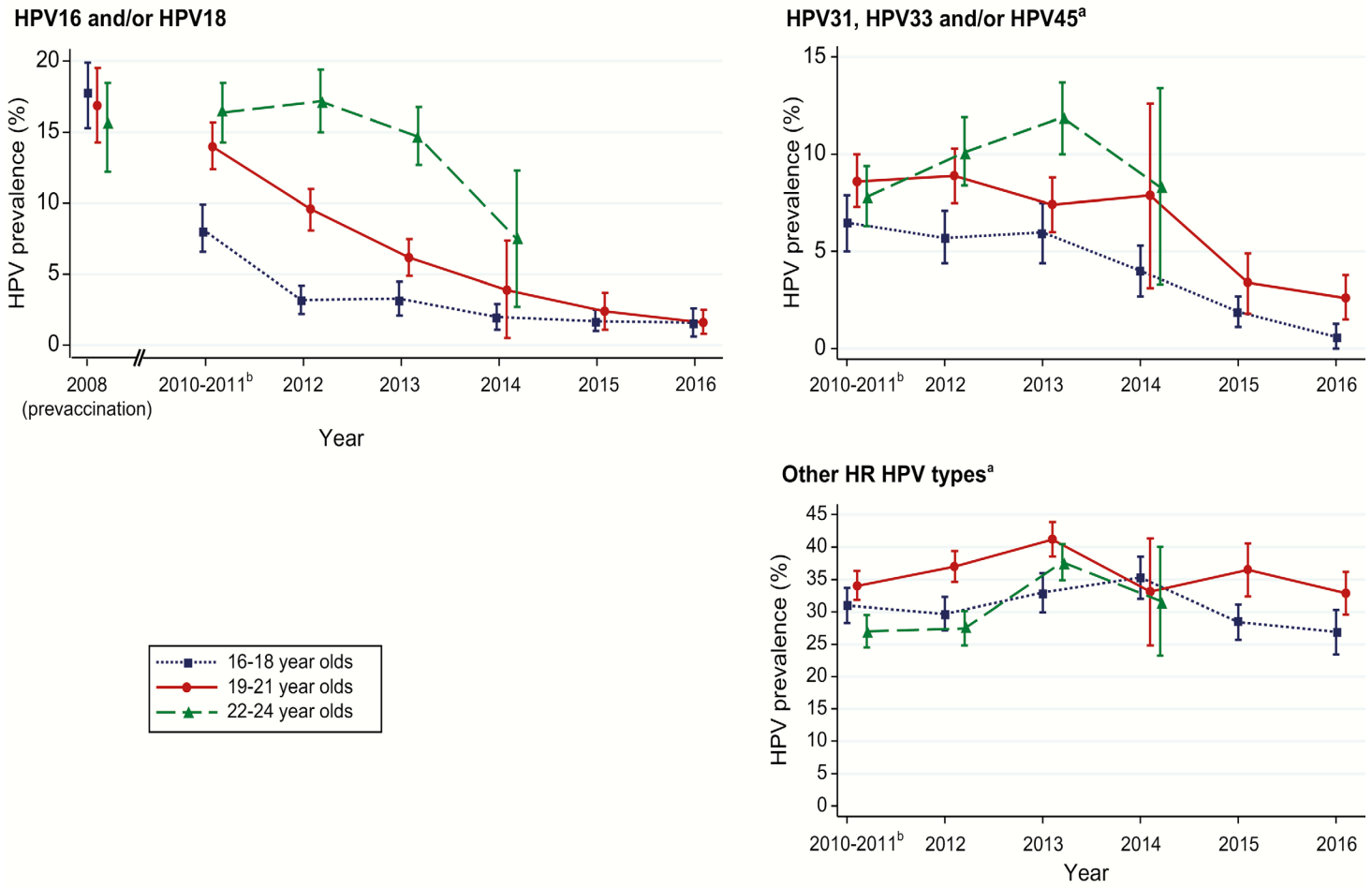
Cervical screening rates are declining in England. London has a particular problem. *NHS Digital*





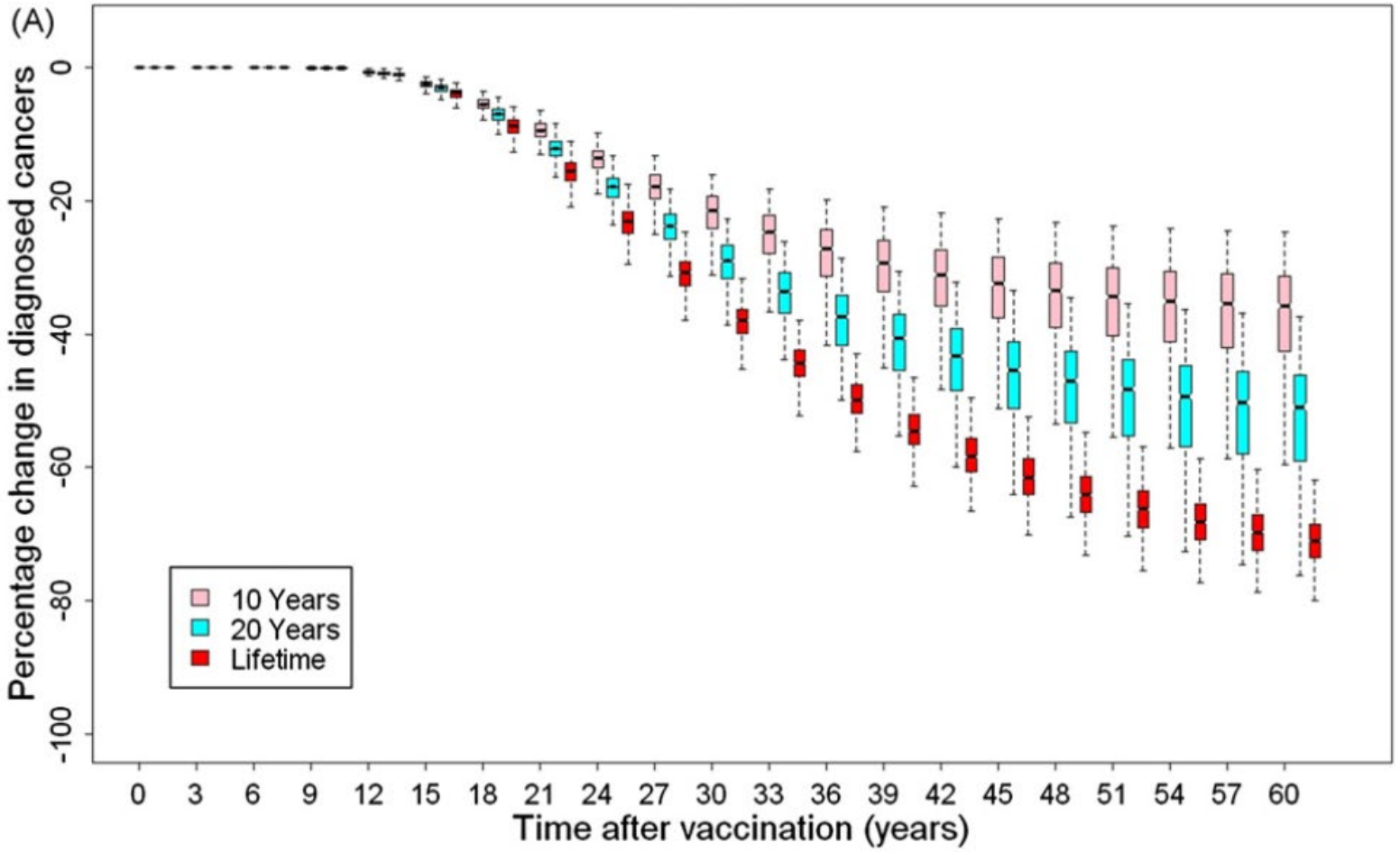
UK vaccine for girls against HPV 16, 18 introduced in 2008.

- Prevalence of HPV16/18 decreased between 2010/2011 and 2016 from 14.0% to 1.6% in 19–21 year olds attending chlamydia screening.
- Vaccine effectiveness for HPV16/18 was 82%.



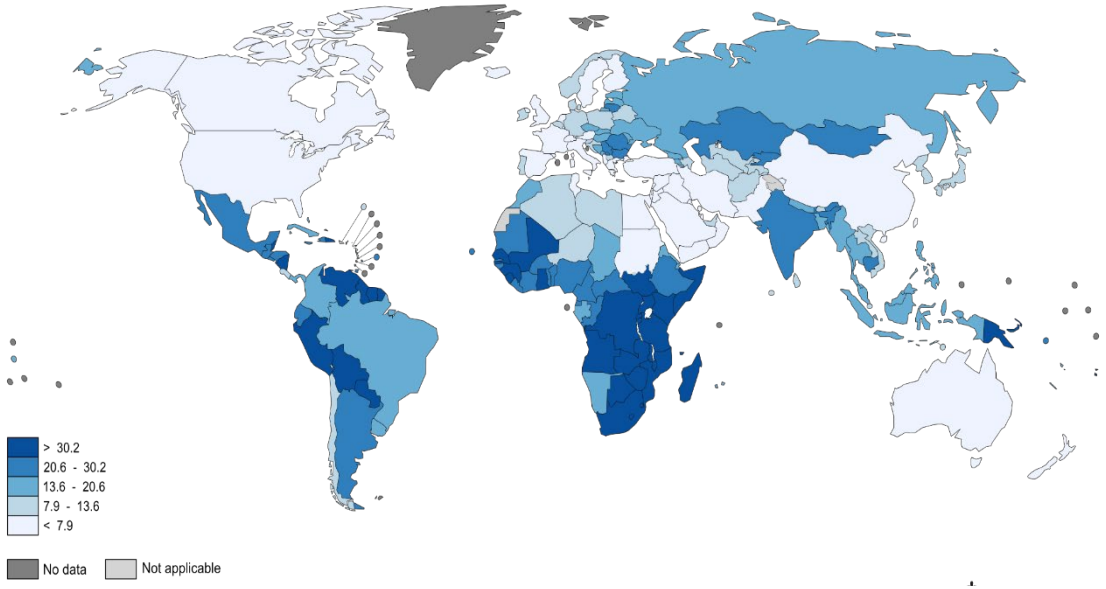
Mesher D et al JID 2018. In girls/women for chlamydia screening.

Reduction in cancer depends on how long immunity lasts, what % coverage vaccine. HPV 16, 18 only vaccine model. *(Yoon Hong Choi et al)*



Vaccination will lead to a substantial global reduction in cervical cancer. Provided vaccine uptake remains high.

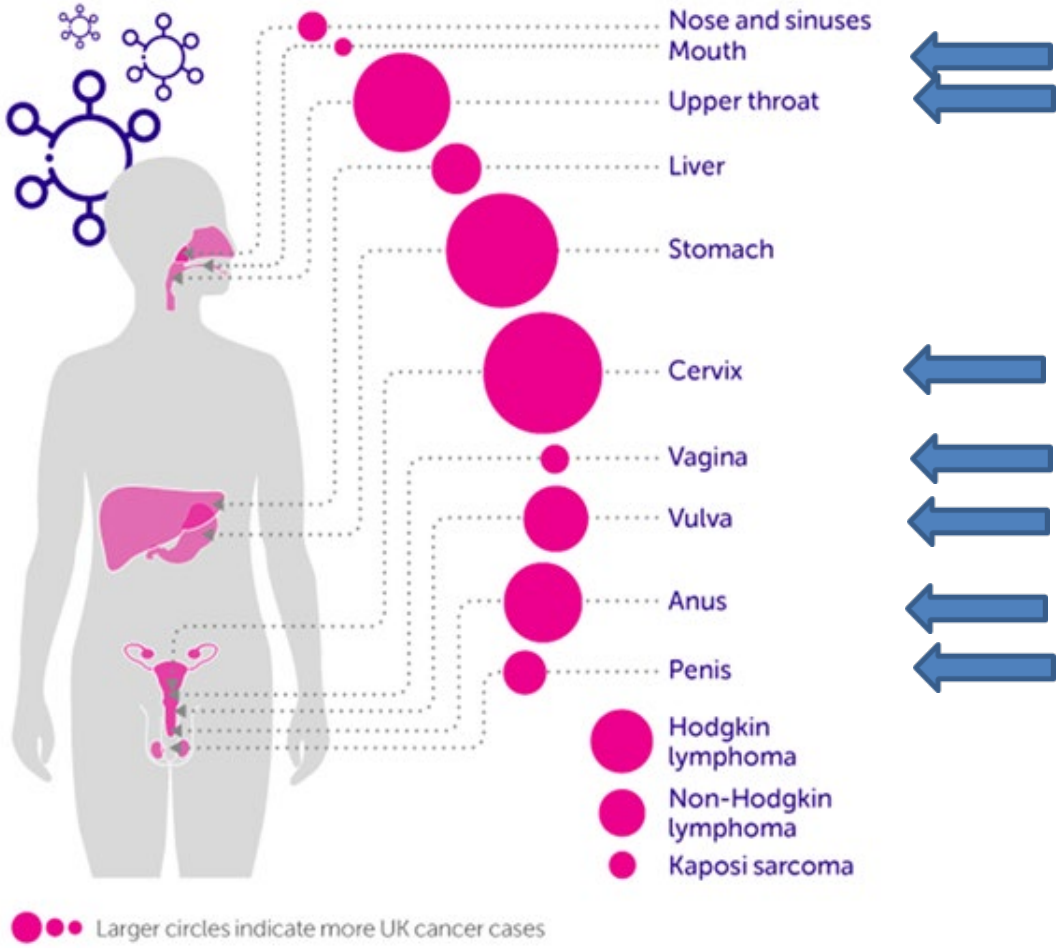
- Recent meta-analysis of 60 million people with up to 8 years follow up. Population based.
- Prevalence of HPV 16, 18 reduced by 83%, HPV 31, 33, 45 by 54% in girls 15-19.
- After 5-9 years of vaccination, CIN2+ decreased significantly by around 50% (RR 0·49, 95% CI 0·42-0·58) among screened girls aged 15-19 years.



WHO map on cervical cancer.
Drolet et al Lancet 2019

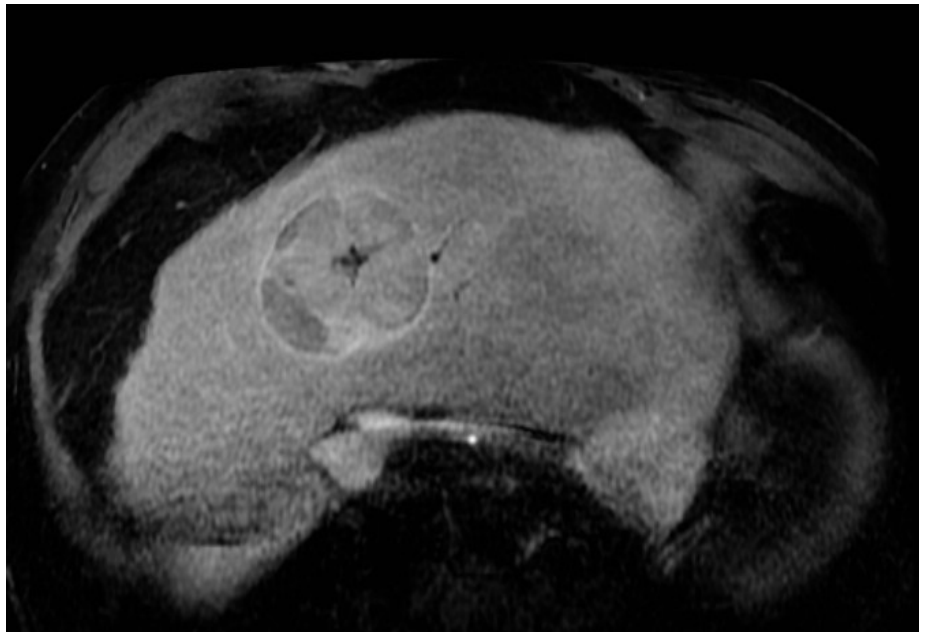
Improvements in combatting HPV driven cancer are continuing.

- Vaccines covering a wider range of HPV viruses developed.
- Robust data on safety continues to accumulate.
- Extension of vaccination to boys.
- Most vulval, penile, anal cancers caused by HPV, and some mouth tongue and throat cancers: HPV vaccines also protects against these.



Liver cancer and hepatitis.

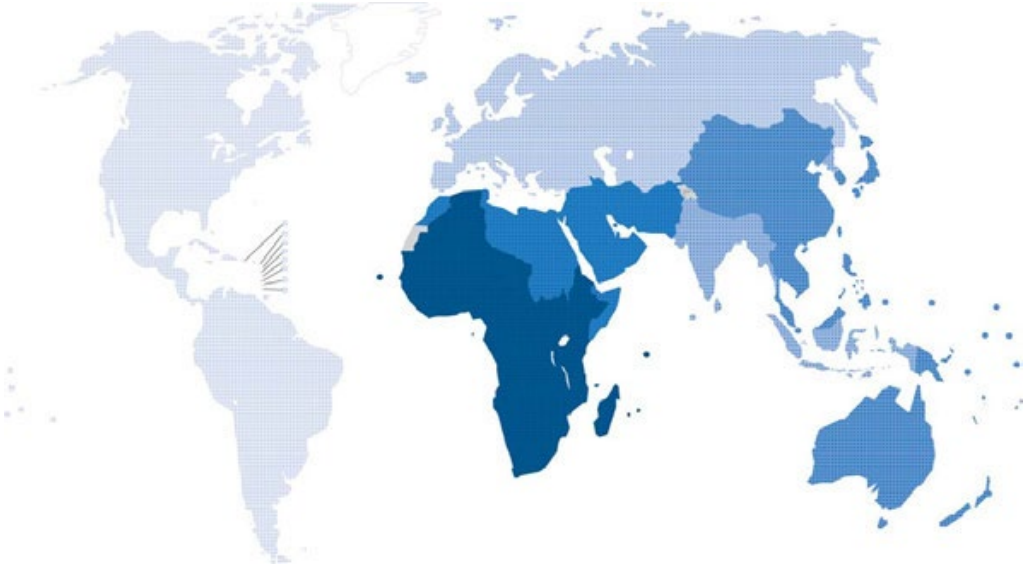
- Around 10% of primary liver cancer in the UK due to Hepatitis B or C.
- Mainly secondary to cirrhosis.
- Up to 90% of liver cancer (hepatoma) in developing countries and 40% in developed countries due to Hepatitis B and C.
- In some countries hepatoma the most common major cancer.



Dr Natalie Yang, Radiopaedia.org

Hepatitis B- bloodborne and sexual.

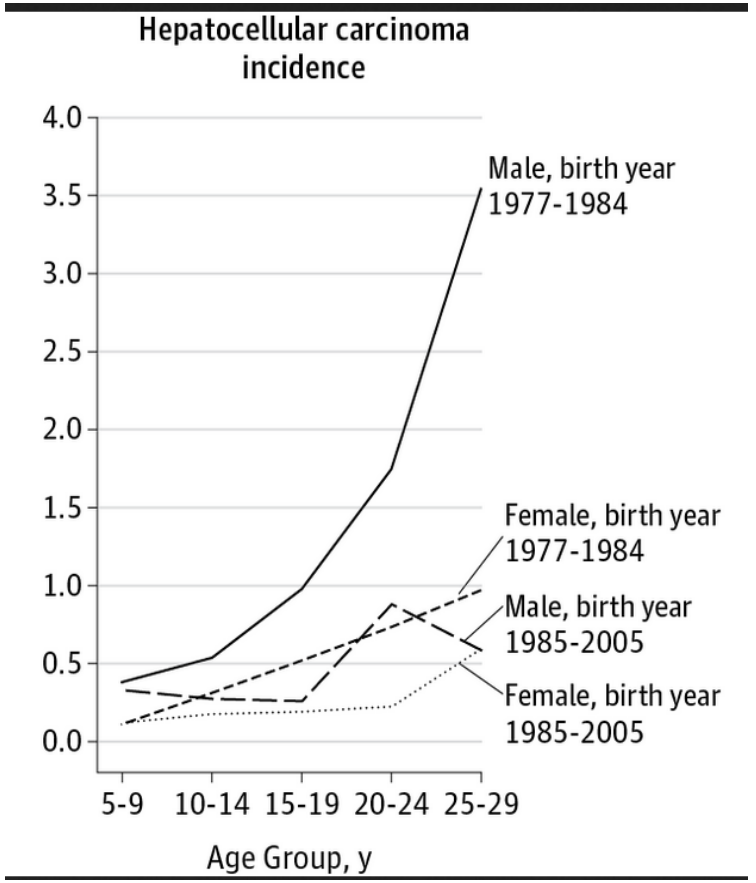
- Hepatitis B common, easy to catch.
- WHO estimates over 250 million infected.
- Vertical transmission mother-to-child.
- Horizontal transmission between children. Most infection is before 5 y.
- Sexual / IVDU transmission in adults.
- Drugs to suppress, but not cure, available.



Hepatitis B. WHO

Prevention by vaccination: Hepatitis B and hepatocellular carcinoma (liver cancer, HCC).

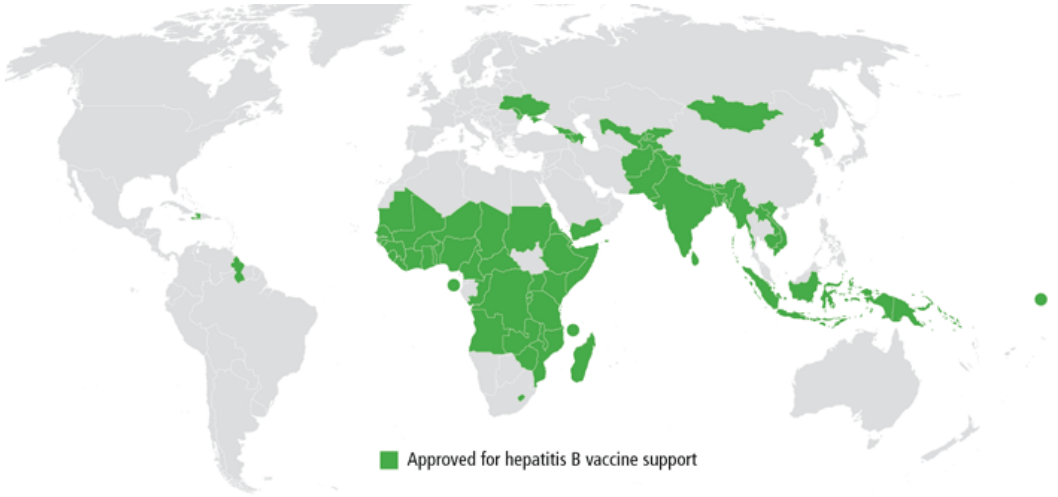
- Whilst Hepatitis B and C rare causes of liver cancer in the UK, major ones in Asia and Africa. High mortality.
- A significant risk in migrants.
- Taiwan Hep B vaccination programme for infants 1984. Reduced cancer incidence by 80%, mortality by over 90%.
- In Africa potentiated by a fungal toxin of peanuts (aflatoxin).



C. Chaing et al JAMA 2013

There is now a concerned attempt to eliminate Hepatitis B associated cancer globally.

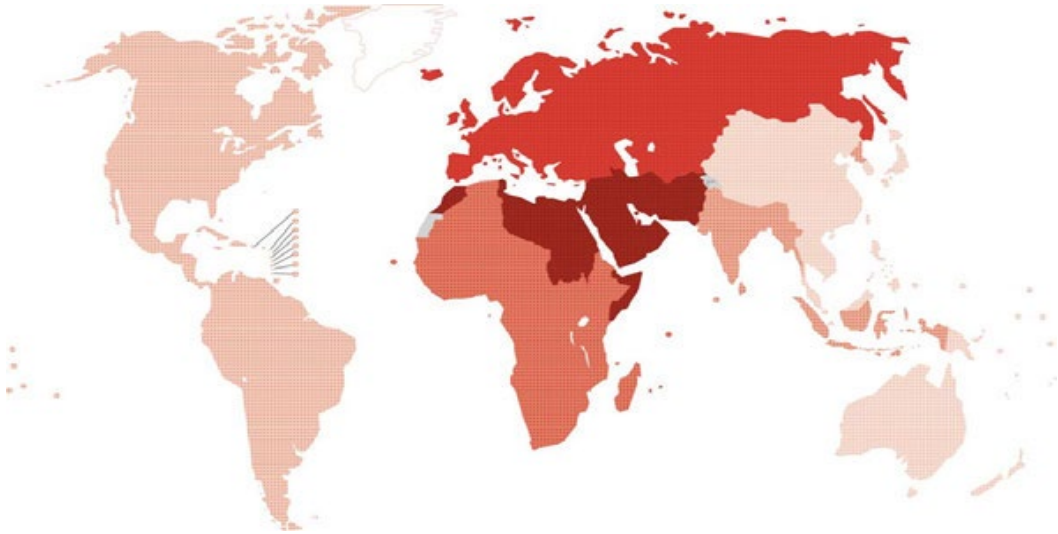
- Most children globally, including in the UK, are now vaccinated with combined Diphtheria, tetanus, pertussis, Hib, Hepatitis B (+/- polio). 84% coverage.
- Provides 95-100% Hepatitis B protection.
- Whilst complete eradication may be an ask too far, there will be a dramatic fall in Hepatis B in our lifetime.
- We will therefore see a substantial fall in liver cancer globally.

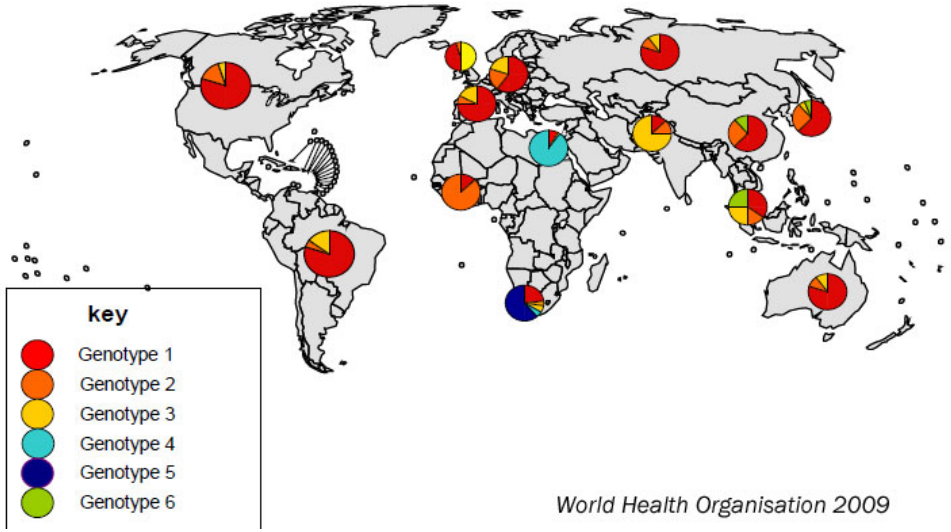


GAVI

Hepatitis C.

- Different epidemiology from Hep B.
- Great majority acquired in adults, mainly unsafe medical practice and IVDU.
- >1.5M new cases a year (WHO).
- No vaccine. Different genotypes.
- In the last 10 years several highly effective oral drugs.
- Up to 90% cure rate.





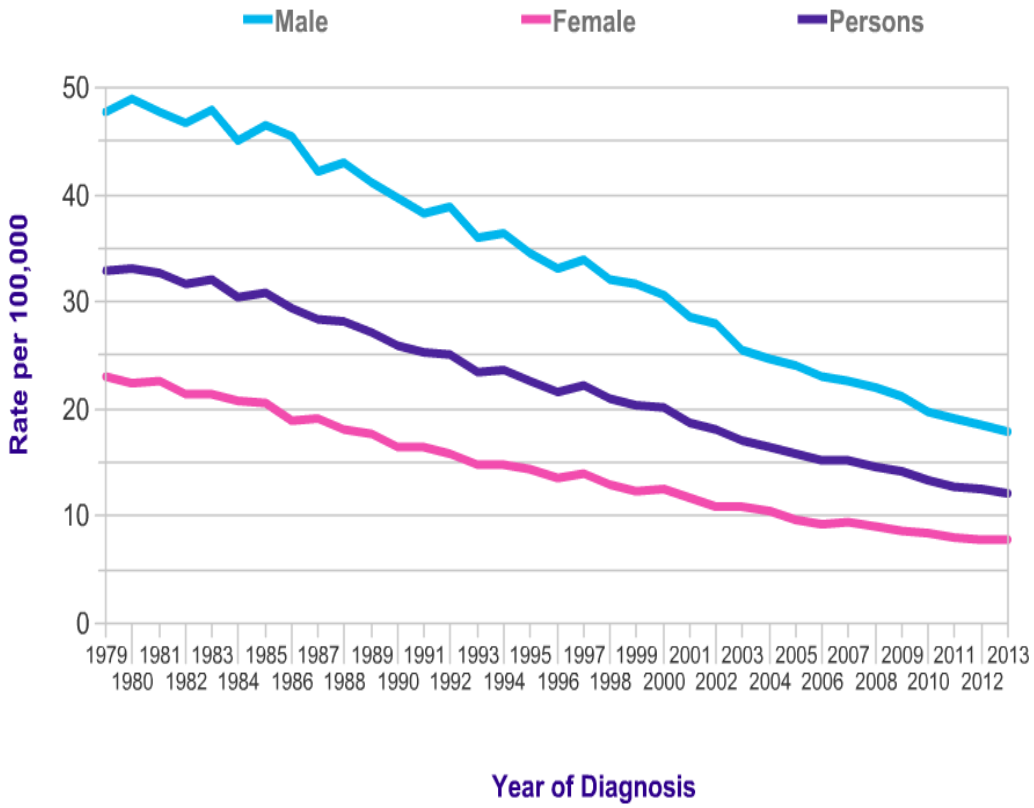
H. pylori and gastric (stomach) cancer.

- Best known as the major cause of peptic ulcer disease.
- Increases risk around 6-8x for non-cardia gastric cancer (the main type).
- May reduce cardia gastric cancer (not yet clear).
- A major risk for a rare gut lymphoma (MALToma).

Electron micrograph *H. pylori.*
Dr. Y. Tsutsumi

Does treating *H. pylori* prevent gastric (stomach) cancer?

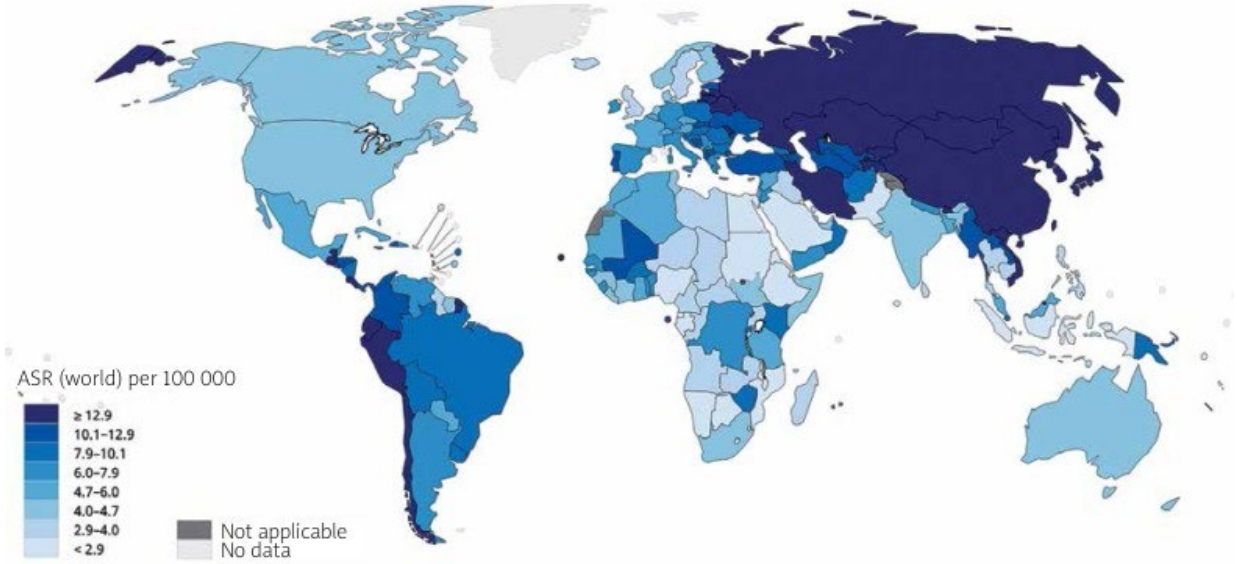
- Almost certainly yes, RR around 0.65 in meta-analyses in trials of around 8000 patients. Most from China.
- May not once pre-cancerous cells identified.
- Around 6700 cases of stomach cancer in UK annually. High mortality, although improving.
- Around a third of UK stomach cancer *H. pylori* related. Often treated for ulcers.
- Smoking, diet also important.



Stomach cancer incidence decreased 62% in UK since 1970s. Projected to fall 17% more by 2035 *(CRUK)*

Stomach cancer is particularly common in Asia

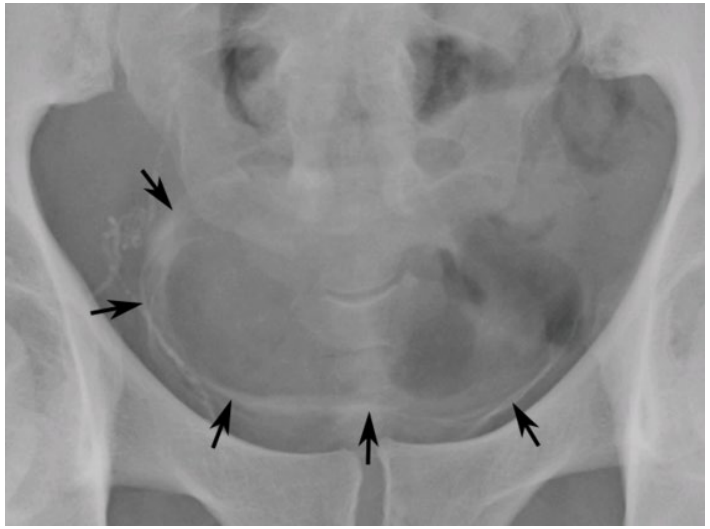
- Globally stomach cancer is common. Around 2/3rds due to *H. pylori*.
- Most people with *H. pylori* do not get cancer.
- Epstein-Barr virus may also contribute.
- Around 950,000 cases globally.
- Historically (pre 1930s) probably the most common fatal cancer.



IARC data

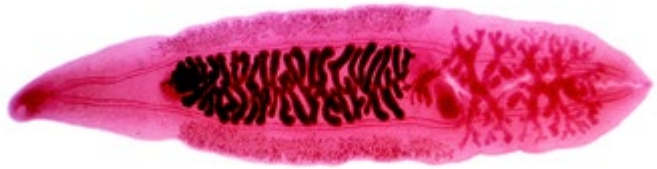
Parasitic infections. Schistosomiasis and bladder cancer.

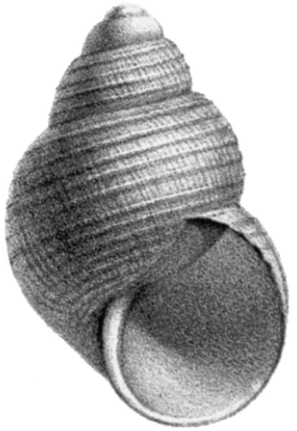
- Bladder cancer with urinary schistosomiasis.
- Exposure to fresh water containing specific snails in Africa and Middle East.
- Development, sanitation and mass drug administration helping to control it.



Parasitic infections- liver flukes.

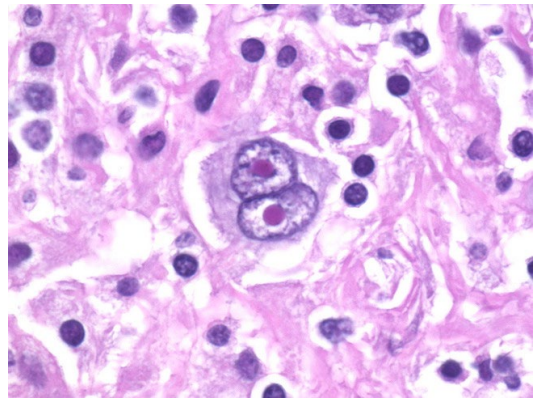
- Cholangiocarcinoma (bile duct cancer) with liver flukes.
- Snail-fish-human/carnivore cycle.
- Uncooked fish (especially carp) and shrimps. Mainly East Asia.
- Cooking, freezing and mass drug administration.





Other viruses: EBV and cancer.

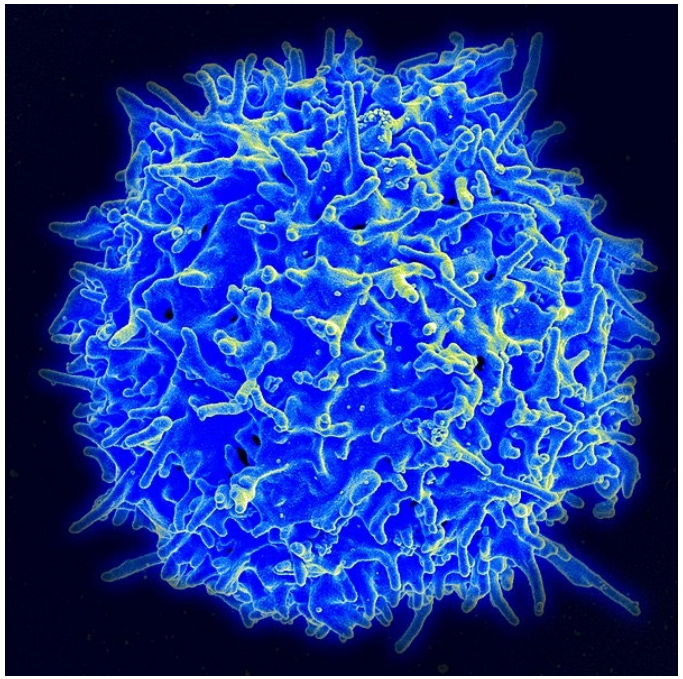
- Epstein-Barr virus (EBV) very common, around 90% infected. Chronic.
- Associated with about 40% of Hodgkin lymphoma. EBV nucleic acid and protein in the lymphoma cell.
- Some non-Hodgkin lymphomas.
- EBV and malaria associated with Burkitt's lymphoma in Africa.
- Some throat and stomach cancers.



Mike Blyth / Reed-Sternberg cell Wikimedia

HTLV and cancer

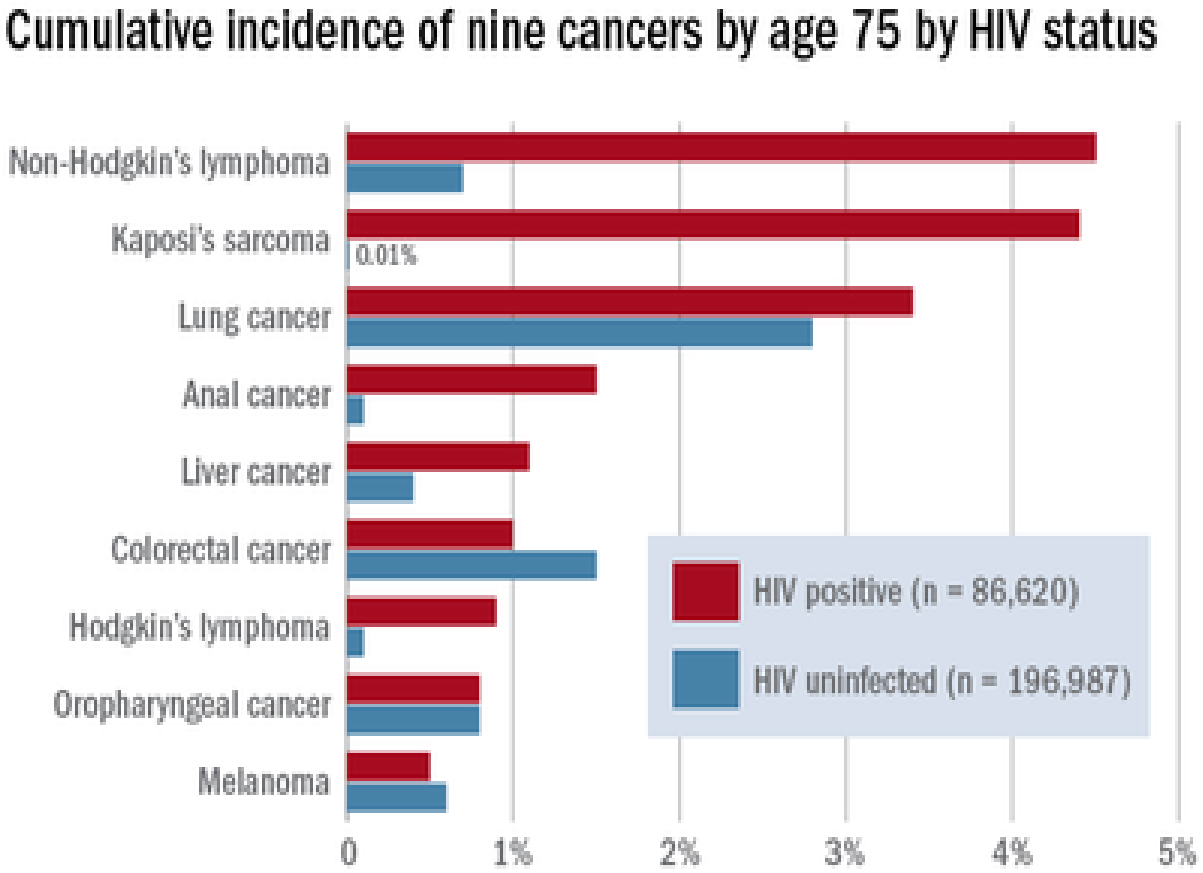
- Human T-lymphotropic virus 1 (HTLV1) is a retrovirus.
- Some biological similarities to HIV.
- Most common Japan, Caribbean, but does rarely occur in UK and USA.
- Associated with a rare, aggressive Adult T-cell leukaemia/lymphoma (ATL).



Healthy T-cell. NIH

HIV and cancer

- HIV/AIDS increases the risk of several cancers, including:
- Kaposi's sarcoma.
- Non-Hodgkin and Hodgkin lymphoma.
- Cervical cancer and other HPV cancers.
- Liver cancer.



Rodrigues, Adapted from Silverberg M et al 2015. US data 1996-2009.

Kaposi’s sarcoma (KS).

- Caused by the herpesvirus HHV8.
- Aggressive cancer of skin, mouth, respiratory tract and gut.
- Very rare in those without immunosuppression.
- Very common in those with AIDS. Was 35% or more in some groups.
- Usually regresses with antiretroviral treatment.
- If ARV treatment started early in HIV disease KS will not occur.

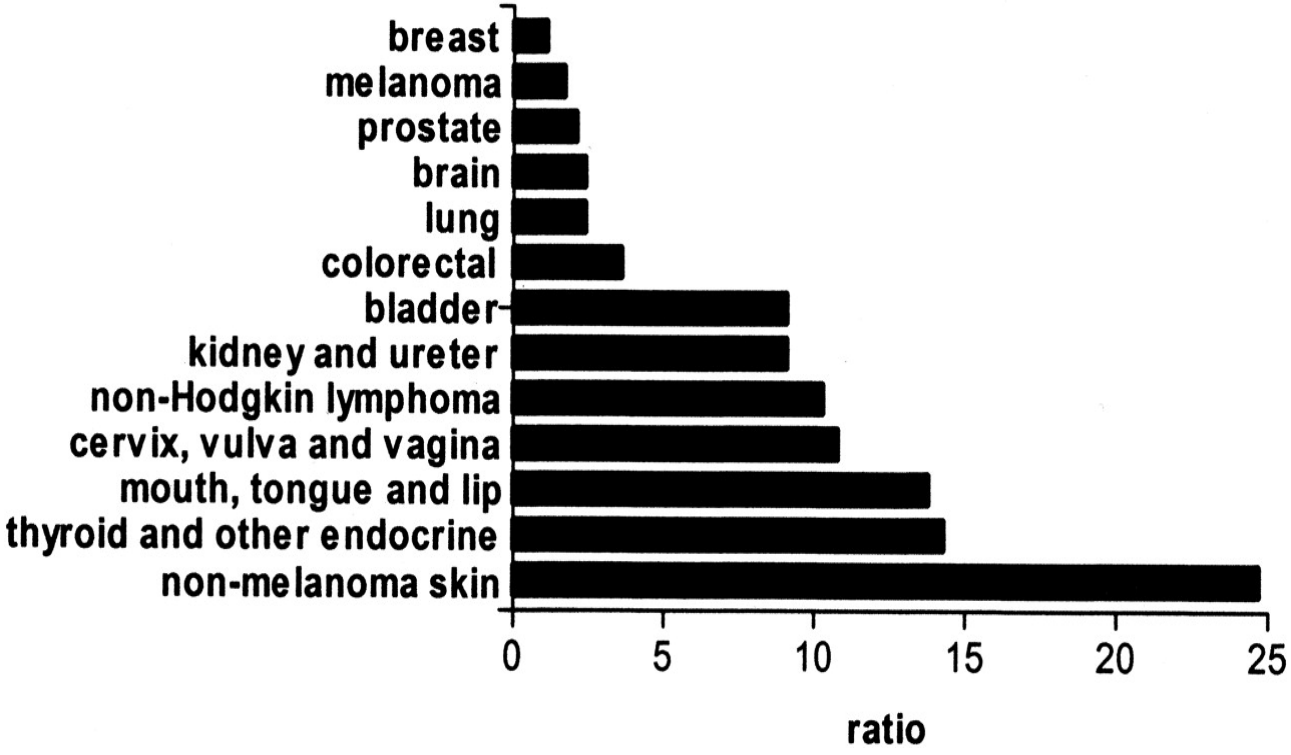
HIV disrupts the immune system. So do doctors.

- Several medical treatments suppress the immune system.
- Some is temporary, including some cancer chemotherapy.
- Some is relatively limited for inflammatory diseases.
- Organ transplant requires significant immune suppression to prevent organ rejection.

Reconstruction of first successful heart transplant.

Following transplant increased cancer risk.

- 2-3x increased risk of getting cancer.
- Higher risk of that cancer progressing fast.
- Some are cancers, like Kaposi's sarcoma, which are infectious in origin.
- But also several other cancers. Non-infectious skin cancers example.

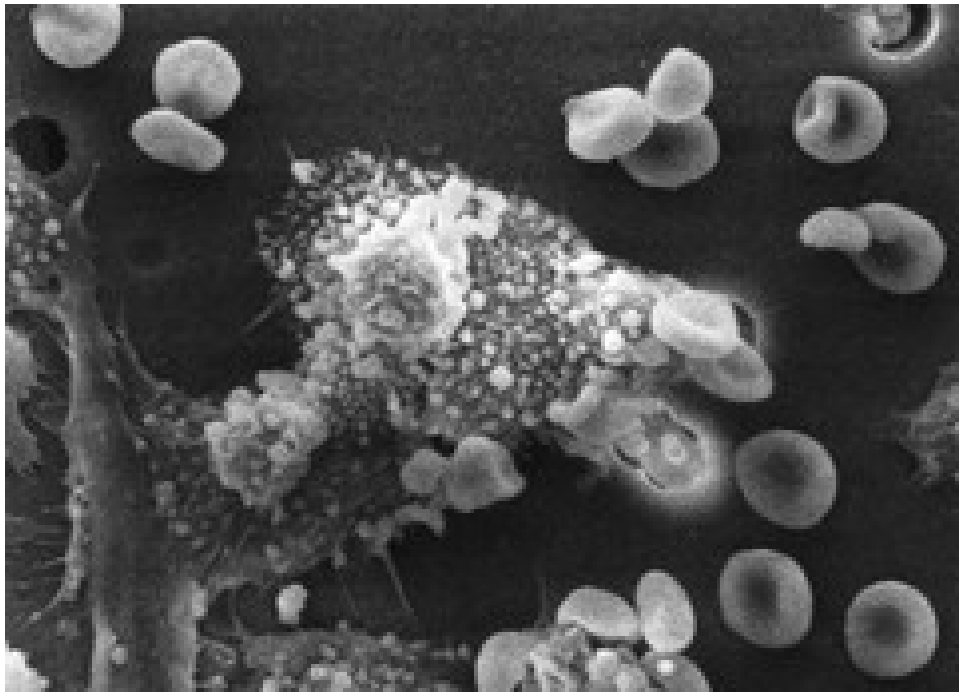


Ratio observed/expected malignancies in graft recipients.

Morath et al 2004

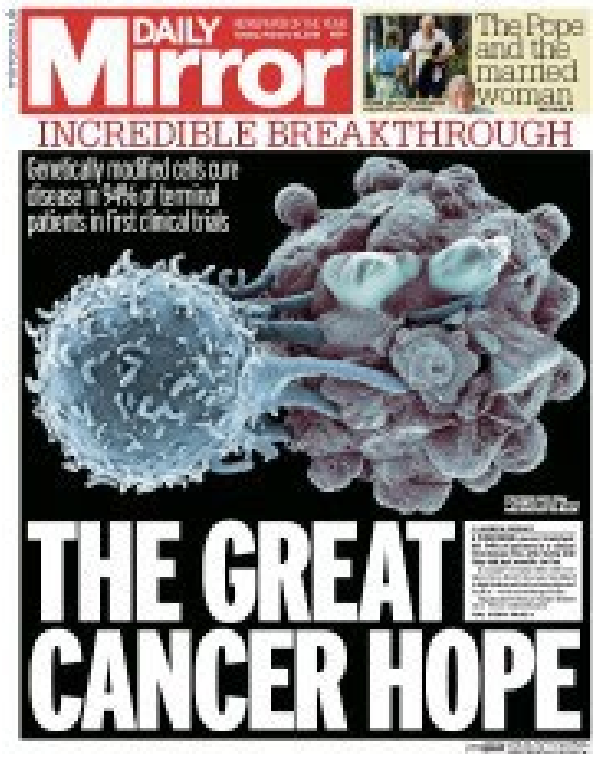
Immune system very important in cancer and infection.

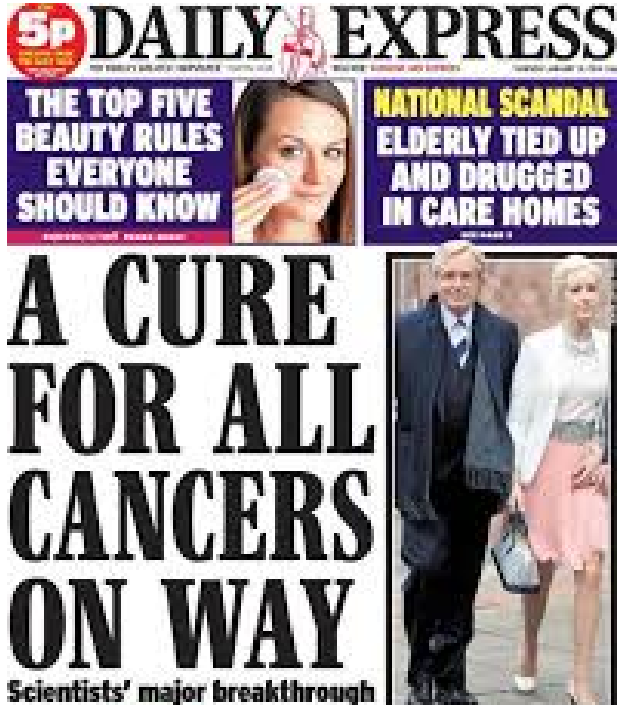
- It is constantly scanning our cells, and killing early cancer cells and infections.
- If it is weakened cancer risk can go up.
- Some cancer treatment can damage the immune system leading to increased infection risk.
- Increasingly immune system tools are used in cancer treatment.



Macrophages killing a cancer cell.
Susan Arnold, 8000x, NIH.

‘Breakthrough’ an easy headline, seldom realistic science. But immunotherapy is advancing rapidly.





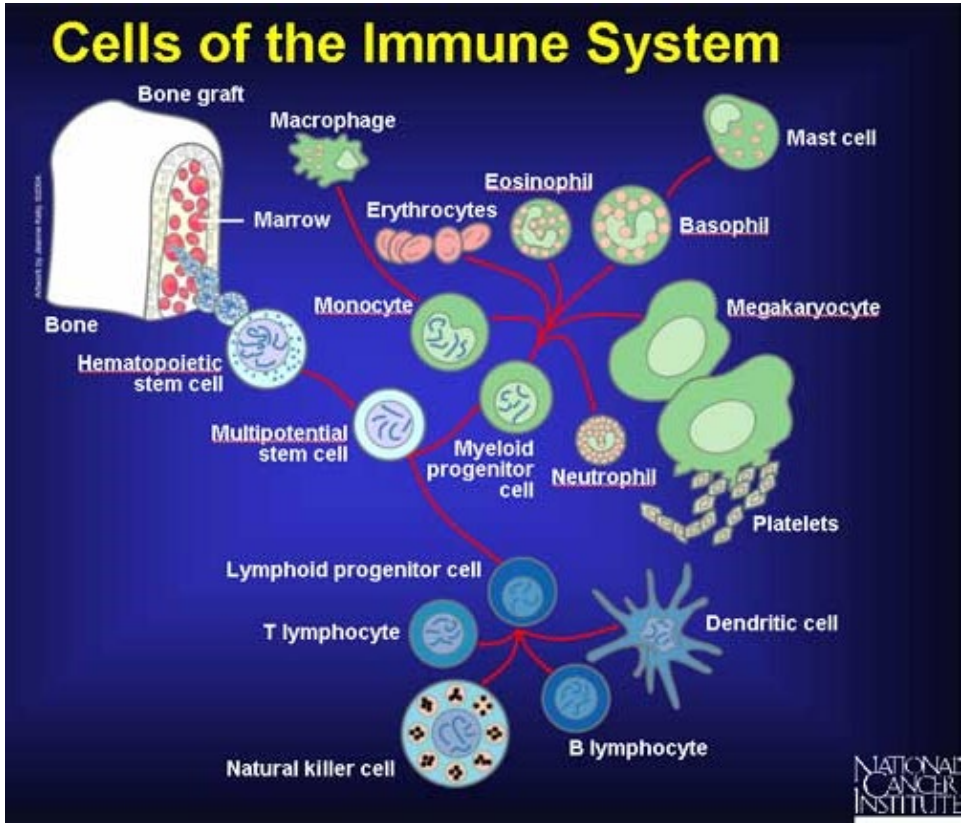
Some important components of the immune system for cancer.

Innate immune system.

- Natural killer (NK) cells. Recognise missing-self (cell surface marker MHC).

Adaptive immune system. Recognise a specific non-self antigen.

- B-lymphocytes. Produce antibodies.
- T-lymphocytes. Killer T cells identify a cell with the antigen, and kill it.

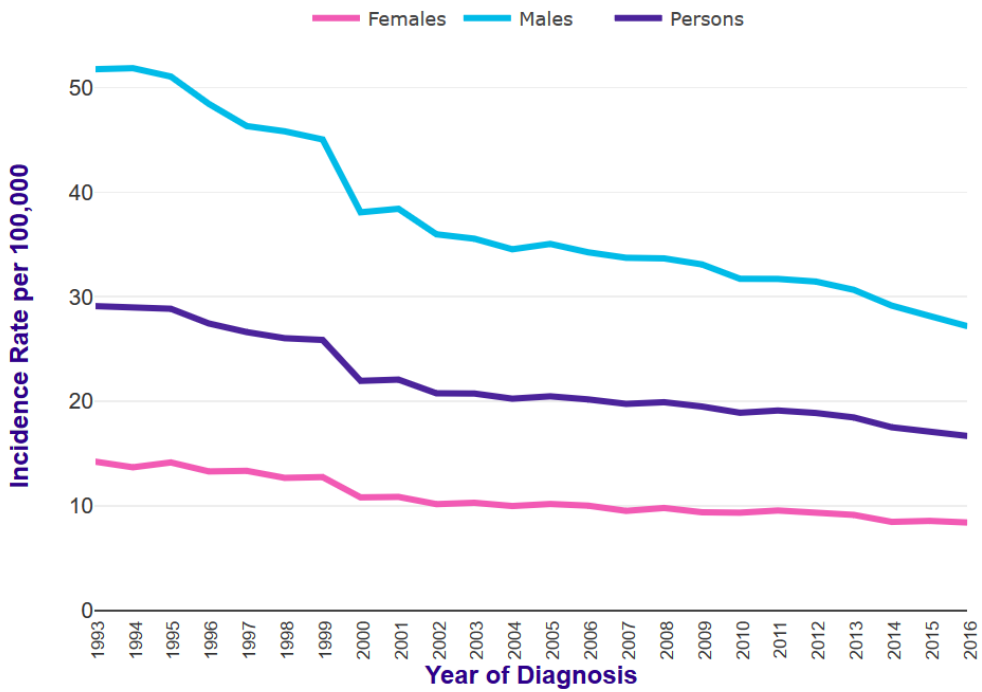


Immunotherapy.

- The immune system fights infection- it also attacks cancerous cells.
- By definition, cancer is in cells which have evaded this.
- If the immune system can be allowed, or trained, to identify cancer cells it will kill them.
- Antibodies have many uses.
- The most rapidly growing field in cancer treatment.

The oldest immunotherapy- BCG infection for bladder cancer.

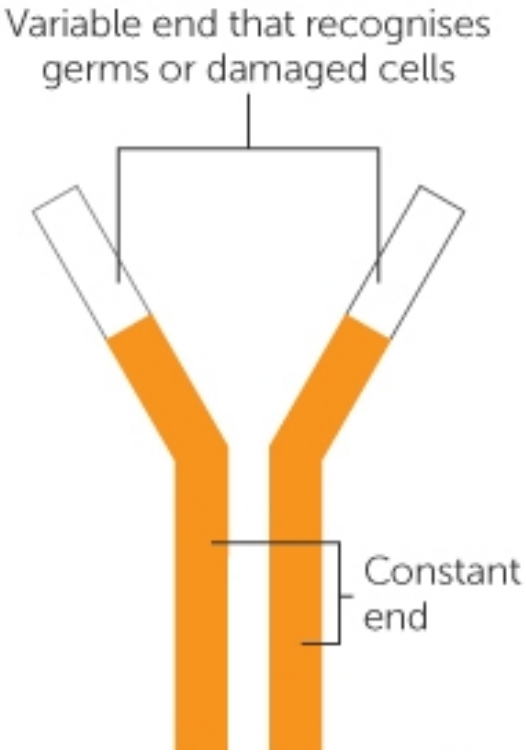
- Bladder cancer ~10,000 UK cases a year.
- Around 45% in UK caused by smoking. >40% reduction since 1970s.
- Superficial tumours cauterised.
- BCG, a modified mycobacteria like TB infused into bladder.
- Causes inflammation and immune activation. Reduces progression by about 27%.
- Currently 50% of people with bladder cancer alive 10 years later.



CRUK

Antibodies have many uses in cancer treatment.

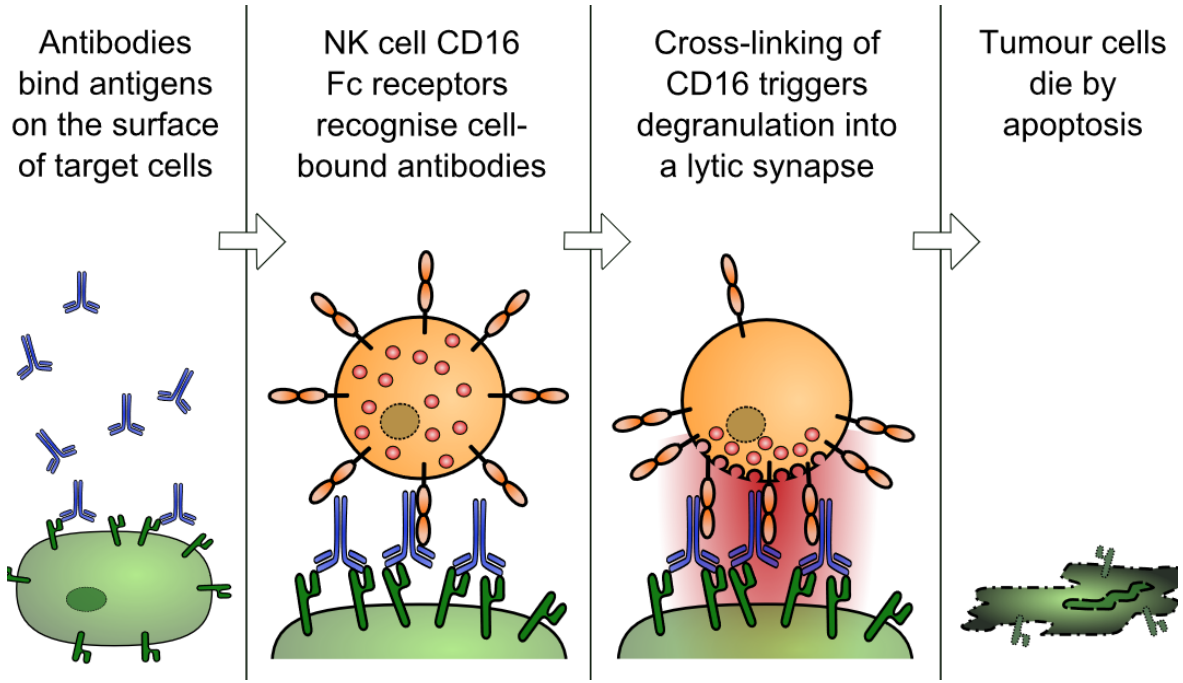
- Like a key, they have a constant end, and a variable end.
- The variable end is highly specific to a receptor or protein.
- They can be manufactured very precisely to a cancer receptor.



CRUK

Antibodies which flag a tumour cell for destruction.

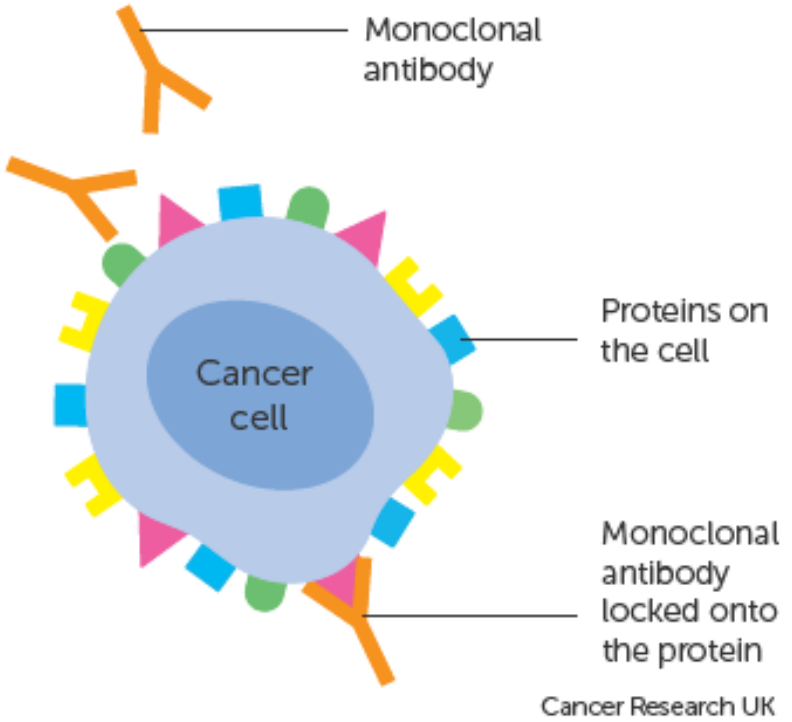
- One role for antibodies is to flag a cell for the innate immune system to destroy.
- Alemtuzumab targets CD52 on mature B lymphocytes in chronic lymphocytic leukaemia (CLL).
- Ofatumumab targets CD20 in CLL.
- Complement and cell pathways.



Sachmo/Wiki)

Antibodies which by binding interfere with cancer cell function.

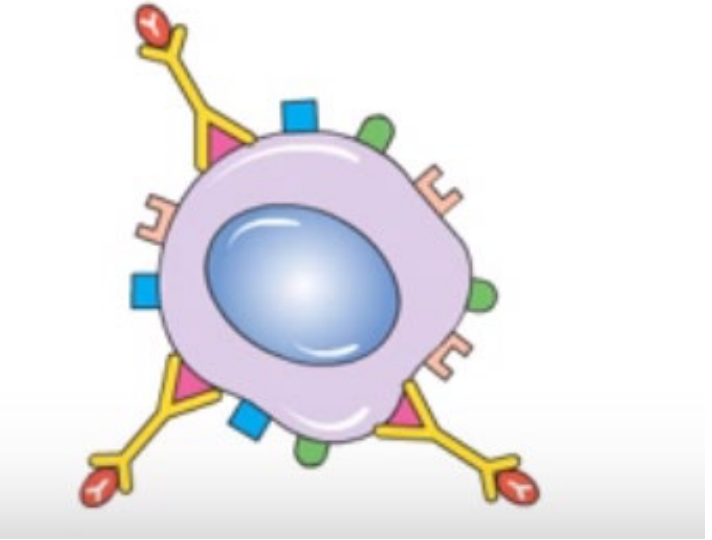
- An example Trastuzumab (Herceptin).
- Binds to HER-2 positive breast cancer cells. Also some stomach cancer.
- Causes the cancer cells to arrest their development.
- Bevacizumab (Avastin) targets a protein which helps cancer grow blood vessels. Various solid tumours.

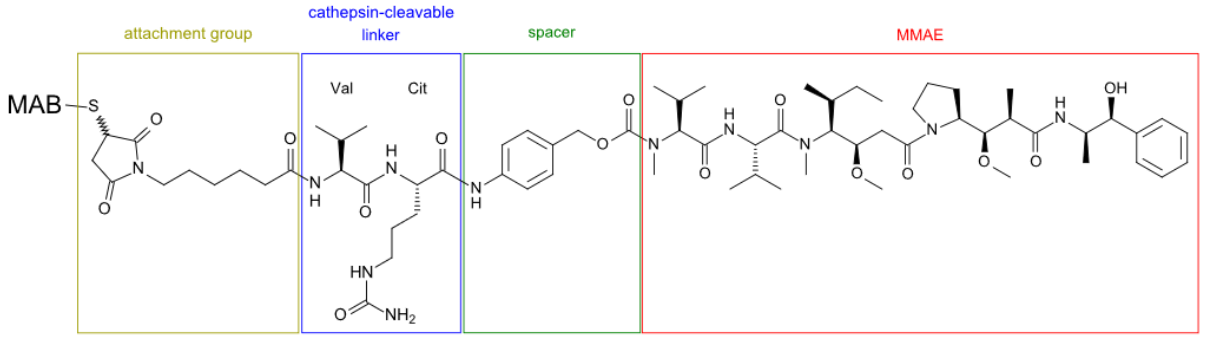


CRUK

Antibodies to deliver chemotherapy.

- Antibodies which recognise and lock onto cancer cell receptors.
- Carry dangerous cytotoxic drugs in a very targeted way.
- An example Brentuximab vedotin (Adcetris) for refractory Hodgkin lymphoma. MMAE.

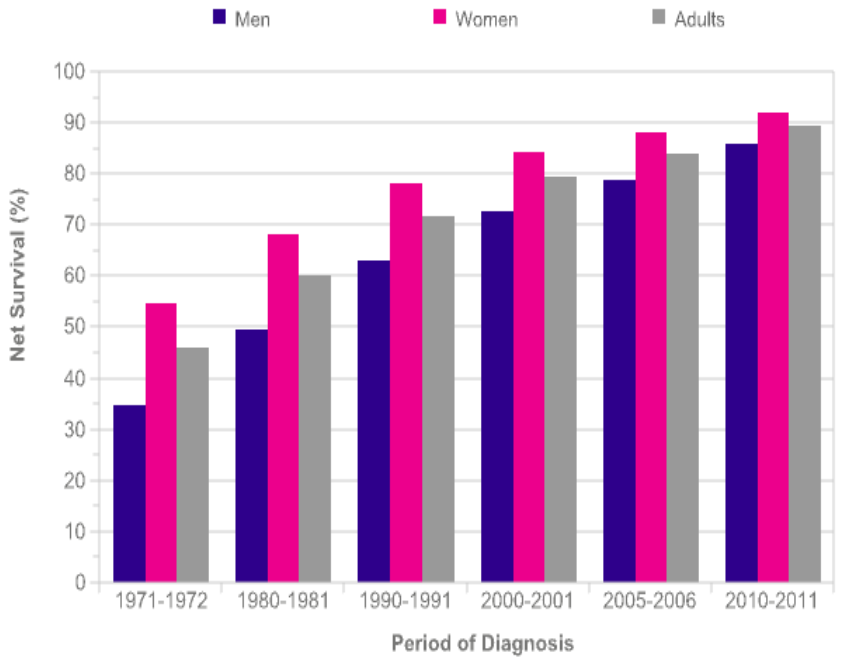




CRUK/Anypodetos

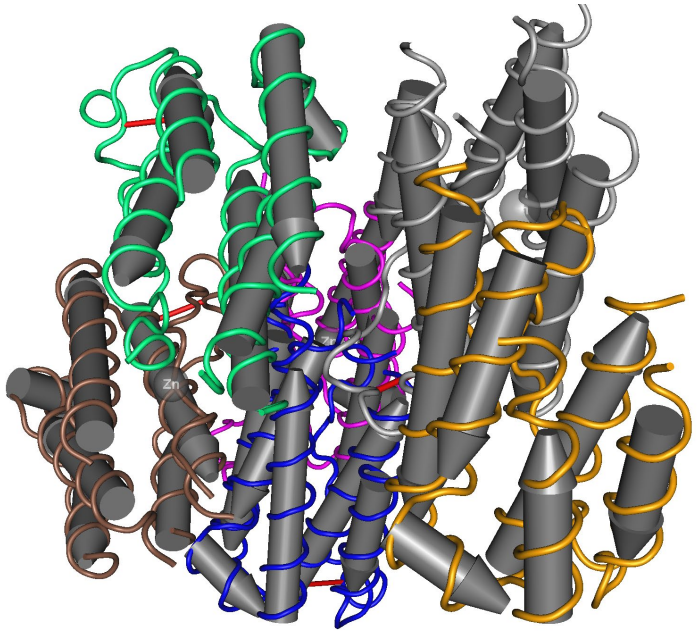
Melanoma- a dangerous skin cancer.

- Increasing in incidence due to sun and sunbed exposure.
- Around 16,000 cases a year UK.
- Around 90% survival- up from <50% in 1970s.
- Mainly early diagnosis and surgery.
- Once it has spread it was until recently very difficult to treat.



Early attempts to stimulate the immune system: interferon.

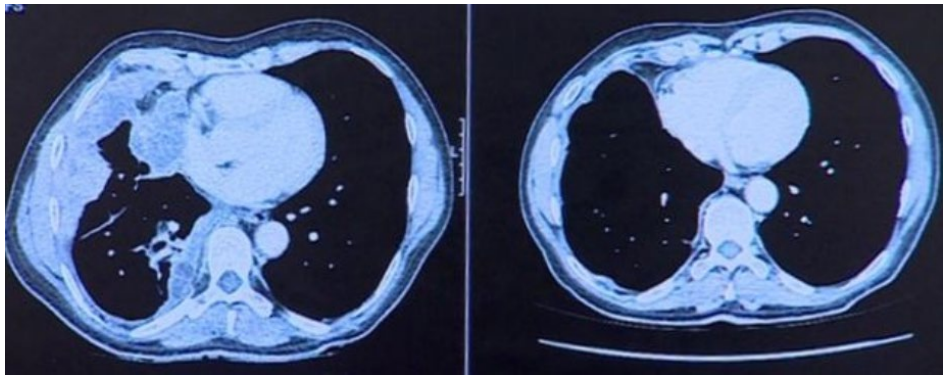
- Interferons a group of proteins (cytokines) that activate the immune system.
- Released in viral infections.
- There were high hopes in the 1970s they would be wonder drugs for cancer.
- They have some activity in reducing progression of recurrent melanoma.
- Also used in some lymphoma and leukaemia and renal cancer.
- They have proved very useful in other diseases, eg MS, hepatitis.



Interferon-Alpha 2b.
Nevit Dilman / Wiki

Immune-checkpoint blockade.

- Immune checkpoints protect healthy cells- and cancer cells.
- Blocking them takes the brakes off.
- Can have substantial effects in some cases and severe side effects in others.

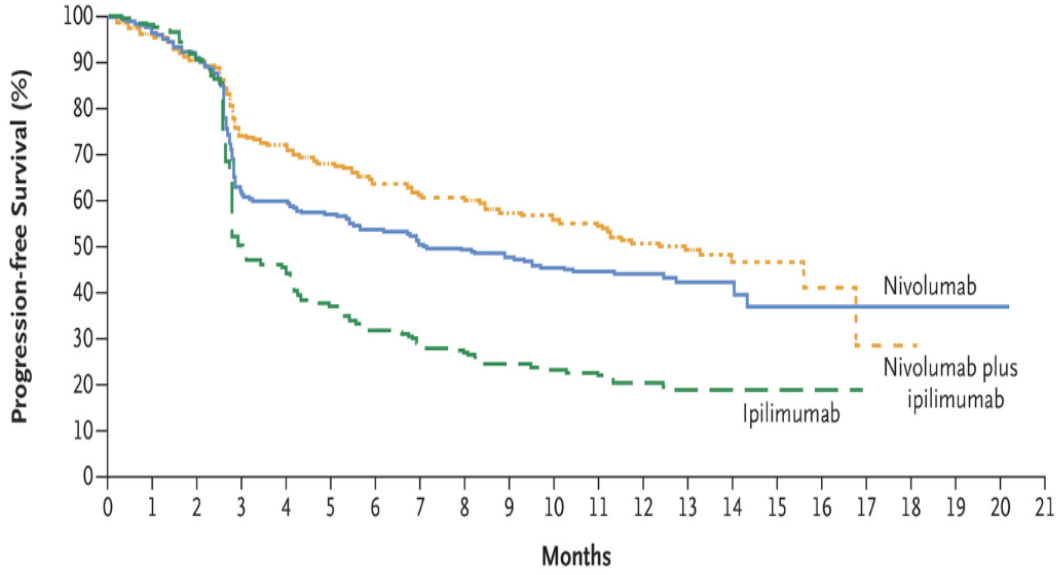


Pembrolizumab in melanoma. BBC

Recent trial reported 5 year survival unresectable melanoma.

- Two different immune checkpoint blockers: nivolumab blocks the off-switch on white blood cells PD-1, ipilimumab CTLA-4.
- At 5 years (2019):
- 26% still alive on ipilimumab alone
- 44% still alive on nivolumab alone
- 52% still alive when given both.

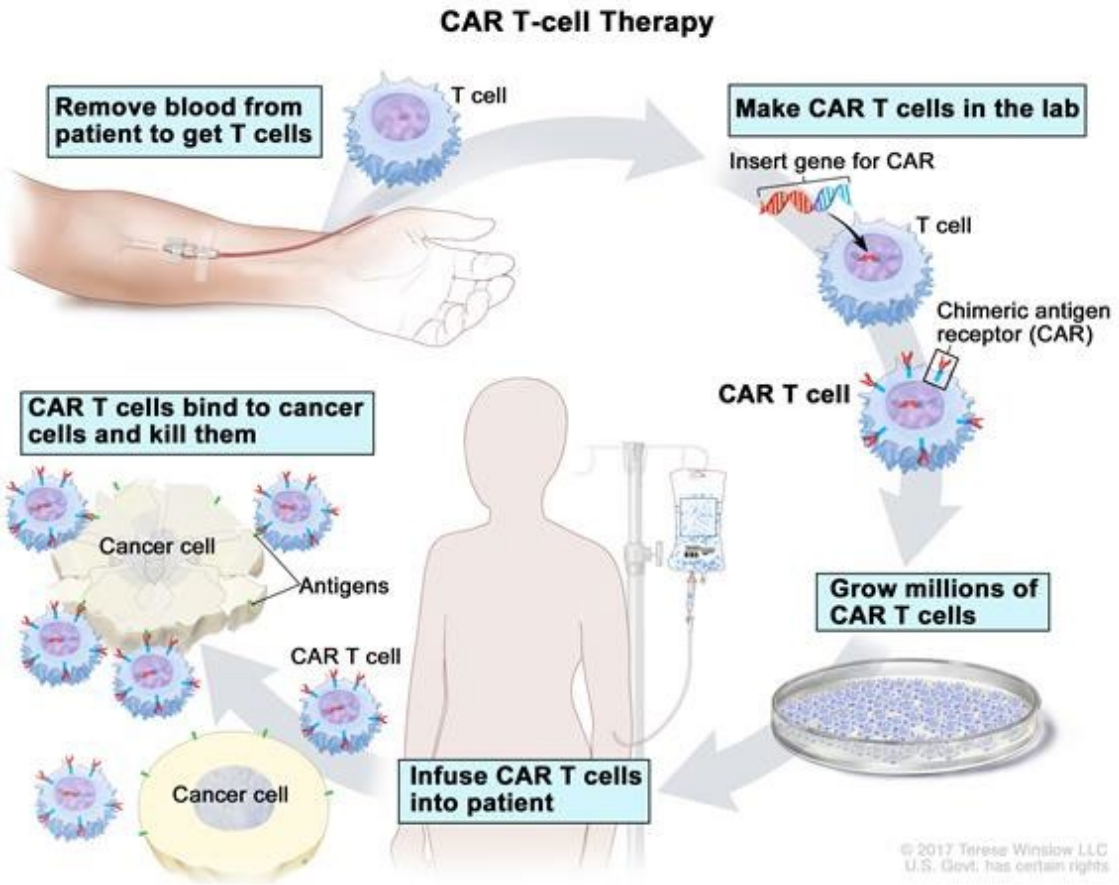
Treatment-related adverse events higher in the combination.



Larkin J et al, NEJM 2015.

CAR-T therapy.

- T-cells harvested from patient with cancer.
- Gene for the receptor common in cancer inserted (CAR).
- Cells grown.
- Infused into the patient again.
- They then hunt down and kill cells with the receptor.
- Currently only used in some lymphomas.



NIH

Vaccines for cancer?

- Therapeutic vaccines.
- Preventive vaccines.
- They have so far proved difficult to get to work.
- But the concept is reasonable.

Infection, immunity and cancer.

- Some cancers have a strong infectious driver.
- If these can be identified, and then prevented or treated cancer may not occur.
- The immune system protects against infection and cancer.
- Using the immune system an increasingly important area of cancer treatment.