

Fighting Cancer

Paul Moss



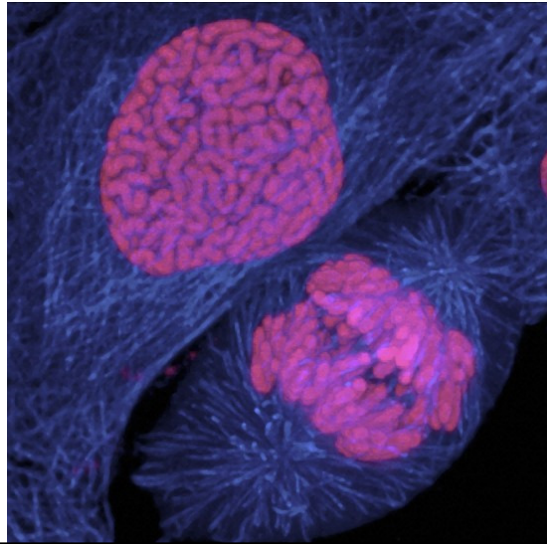
Birmingham Heroes:
Solving tomorrow's problems today
www.bham.ac.uk/heroes

Summary

- Introduction to cancer
- Cancer Statistics
- The development of cancer therapy
- The Birmingham contribution
- Future prospects

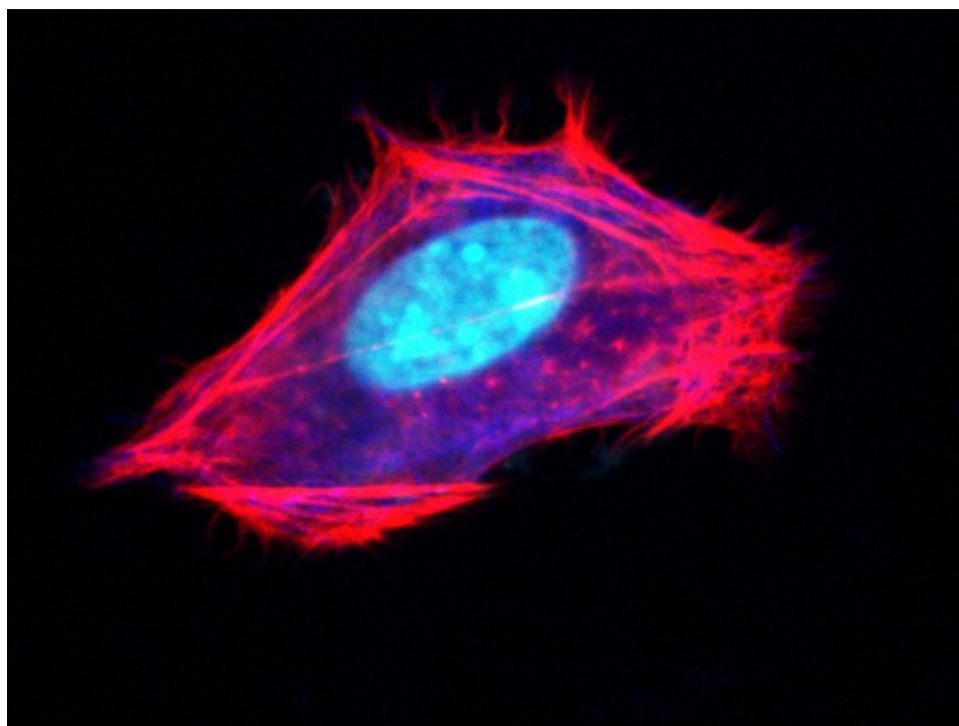
The biology of cancer

Cancer results from the uncontrolled division of cells



- Current lifetime risk of cancer is 45% in men and 39% in women

Why is cancer so uncommon ?

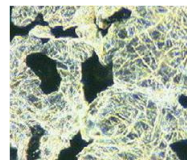
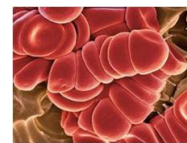


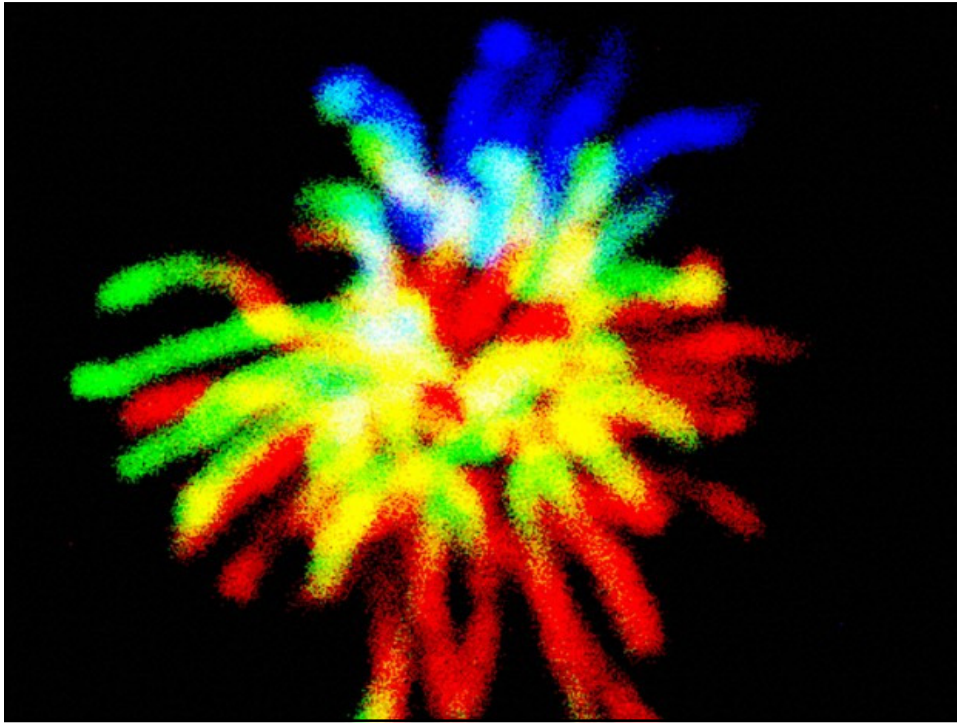
Our body is designed to control the development of cancer

- We have 10^{14} cells
- Estimated to undergo 10^{24} cell divisions in a lifetime
- May be up to 20,000 breaks in DNA in each cell division
- Each of these must be repaired

In the past minute...

- Your body has made:
 - 300 million new red blood cells
 - 12,000 million new gut cells
 - 40,000 new skin cells





Cancer Statistics

International Agency for Research on Cancer



Cancer Worldwide

September 2011

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Figure One: The 20 Most Commonly Diagnosed Cancers Worldwide, 2008 Estimates

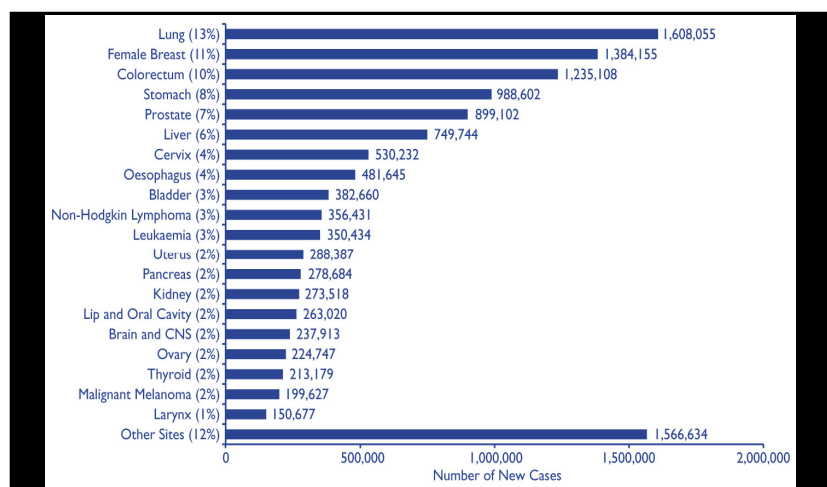
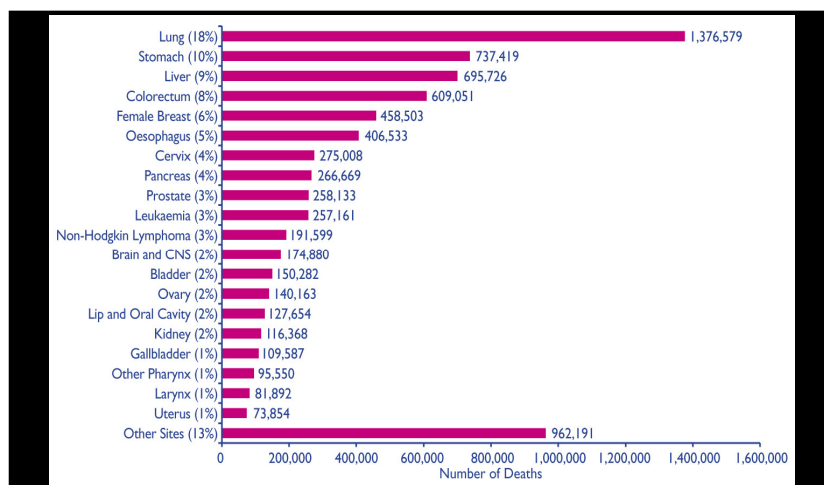


Figure Three: The 20 Most Common Causes of Death from Cancer Worldwide, 2008 Estimates



Number of new cases and rates of all malignant neoplasms - UK

		England	Wales	Scotland	N.Ireland	UK
Number of new cases	Males	117,805	8,730	13,164	3,427	143,126
	Females	115,816	8,076	13,949	3,593	141,434
	Persons	233,621	16,806	27,113	7,020	284,560
Crude rate per 100,000 population	Males	480.2	608.4	539.8	409.7	489.4
	Females	453.8	531.2	531.1	411.3	463.1
	Persons	466.7	568.7	535.3	410.5	476.0
Age-standardised† rate per 100,000 population (CI 95%)	Males	400.1 (397.9-402.4)	464.8 (455.0-474.5)	452.6 (444.9-460.3)	401.6 (388.2-415.1)	408.1 (406.0-410.2)
	Females	342.1 (340.1-344.0)	372.2 (364.1-380.3)	388.9 (382.4-395.3)	352.0 (340.5-363.5)	348.1 (346.3-350.0)
	Persons	363.7 (362.2-365.2)	408.4 (402.2-414.5)	411.0 (406.1-415.9)	369.6 (360.9-378.2)	370.4 (369.0-371.8)

* excluding non-melanoma skin cancer † to the European population

Figure Six: The ten most common causes of cancer death, males, UK, 2005

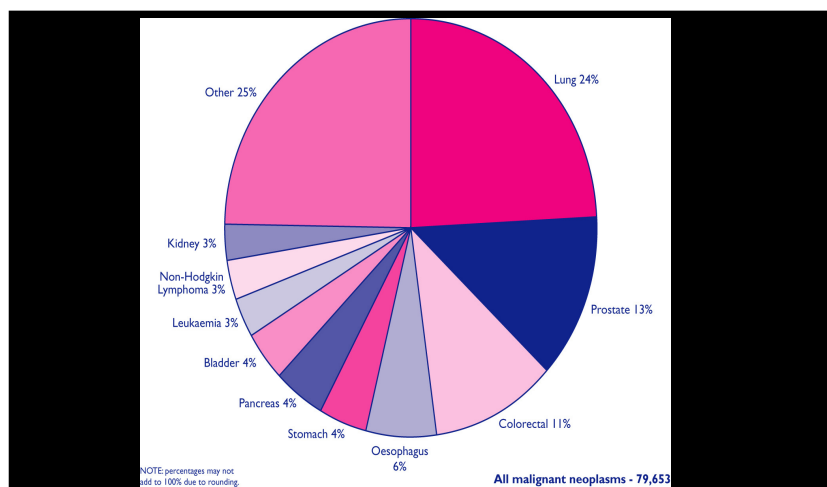
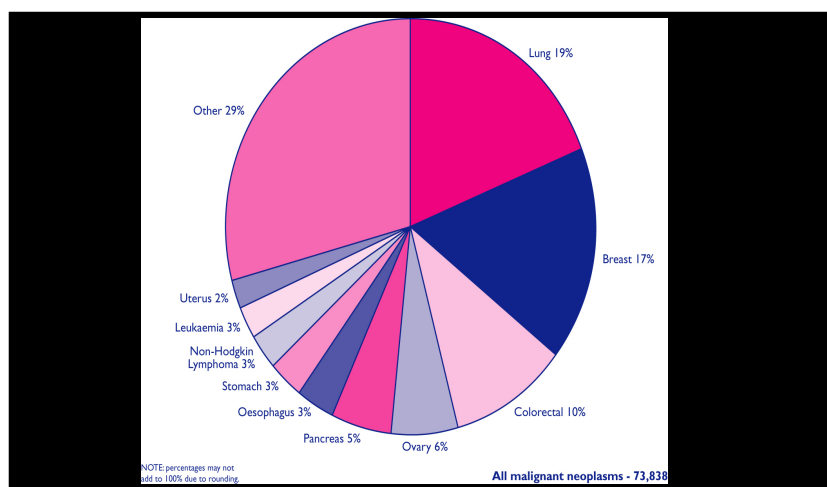
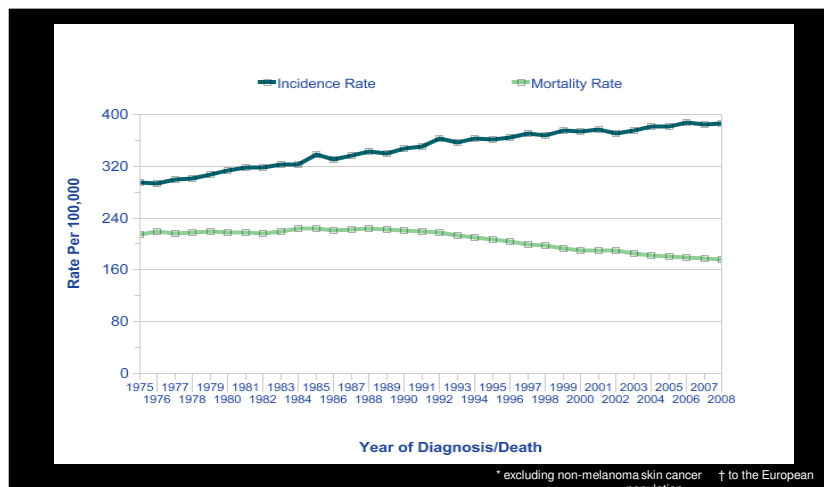


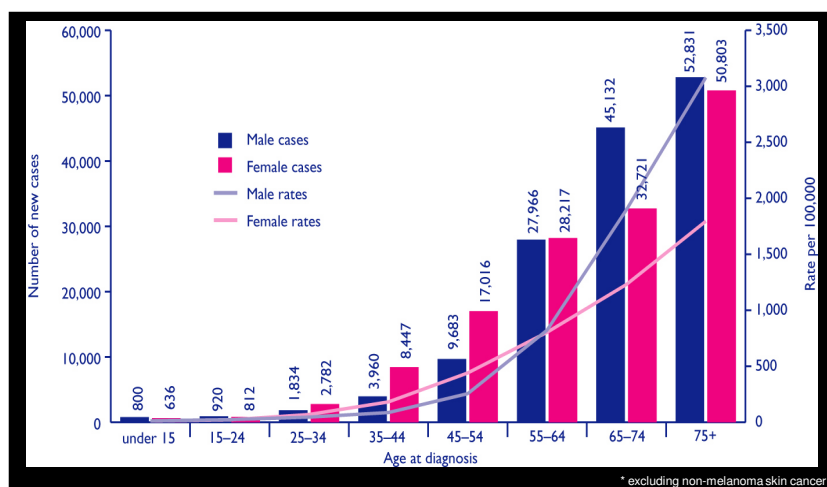
Figure Seven: The ten most common causes of cancer death, females, UK, 2005



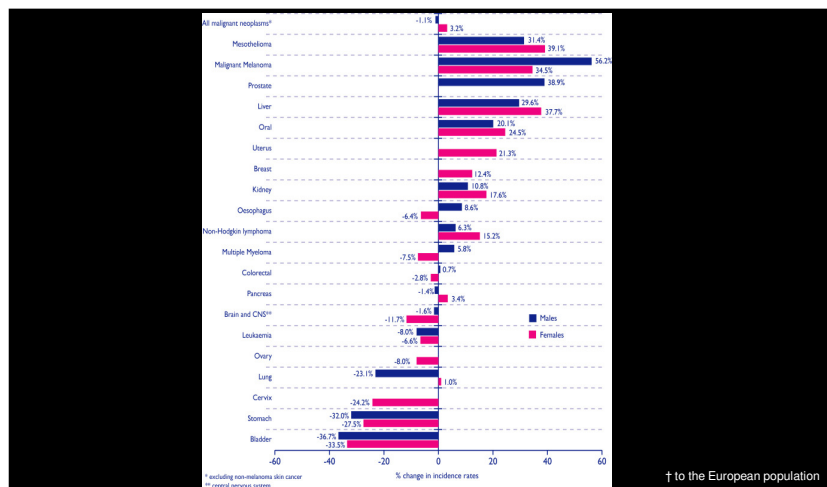
The mortality rate is decreasing



Cancer is a disease of ageing

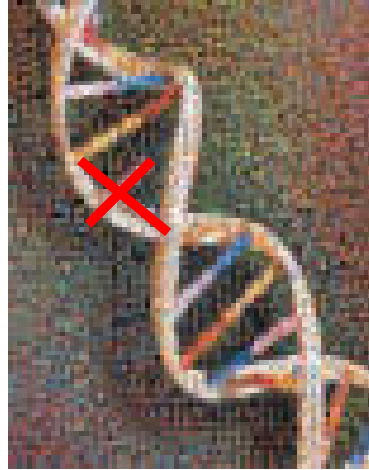


There are changes in the types of cancer over time



How does cancer develop ?

Cancer is caused when there is damage to this genetic material



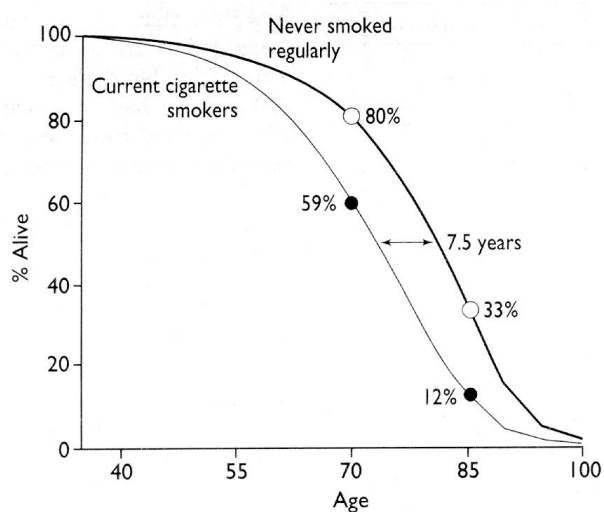
What determines if someone is going to develop cancer ?



A combination of genetic susceptibility and environmental factors



Survival after age 35 in smokers and non-smokers

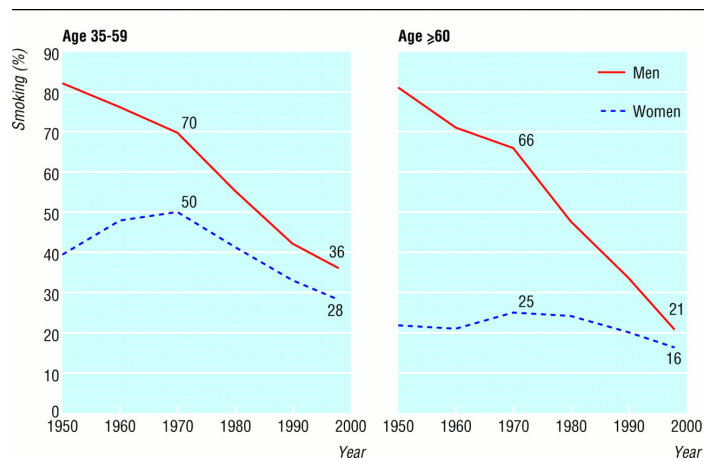


Doll, R et al. BMJ 1994;309:901-911

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BMJ

Smoking rates are dropping substantially

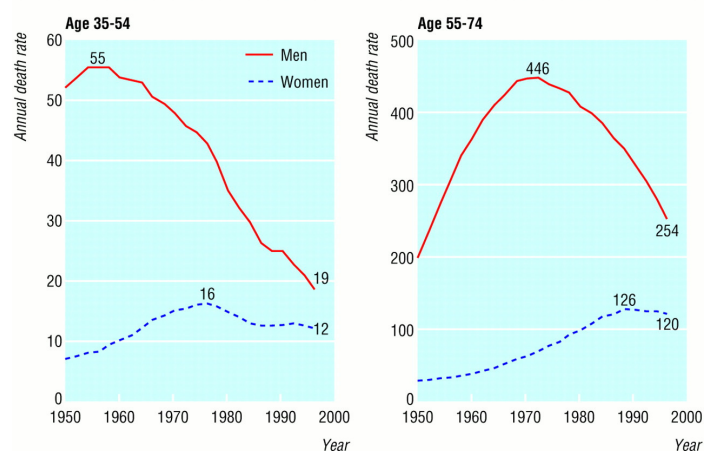


Peto, R. et al. BMJ 2000;321:323-329

BMJ

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Lung cancer is becoming less common



Peto, R. et al. BMJ 2000;321:323-329

BMJ

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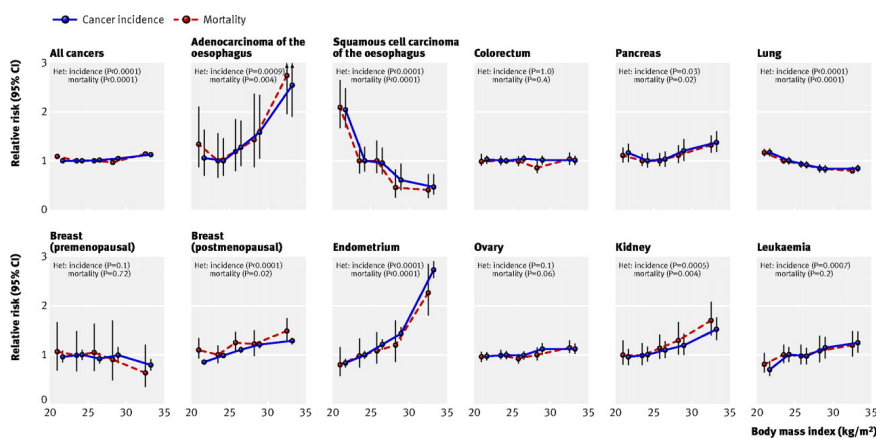
Worldwide deaths from tobacco -if current smoking patterns continue

- 2000-2025 150 million
- 2025-2050 300 million
- 2050-2100 >500 million
- Total for 21st century 1 billion
- Compare with 100 million for 20th century

Obesity - a new epidemic

- Body Mass Index (Kg / m²)
- 22-25 ok
- 25-30 overweight
- 30+ obese (W.H.O.)

Increasing weight predisposes to many types of cancer

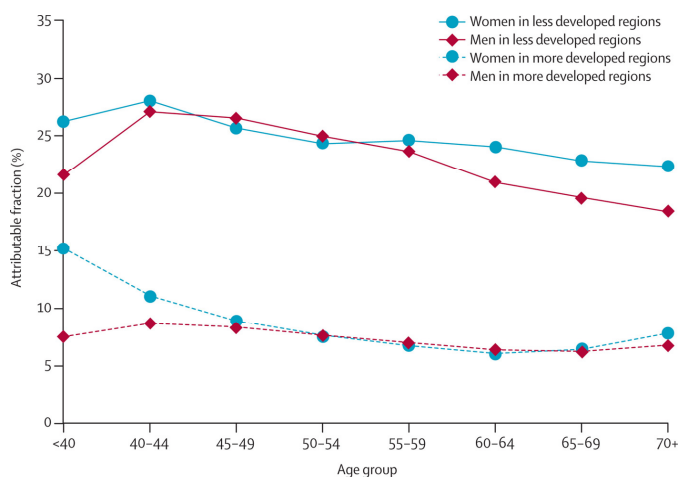


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Reeves, G. K et al. BMJ 2007;335:1134

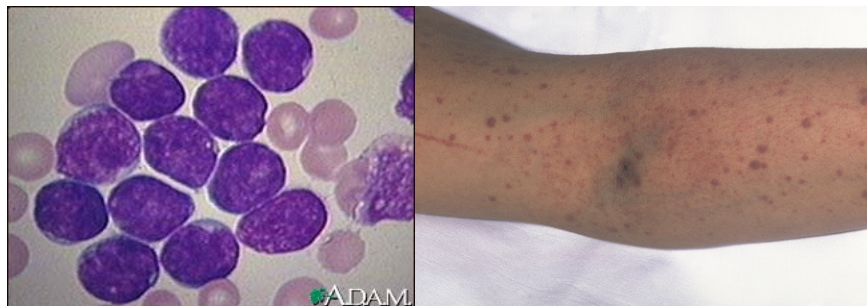
Infection causes 20% of all cases of cancers



De martel , 2012

The development of cancer therapy

Acute lymphoblastic Leukaemia



The discovery of chemotherapy agents

- Alkylating agents were identified through poisoning effect of mustard gas
- Folate antagonists from treatment of anaemia

9. Rfm. J. C. W., lived 15 days. Gassed September 30, 1918. Moderately severe burns and conjunctivitis. Apparently passed through broncho-pneumonia but continued to have much circulatory difficulty. Eyes and burns almost healed. Developed edema of the lungs in last forty-eight hours.

Day.	Leucocytes.	Polys. %	Lymphocytes. %	Mononuclear and Transitional. %	Myelocytes and Metamyelocytes. %
8th	900	34	34	6	26
12th	4,200	26	18	6	50
14th	6,200	2	16	2	80

At autopsy (partial). Face and skin as above. Bone marrow yellow throughout. Histologically, almost complete aplasia of bone marrow. Occasional hemopoietic cells, such as seen in normal adult marrow, but not enough to give an idea of the relative frequency of the different types. In the presence of an increasing leucocytic count, this state of the bone marrow illustrated the difficulty that has previously been referred to of comparing the two conditions.

Krumbhaar et
al 1919



Lucy Wills

Went to slums of Bombay to study cause of anaemia in pregnancy women

Determined the preventative effect of yeast and marmite

Led to isolation of folic acid

Development of chemotherapy

- 1946 - Folic acid was good for anaemia - and so was given to children with leukaemia but caused an *acceleration* of symptoms
- Folic acid antagonists were developed and used as chemotherapy

SOME OBSERVATIONS ON THE EFFECT OF FOLIC ACID ANTAGONISTS
ON ACUTE LEUKEMIA AND OTHER FORMS OF INCURABLE CANCER

By SIDNEY FARBER, M.D.

Nature of Leukemia

Observations on a girl (M. D.), 8 $\frac{1}{2}$ years old at the time of her death, and similar experiences with other children have raised a question concerning present conceptions of leukemia. This child lived for twenty-two months after the onset of acute leukemia. Treatment with pteroylaspartic and methylpterotic acid was followed by repeated temporary periods of improvement. She died following uncontrollable oozing from the mucous membranes. Postmortem examination revealed leukemic cells so few in number, in scattered areas throughout the body that the diagnosis of acute leukemia would have been made with hesitation on the basis of that evidence alone. It seems probable that hemorrhage in acute leukemia may be produced by a number of different factors apart from the effect of leukemic infiltrates on the

1950s

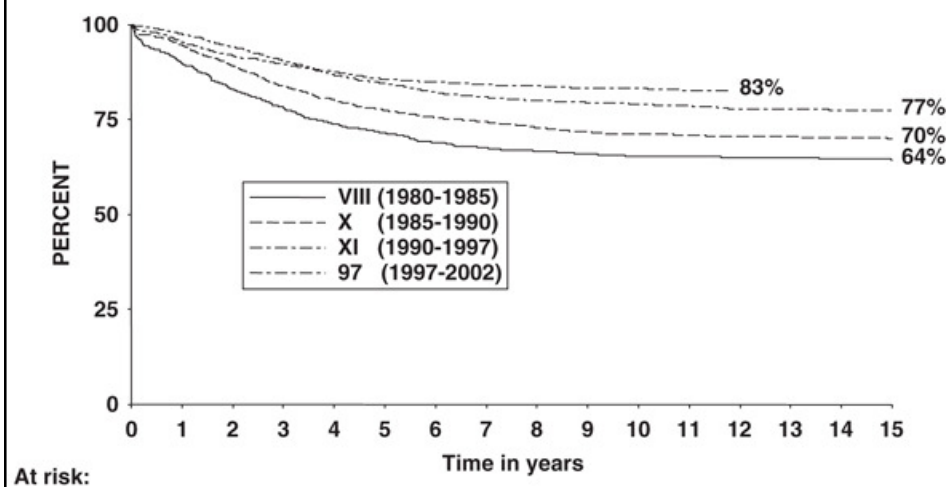
- Generally believed that cancer would never be cured by chemotherapy

Li reported 'cure' of choriocarcinoma with methotrexate – was threatened with suspension

Continued work and went on to produce cures in testicular cancer and win Lasker prize



Current survival for children with acute leukaemia



Breast Cancer



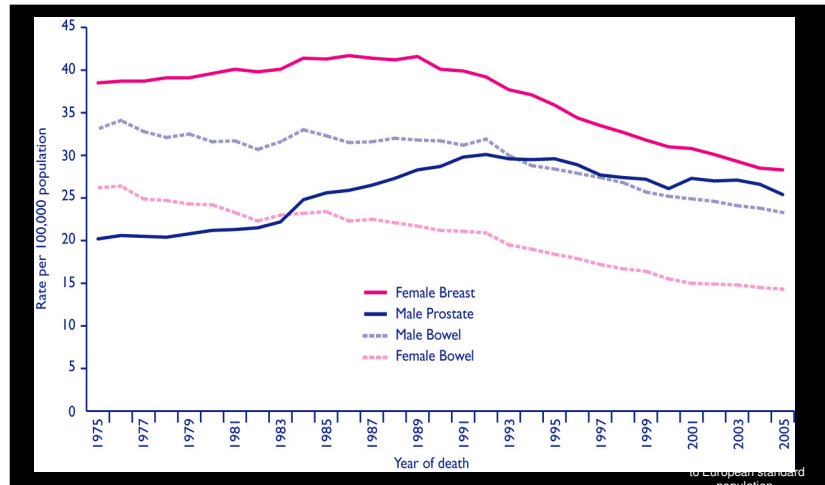
The epidemiology of breast cancer

- Risk factors for development of breast cancer
 - few pregnancies
 - Alcohol - 5000 cases /year
 - HRT – - 1000 cases /year
 - Obesity - 4000 cases/year

Pregnancy and protection from breast cancer — lessons from 'Million Women Study'

- “Occupational disease of nuns”
 - Ramazzini 1743
- Each pregnancy reduces risk by 9%
- Need to be full term
- Not related to age at pregnancy
- Mechanism not clear

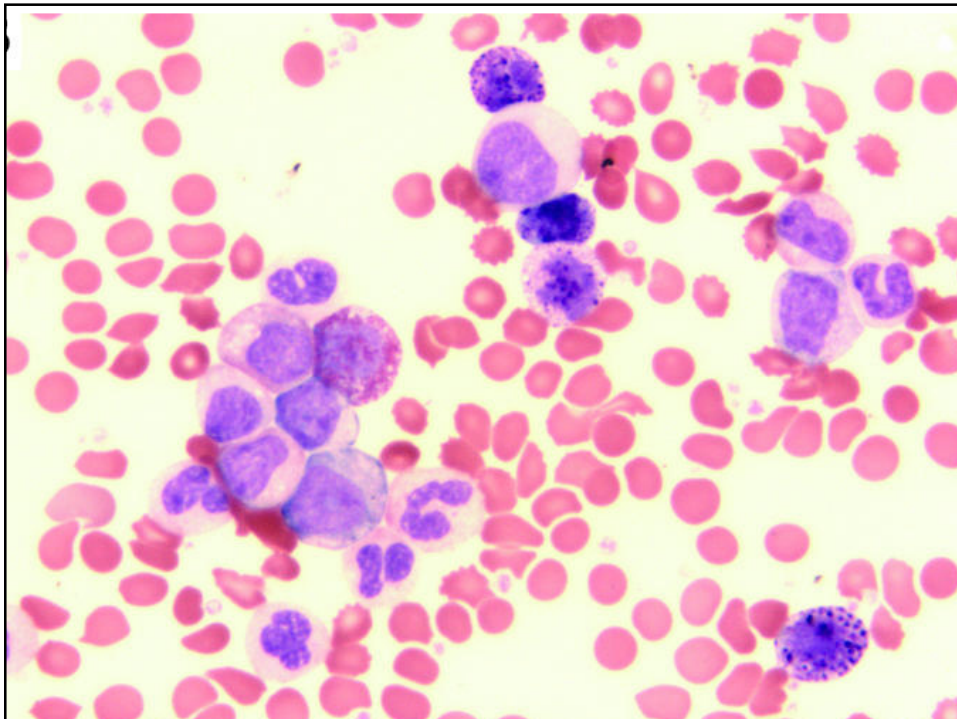
Mortality from breast cancer is falling

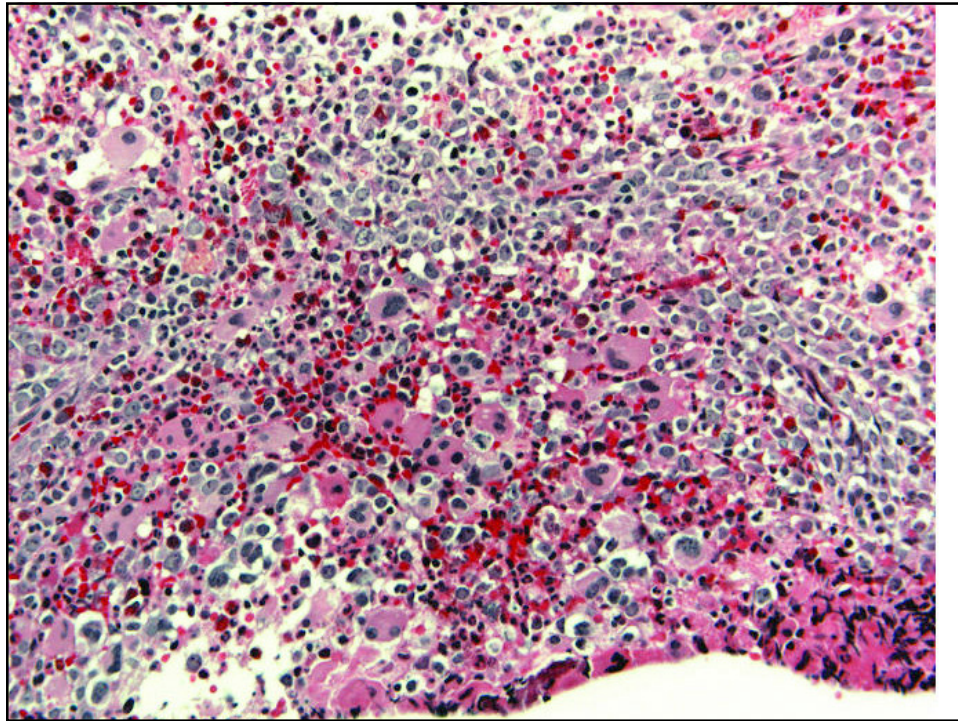


Several improvements have been seen in treatment of breast cancer

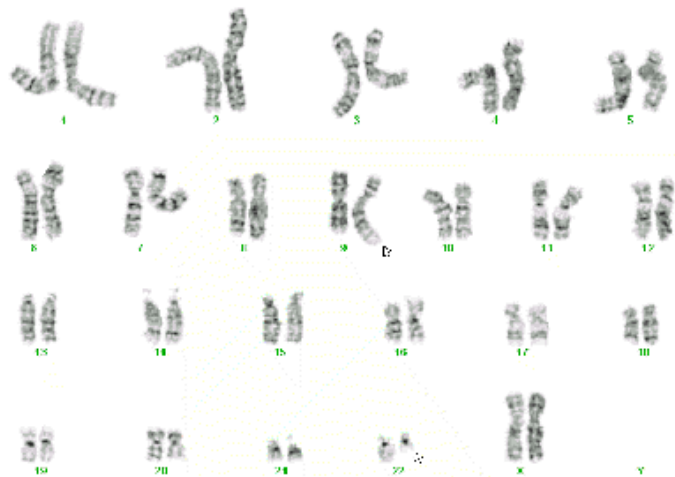
- **Surgery**
 - Less extensive
- **Radiotherapy**
 - Addition to lumpectomy
- **Adjuvant chemotherapy**
 - 10% reduction in mortality with CMF
 - Extra 10% reduction in mortality with epirubicin
- **Hormonal therapies**
 - Best prognostic factor is ER+ - due to tamoxifen

Chronic Myeloid Leukaemia





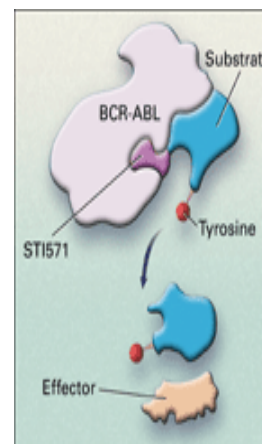
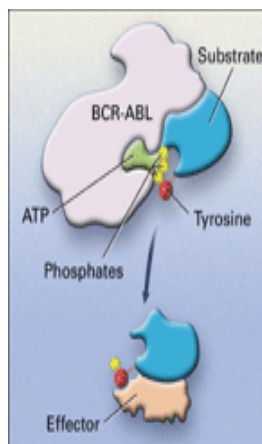
CML is characterised by the Philadelphia Chromosome



This joins two genes together

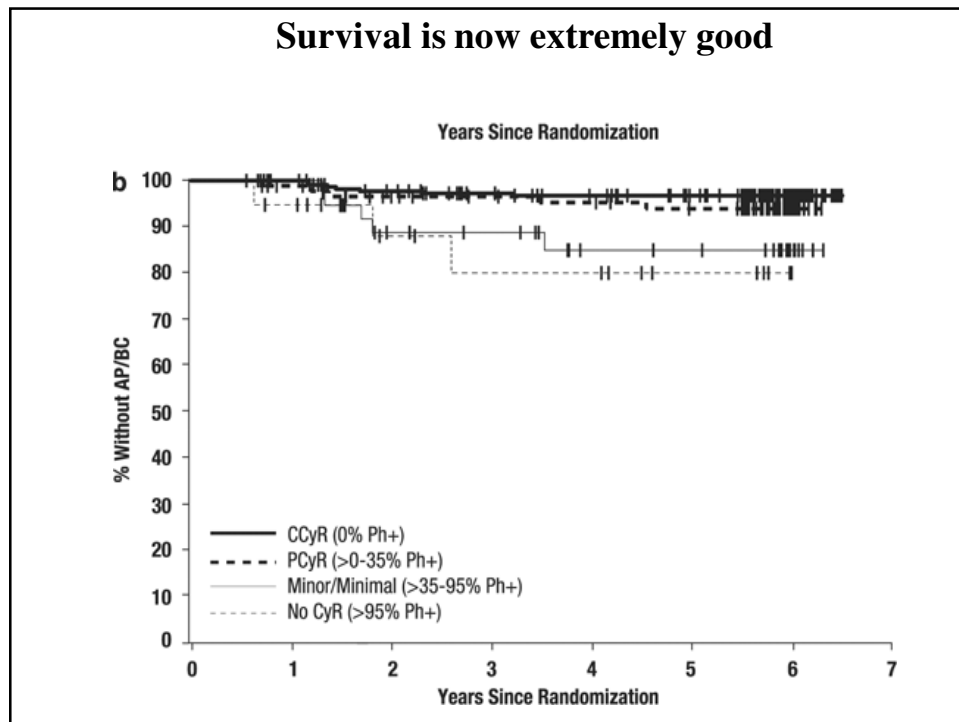


It is possible to design a drug that blocks the action of this abnormal 'fused protein'



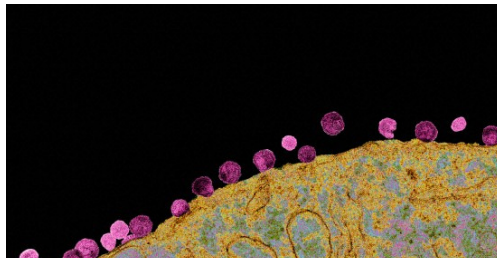
NEJM April 2001

Survival is now extremely good



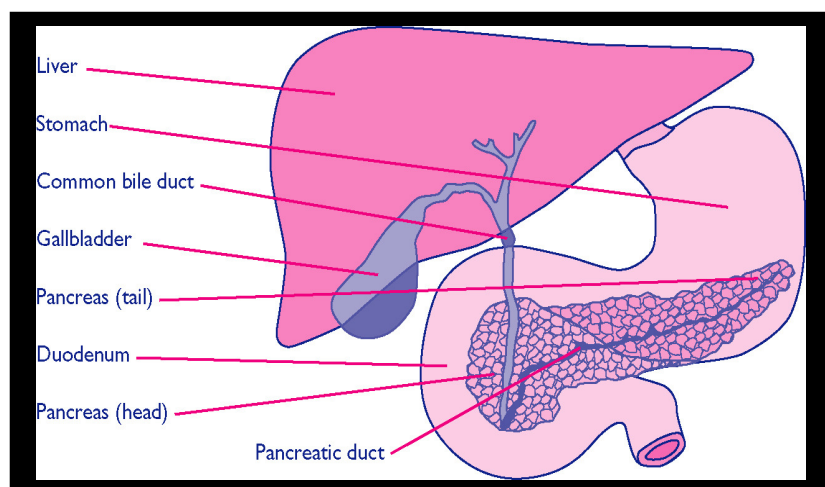
Imatinib as a 'cure' for CML ?

- CML can now be considered as a chronic disease
- Therapy resembles early days of HIV treatments

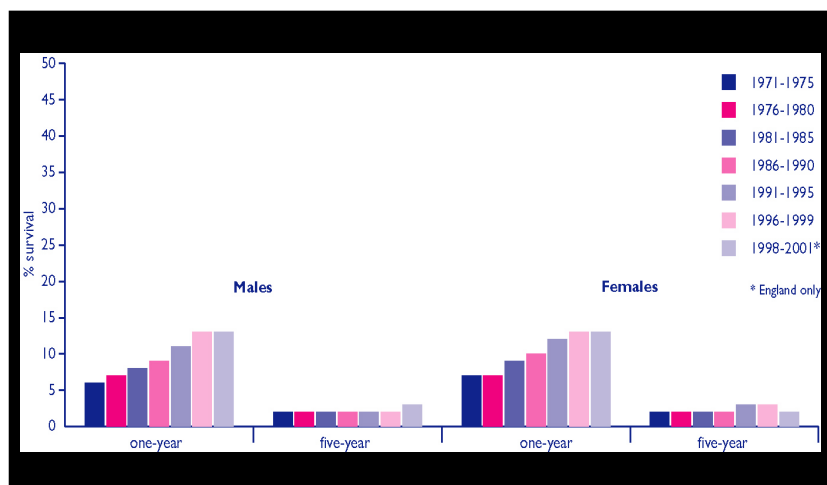


However there are huge challenges in cancer treatment

Pancreatic Cancer



No improvement in 5 year survival for pancreatic cancer



Cancer Research - The Birmingham Contribution

The first Cancer Research UK Centre



Partnership between:

- Cancer Research UK
- University of Birmingham
- University Hospitals Birmingham NHS Foundation Trust

The role of Centres

- Ensure that cancer research feeds through to improved patient benefit and public health
- Expand public engagement, information provision and local fundraising
- Ensure a broad research coverage across the UK
- First port of call for new developments and strategic initiatives instigated by Cancer Research UK
- Train the research workforce of the future



The Centre brings together a range of activities



We have many areas of strength at Birmingham

Disease site

- Haematological
- Paediatric
- Surgery
- Urological tumours
- Brain tumours

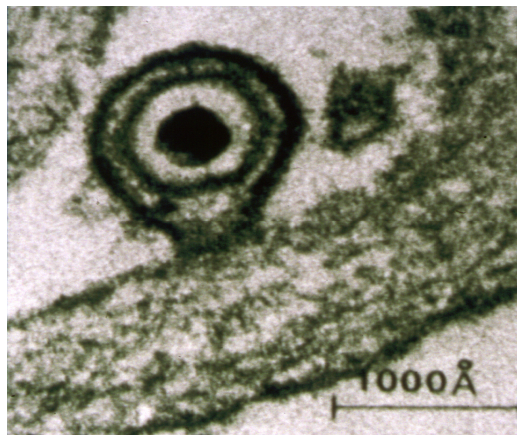
Research

- Cancer immunology
- Clinical trials
- DNA repair
- Epidemiology
- Viral oncology

Examples of Birmingham research

- Role of infection in cancer
- Study of immune response to leukaemia
- Clinical trials in bladder cancer

Epstein-Barr Virus



EBV and disease



-Almost all of us carry EBV infection

-It can cause 'glandular fever'

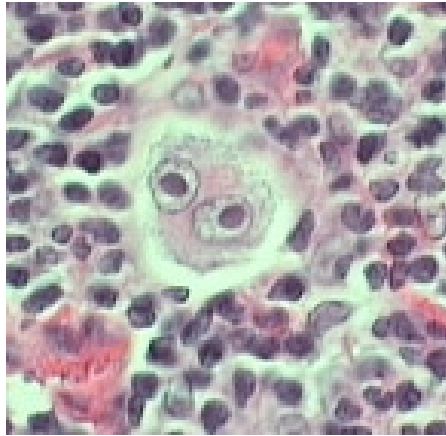
-It is excreted in saliva

- What about its role in cancer ?

Hodgkin Lymphoma



Hodgkin lymphoma is caused by an unusual cancer cell



**Birmingham
scientists
have shown
that EBV
causes 1/3 of
cases**

The EBV team



Prof Alan Rickinson FRS



Prof Lawrence Young

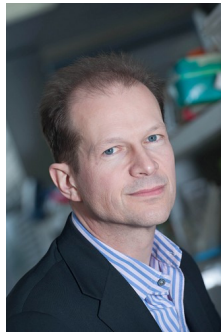


Prof Martin Rowe



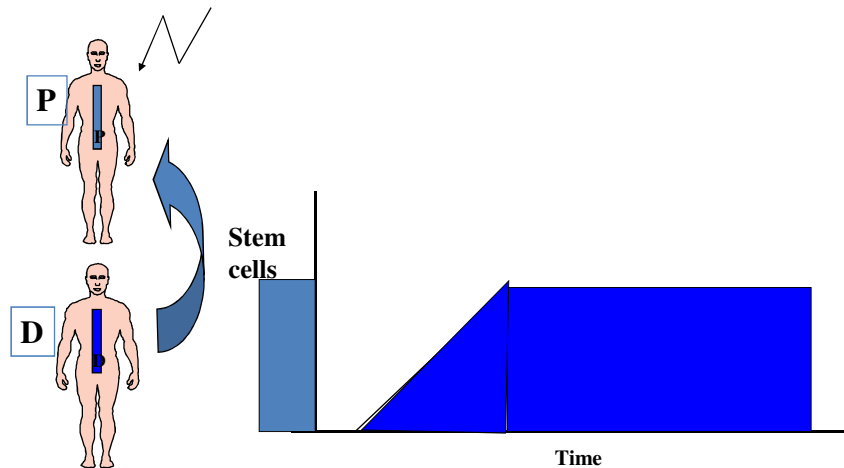
Prof Paul Murray

Bone marrow transplantation

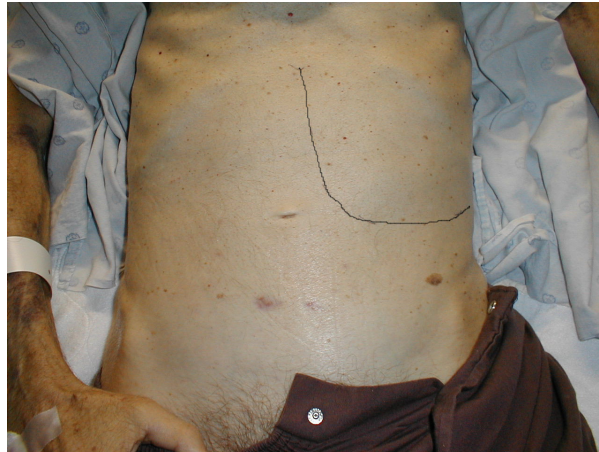


Prof Charles Craddock

BMT replaces the blood of one person with that from another



Transplants are useful for patients with leukaemia



The immune system of the donor can attack the patient



Infection is also a major problem



CMV pneumonitis

We can now select white cells from the donor to prevent infection



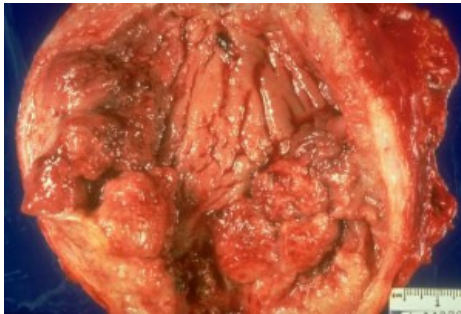
Recent work is allowing 'personalised transplantation'

- We can take white cells that fight viral infection
 - Large trial being performed in UK
- We have new data to show that a simple test at 12 days can predict the clinical course
- We are planning to 'tailor' treatment to individual patients

Clinical trials

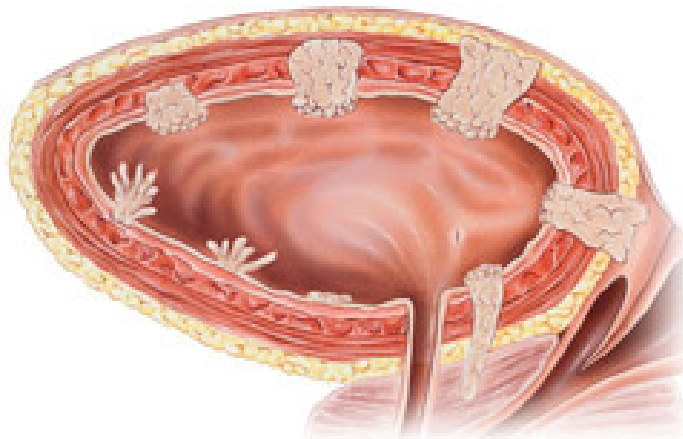


Improving treatment for Bladder Cancer

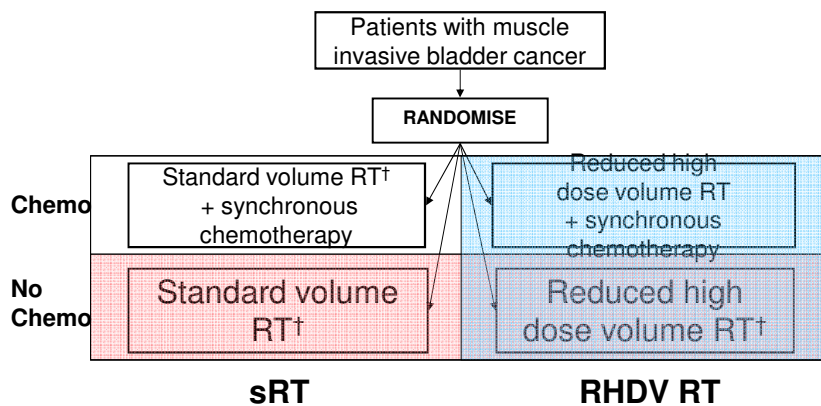


Professor Nick James

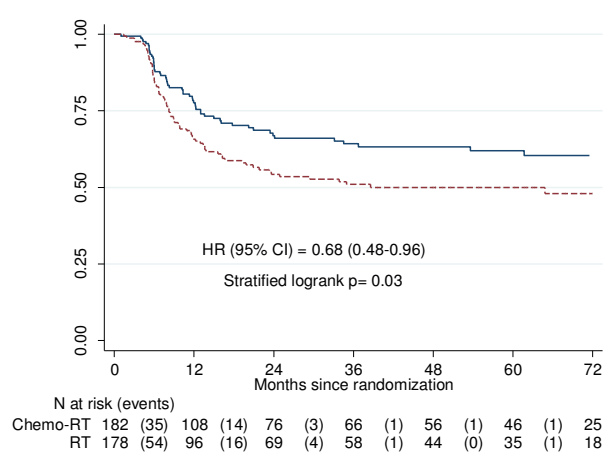
Bladder cancer can invade the muscle – standard treatment is then to remove the bladder



Trial design for bladder cancer trial

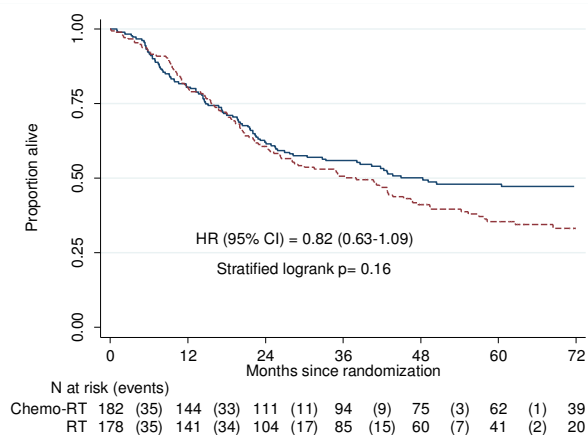


Local disease control is much improved



James et al, NEJM 2012 366, 1477-1488

Overall survival is better



We have a huge local engagement programme

- Teaching others about cancer



- 'Reduce the risk' messages



Future prospects in the management of cancer

- Prevention
- Early Detection
- Treatment

Prevention

- Risk Factors
- Diet
- Vaccination
 - Papillomavirus
 - EBV
 - HIV ?

‘ Reducing the risk’

- Be as lean as possible without being underweight
 - BMI 18.5-24.9
- Be physically active for at least 30 minutes each day
- Avoid sugary drinks and energy dense food
- Eat fruit , vegetables, wholegrains and pulses
 - 2.5% reduction (7000/year in UK)
- Limit red meat and avoid processed meats
- If consuming at all, limit alcoholic drinks to 2 for men and 1 for women each day
- Limit salt intake
- No tobacco
- Breast feed exclusively for up to 6 months
- Don't use supplements against cancer

World Cancer Research Fund

Early Detection

- Determination of genomic risk
 - Cancer risk can be predicted from genome
- Screening of tissue samples

Treatment

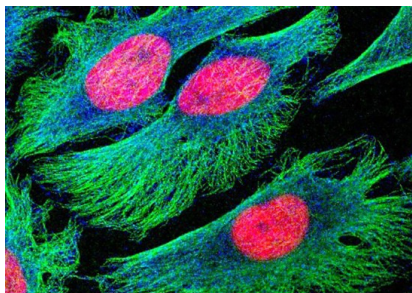
- Personalised therapy based on genome sequence
- Introduction of targeted drug combinations
- Cost and drug side effects will be concerns

Cancer Genomics at Birmingham

- One of three national centres that tests cancer specimens from across the UK for mutations in cancer genes
- A national collection centre for tumours
- Working with industry to develop new tests for cancer genetics
- An internationally leading position

Outlook

- University entrants in 2012 should have a much reduced die of cancer
- The control of this disease will rank as one of our greatest achievements



Acknowledgements

- Staff at CRUK Centre
- Funding agencies
 - Cancer Research UK
 - Leukaemia and Lymphoma Research
 - Many others
- University

