Fighting Cancer

Paul Moss

Research programmes broadly based in immunology, genetics and epidemiology
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
Cancer Worldwide

September 2011

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

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number of New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (13%)</td>
<td>1,608,055</td>
</tr>
<tr>
<td>Female Breast (11%)</td>
<td>1,304,135</td>
</tr>
<tr>
<td>Colorectum (10%)</td>
<td>1,235,108</td>
</tr>
<tr>
<td>Stomach (8%)</td>
<td>898,662</td>
</tr>
<tr>
<td>Prostate (7%)</td>
<td>899,302</td>
</tr>
<tr>
<td>Liver (6%)</td>
<td>530,122</td>
</tr>
<tr>
<td>Cervix (5%)</td>
<td>481,645</td>
</tr>
<tr>
<td>Oesophagus (4%)</td>
<td>382,660</td>
</tr>
<tr>
<td>Bladder (3%)</td>
<td>330,049</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (3%)</td>
<td>288,387</td>
</tr>
<tr>
<td>Leukaemia (3%)</td>
<td>280,434</td>
</tr>
<tr>
<td>Uterus (2%)</td>
<td>280,434</td>
</tr>
<tr>
<td>Pancreas (2%)</td>
<td>278,684</td>
</tr>
<tr>
<td>Kidney (2%)</td>
<td>273,318</td>
</tr>
<tr>
<td>Lip and Oral Cavity (2%)</td>
<td>263,020</td>
</tr>
<tr>
<td>Brain and CNS (2%)</td>
<td>237,913</td>
</tr>
<tr>
<td>Ovary (2%)</td>
<td>224,747</td>
</tr>
<tr>
<td>Thyroid (2%)</td>
<td>313,179</td>
</tr>
<tr>
<td>Melanoma (2%)</td>
<td>199,627</td>
</tr>
<tr>
<td>Larynx (1%)</td>
<td>150,677</td>
</tr>
<tr>
<td>Other Sites (12%)</td>
<td>1,566,634</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>England</th>
<th>Wales</th>
<th>Scotland</th>
<th>N. Ireland</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new cases</td>
<td>Males</td>
<td>117,805</td>
<td>8,730</td>
<td>13,164</td>
<td>3,427</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>115,816</td>
<td>8,076</td>
<td>12,949</td>
<td>3,593</td>
</tr>
<tr>
<td>Crude rate per</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000 population</td>
<td>Males</td>
<td>480.2</td>
<td>608.4</td>
<td>537.8</td>
<td>470.7</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>453.8</td>
<td>531.2</td>
<td>531.1</td>
<td>411.3</td>
</tr>
<tr>
<td></td>
<td>Persons</td>
<td>466.7</td>
<td>568.7</td>
<td>535.3</td>
<td>410.5</td>
</tr>
<tr>
<td>Age-standardised† rate</td>
<td>Males</td>
<td>400.1 (397.9-402.4)</td>
<td>464.8 (455.0-474.5)</td>
<td>452.6 (444.4-460.1)</td>
<td>401.6 (398.2-415.0)</td>
</tr>
<tr>
<td>per 100,000 population</td>
<td>Females</td>
<td>342.1 (340.3-344.0)</td>
<td>372.2 (364.1-380.3)</td>
<td>388.9 (380.3-396.1)</td>
<td>352.0 (345.3-358.7)</td>
</tr>
<tr>
<td></td>
<td>Persons</td>
<td>363.7 (362.3-365.2)</td>
<td>408.4 (402.3-414.5)</td>
<td>411.0 (406.1-415.3)</td>
<td>369.6 (366.9-372.3)</td>
</tr>
</tbody>
</table>

* excluding non-melanomas 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
Smoking rates are dropping substantially


Lung cancer is becoming less common

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

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Leucocytes</th>
<th>Polys.</th>
<th>Lymphocytes</th>
<th>Mononuclear and Transitional</th>
<th>Myelocytes and Metamyelocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th</td>
<td>900</td>
<td>34</td>
<td>34</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>12th</td>
<td>4,200</td>
<td>26</td>
<td>18</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>14th</td>
<td>6,200</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>80</td>
</tr>
</tbody>
</table>

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
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
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
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
- Ensure a broad research coverage across the UK
- First port of call for new developments and strategic initiatives instigated by Cancer Research UK
- Expand public engagement, information provision and local fundraising
- 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

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

Bladder cancer can invade the muscle – standard treatment is then to remove the bladder
Trial design for bladder cancer trial

Patients with muscle invasive bladder cancer

Randomise

Chemotherapy

No Chemotherapy

Standard volume RT† + synchronous chemotherapy

Reduced high dose volume RT† + synchronous chemotherapy

Standard volume RT†

Reduced high dose volume RT†

sRT

RHDV RT

Local disease control is much improved

HR (95% CI) = 0.68 (0.48-0.96)
Stratified logrank p= 0.03

James et al, NEJM 2012 366, 1477-1488
Overall survival is better

<table>
<thead>
<tr>
<th>N at risk (events)</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo-RT</td>
<td>0 12 24 36 48 60 72</td>
</tr>
<tr>
<td>162 (35)</td>
<td>144 (33)</td>
</tr>
<tr>
<td>111 (11)</td>
<td>94 (9)</td>
</tr>
<tr>
<td>75 (3)</td>
<td>62 (1)</td>
</tr>
<tr>
<td>39</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>0 12 24 36 48 60 72</td>
</tr>
<tr>
<td>178 (35)</td>
<td>141 (34)</td>
</tr>
<tr>
<td>104 (17)</td>
<td>85 (15)</td>
</tr>
<tr>
<td>60 (7)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.82 (0.63-1.09)
Stratified logrank p = 0.16

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