Overview

- Background
  - Determinants of mortality
  - Cancer mortality
- Recent advances in cancer treatment
- From the laboratory to clinical practice
  - Pharmaceutical development pipeline
  - Regulation
  - NICE guidance
- Evidence for survival extension
  - Clinical trials
  - Models over life-time horizons
- Impedance to inference
  - Pitfalls, caveats and conundrums
- Context of longevity research
- Discussion and questions
Thomas McKeown

- Physician and Demographic Historian – put forward a body of research between the 1950’s and the 1980’s ‘The McKeown Thesis’

- Principally concerned with the role of medicine and population change

- Proposed that ‘population growth was due primarily to a decline in mortality from infectious disease driven by improved economic conditions…other variables such as medical interventions, sanitary reforms and the decline in infectious organisms played a marginal role…’

Historical markers in public health

<table>
<thead>
<tr>
<th>Era 1</th>
<th>1838</th>
<th>Era 2</th>
<th>1940’s</th>
<th>Era 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1750</td>
<td>1800</td>
<td>1820</td>
<td>1850</td>
<td>1970</td>
</tr>
<tr>
<td>Improved Nutrition</td>
<td>Improved Sanitation</td>
<td>Modern Hospitals, Antibiotics</td>
<td>Modern Medical Care</td>
<td></td>
</tr>
<tr>
<td>E. Jenner 1779–1823 (smallpox vaccination)</td>
<td>J. Snow 1813–1858 (cholera etiology)</td>
<td>J. Goldberger 1901 (pneumonia—nutrition-based, causation)</td>
<td>Fleming 1938 (antibiotics)</td>
<td></td>
</tr>
</tbody>
</table>

The 20 most common causes of death from cancer, UK, 2008

- Lung
- Colorectal
- Breast
- Prostate
- Pancreas
- Oesophagus
- Stomach
- Bladder
- Non-Hodgkin lymphoma
- Ovary
- All leukaemias
- Kidney
- Brain with central nervous system
- Liver
- Multiple myeloma
- Mesothelioma
- Malignant melanoma
- Oral
- Uterus
- Bone and connective tissue
- Other cancers

Source: Cancer Research UK

Lung cancer, five-year relative survival rate, England and Wales, 1971-2006 (age-standardised)

Source: Cancer Research UK
Colon cancer, five-year relative survival rate, England and Wales, 1971-2006 (age-standardised)

Breast cancer, five-year relative survival rate, England and Wales, 1971-2006 (age-standardised)
What about recent medical advances?

- Targeted therapies a major advance in last 20 to 30 years
  - monoclonal antibodies
  - small molecules
- Chemotherapy
  - classes, generations
  - sequences, combinations
- Radiotherapy, surgical techniques, best supportive care
- Important to remember that advances occur at all stages of the life course, not just after diagnosis
  - health promotion, disease prevention, screening, diagnostics, surveillance techniques

Overview of the clinical trial process and regulatory assessment

<table>
<thead>
<tr>
<th>Time</th>
<th>Preclinical testing</th>
<th>Phase I Trials</th>
<th>Phase II Trials</th>
<th>Phase III Trials</th>
<th>Filing/approval</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 - 5 years</td>
<td>1 year</td>
<td>2 years</td>
<td>3 years</td>
<td>2 years</td>
<td>open</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study subject</th>
<th>Laboratory and animal studies</th>
<th>20 - 80 healthy volunteers</th>
<th>100 - 300 patient volunteers</th>
<th>1'000 - 3'000 patient volunteers</th>
<th>open, according to indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study aim</td>
<td>Assess safety &amp; biol. activity</td>
<td>Determine safety &amp; max. dose</td>
<td>Evaluate effective dose, side effects</td>
<td>Verify efficacy, monitor long term</td>
<td>Review process</td>
</tr>
<tr>
<td></td>
<td>IND1 Submission</td>
<td></td>
<td></td>
<td></td>
<td>Post marketing safety monitoring</td>
</tr>
</tbody>
</table>
NICE  
(National Institute for Health and Clinical Excellence)

- Independent organization responsible for providing national guidance on promoting good health and preventing and treating ill health
- Produces several types of guidance
  - Clinical Guidelines, Public Health, Tech Appraisals
- Technology appraisals include rigorous systematic reviews of clinical evidence, economic evaluation, multiple stakeholder opinions and submissions, deliberation of a multidisciplinary committee in public, consultation and right of appeal
- Have carried mandatory funding direction
- Only certain topics are prioritised for appraisal, in accordance with clear criteria

Measures of survival in clinical trials

- Progression-free survival
- Overall survival
  - Median survival
  - Hazard ratios/Relative risks
- Other outcomes
  - Response rates
    - Response definitions
  - Improvement in operability
  - Duration of response / time to relapse
- Adverse effects
Estimating life years gained

- Cost effectiveness models
  - Cost per QALY gained = ICER
  - QALY = quality-adjusted life year
- Time horizon – long enough to capture differences between treatment arms (life time for chronic illness)
- Extrapolation beyond clinical trial data
- Parametric curve fitting and its perils
- Means and medians
- Area under the curve
- LYG, QALYs and ICERs
- Sensitivity and scenario analyses – results can be pretty variable

Extrapolating survival beyond trial data

% of patients surviving

0% 50% 100%

Years

0 5 10 15 20 25 30 35 40
Scope and methods of this exercise

- NICE Technology Appraisals with positive recommendations between 2005 to 2010
- Focus on lung, breast and colorectal cancers, on grounds of being most common causes of cancer death, but note that there are more life years lost per person due to some other cancers
- Limited to clinical trial comparisons and base case assumptions – these are often not the most generalisable and plausible assumptions for current UK setting
  - Clinical trial evidence – usually ITT from regulatory trial
  - Modeled life years gained – manufacturer’s base case (STA); Assessment Group base case (MTA)

Lung cancer treatments

*NB: heterogeneous populations*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Best supportive care</td>
<td>0.70 (0.58, 0.85)</td>
</tr>
<tr>
<td>Pemetrexed/cisplatin</td>
<td>Gemcitabine/cisplatin</td>
<td>0.84 (0.74, 0.96)</td>
</tr>
<tr>
<td>Pemetrexed maintenance</td>
<td>Best supportive care</td>
<td>0.70 (0.56, 0.88)</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Best supportive care</td>
<td>0.61 (0.43, 0.87)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Paclitaxel/carboplatin</td>
<td>0.91 (0.76, 1.10)</td>
</tr>
</tbody>
</table>
Lung cancer treatments

Modelled life expectancy with and without interventions

- Gefitinib
- Topotecan
- Pemetrexed maintenance
- Pemetrexed/cisplatin [Large]
- Pemetrexed/cisplatin [Adeno]
- Erlotinib

Mean survival without intervention

Indicated/recommended populations as a proportion of total incident lung cancer cases

- Pemetrexed TA190
- Topotecan
Colorectal cancer treatments

NB: heterogeneous populations

### Hazard ratios for mortality

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab+FOLFIRI [KRAS Wild-type subgroup]</td>
<td>FOLFIRI</td>
<td>0.84 (0.64, 1.11)</td>
</tr>
<tr>
<td>Irinotecan+5-FU/FA [1st line]</td>
<td>5-FU/FA</td>
<td>0.84 (0.76, 0.93)</td>
</tr>
<tr>
<td>Oxaliplatin+5-FU/FA [1st line]</td>
<td>5-FU/FA</td>
<td>0.93 (0.83, 1.03)</td>
</tr>
<tr>
<td>Raltitrexed [1st line]</td>
<td>5-FU/LV</td>
<td>1.10 (0.97, 1.25)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>5-FU/LV</td>
<td>0.88 (0.74, 1.05)</td>
</tr>
<tr>
<td>Oxaliplatin+5-FU/LV [Stage III Colon subgroup]</td>
<td>5-FU/LV</td>
<td>0.86 (0.68, 1.08)</td>
</tr>
</tbody>
</table>

### Modelled life expectancy with and without interventions

- **Oxaliplatin+5-FU/LV [Adjuvant]**
- **Capecitabine [Adjuvant]**
- **Cetuximab+FOLFIRI [Metastatic]**

*Mean survival without intervention*<br>*Additional survival with intervention*
Indicated/recommended populations as a proportion of total incident colorectal cancer cases

Breast cancer treatments

*NB: heterogeneous populations*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Observation</td>
<td>0.66 (0.57, 0.77)</td>
</tr>
<tr>
<td>Docetaxel[TAC]</td>
<td>FAC</td>
<td>0.70 (0.53, 0.93)</td>
</tr>
<tr>
<td>Anastrazole[HR +ve]</td>
<td>Tamoxifen</td>
<td>0.97 (0.83, 1.14)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Tamoxifen</td>
<td>0.83 (0.67, 1.02)</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Tamoxifen</td>
<td>0.86 (0.70, 1.06)</td>
</tr>
<tr>
<td>Gemcitabine[GT]</td>
<td>Paclitaxel(T)</td>
<td>0.82 (0.67, 1.00)</td>
</tr>
</tbody>
</table>
Breast cancer treatments

Modelled life expectancy with and without interventions

Mean survival without intervention
Additional survival with intervention

Indicated/recommended populations as a proportion of total incident breast cancer cases
Slim pickings, or the hint of distant promise?

• Innovation, much like policy change, tends to happen more often by 'creeping incrementalism', rather than 'step change'
• So, whilst the impact of an individual new treatment might look modest, it could be the first step towards much greater change in the future
• Cumulative effects on survival of extended indications over time:
  • e.g. rituximab for follicular NHL – first marketing authorisation at stage III/IV after prior treatments

Inference considerations and conundrums

• Comparators
• Intervention: licensed regimen and dosing vs clinical practice
• Clinical trial design: endpoint timing, cross over
• Subgroups
• Modelled life years gained
  – Manufacturer vs Assessment Group
  – Base case vs sensitivity/scenario analysis
  – Discounting of health benefits
• Generalisability
• Implementation & uptake: licensed indication vs NICE recommendation
A window into the future: Understanding and predicting longevity, Swiss Re, 2011

Considerations when building a forward-looking, disease-centred approach to assessing future longevity, Swiss Re, 2011
Questions or comments?

Expressions of individual views by members of The Actuarial Profession and its staff are encouraged. The views expressed in this presentation are those of the presenter.