The Actuarial Profession
making financial sense of the future

Survival extension from advances in cancer treatment
Helen Chung and Nicola Oliver, Swiss Re

Realised benefits?
Future promise?

14 September 2011

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

1

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…'

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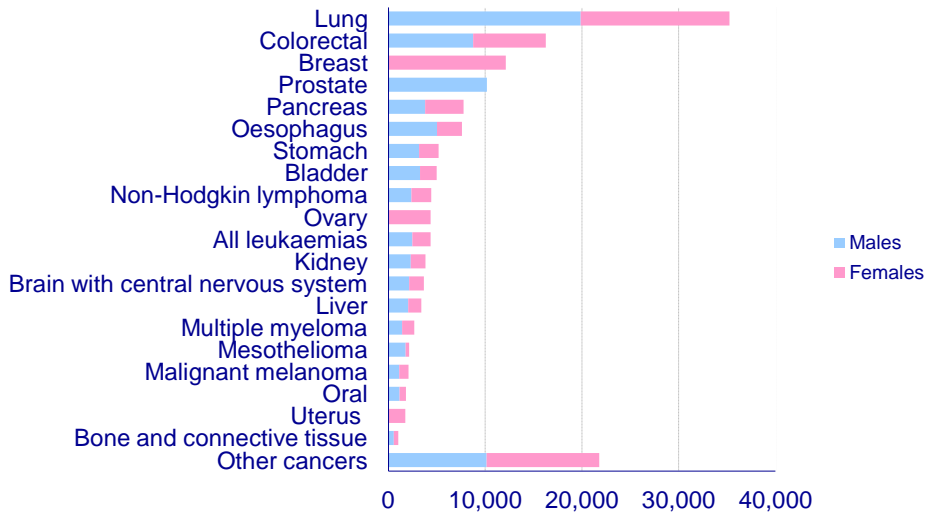## Historical markers in public health

Crude Death Rate per 1000
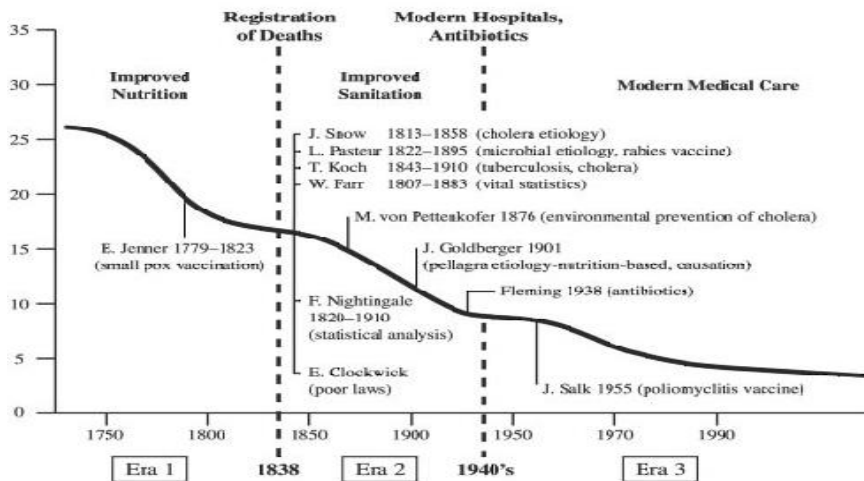
Source: J. McKinlay and S.M. McKinlay in J. Kaufert, Social Change and Public Health: Population Health and Victorian Epidemics, 2000.

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The 20 most common causes of death from cancer, UK, 2008
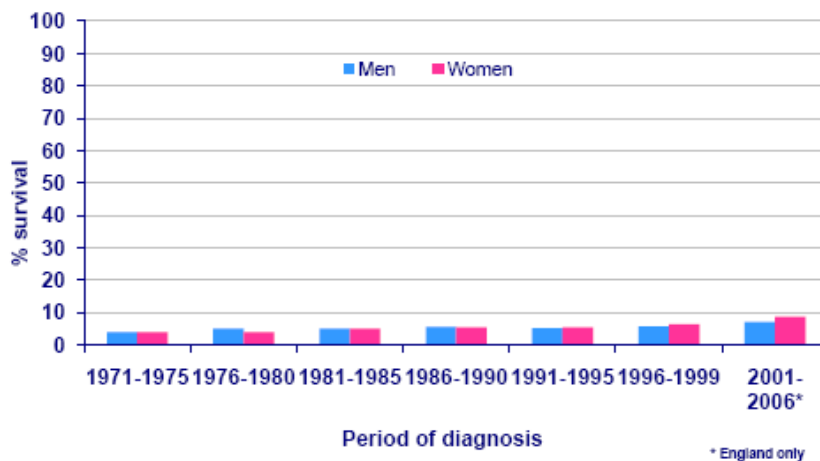
Source: Cancer Research UK

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)

Source: Cancer Research UK

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

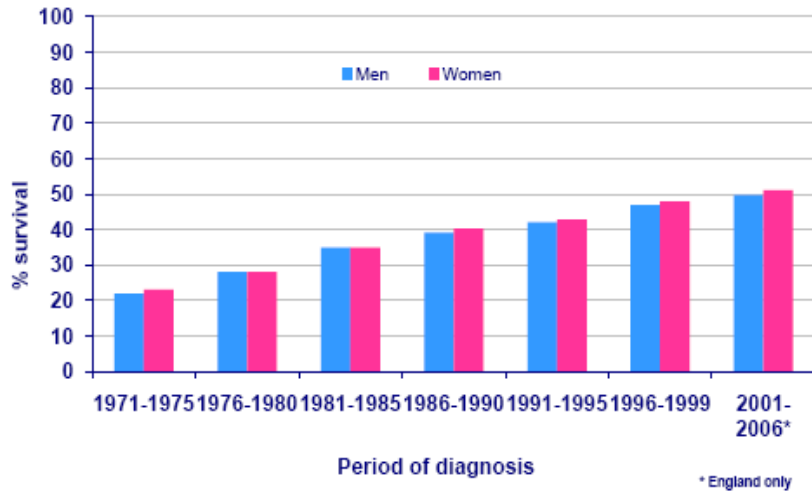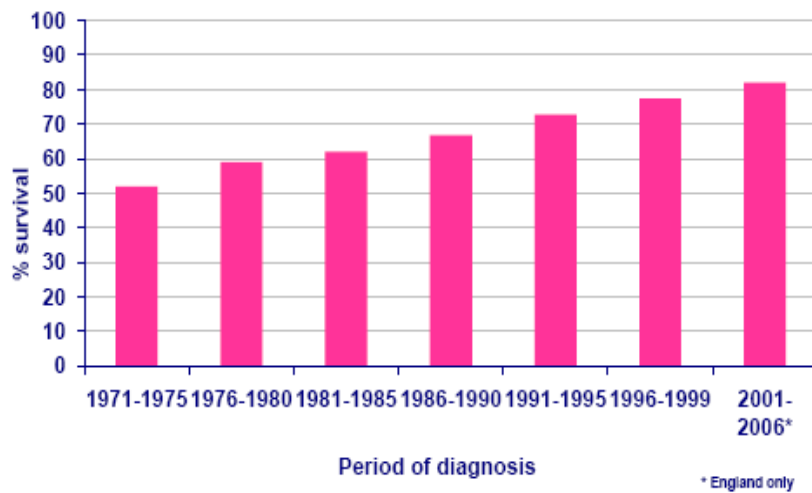Source: Cancer Research UK

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

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Overview of the clinical trial process and regulatory assessment

	Preclinical testing	Phase I Trials	Phase II Trials	Phase III Trials	Filing/ approval	Phase IV
Time	3 – 5 years	1 year	2 years	3 years	2 years	open
Study subject	Laboratory and animal studies	20 - 80 healthy volunteers	100 – 300 patient volunteers	1'000 – 3'000 patient volunteers	–	open, according to indication
Study aim	Assess safety & biol. activity	Determine safety & max. dose	Evaluate effective dose, side effects	Verify efficacy, monitor long term	Review process	Post marketing safety monitoring

➡ IND[1] Submission

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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

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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

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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

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Extrapolating survival beyond trial data

% of patients surviving
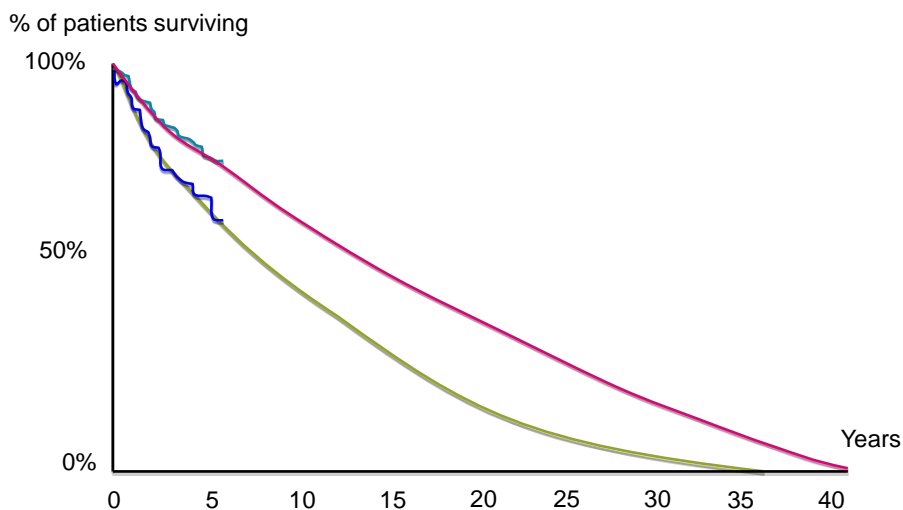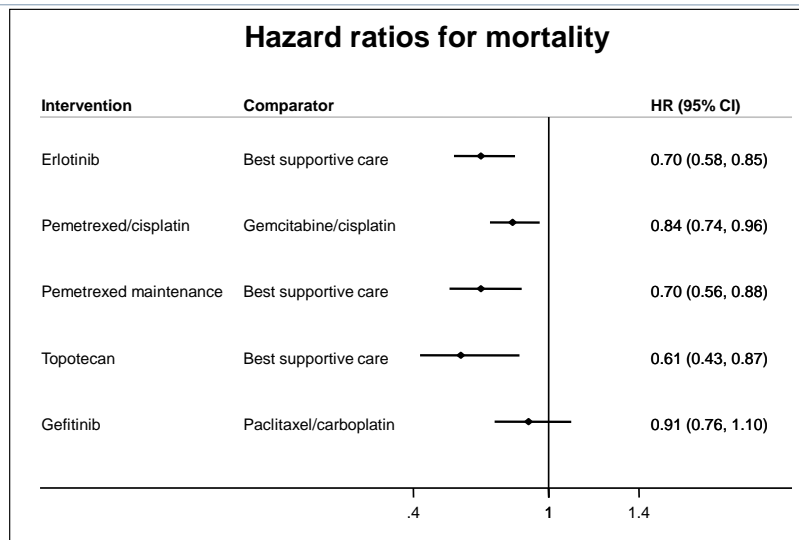
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Scope and methods of this exercise

- 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)*

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Lung cancer treatments
NB: heterogeneous populations

Hazard ratios for mortality

Intervention	Comparator		HR (95% CI)
Erlotinib	Best supportive care		0.70 (0.58, 0.85)
Pemetrexed/cisplatin	Gemcitabine/cisplatin		0.84 (0.74, 0.96)
Pemetrexed maintenance	Best supportive care		0.70 (0.56, 0.88)
Topotecan	Best supportive care		0.61 (0.43, 0.87)
Gefitinib	Paclitaxel/carboplatin		0.91 (0.76, 1.10)

.4   1   1.4

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Lung cancer treatments

Modelled life expectancy with and without interventions

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

0.00   0.50   1.00   1.50   2.00   2.50

■ Mean survival without intervention

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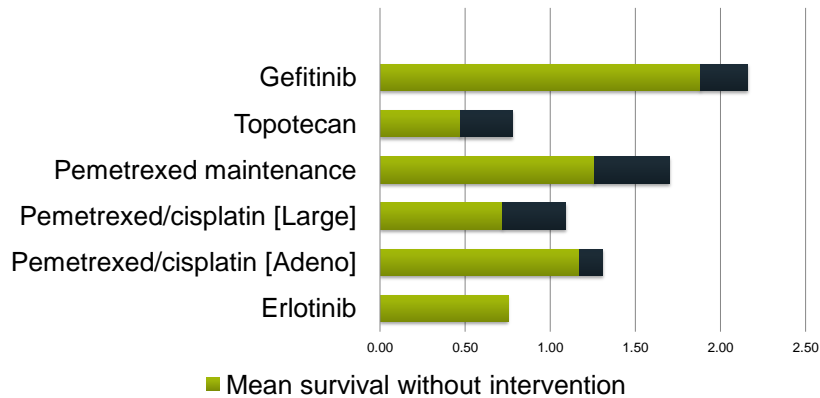
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Indicated/recommended populations as a proportion of total incident lung cancer cases

■ Pemetrexed TA190

■ Topotecan

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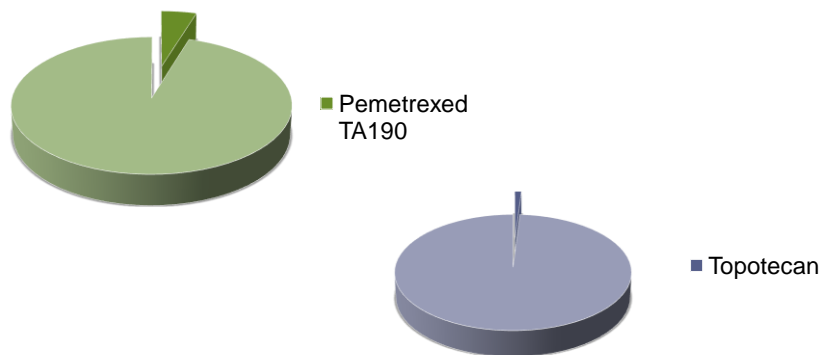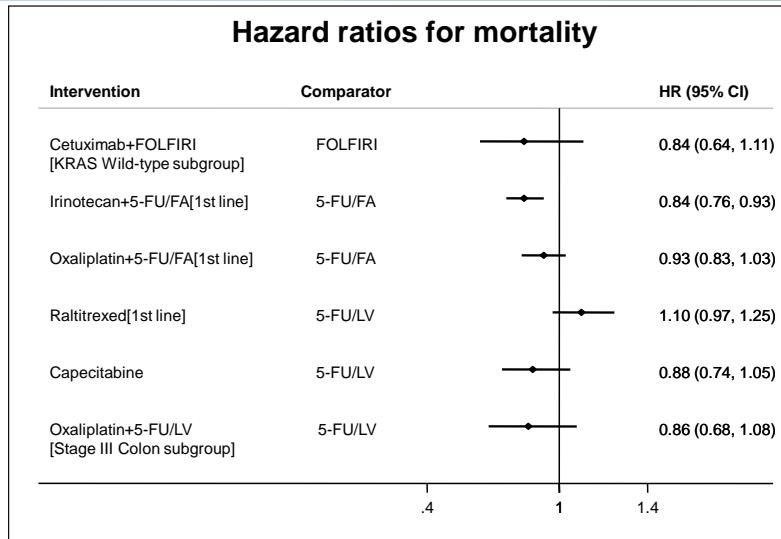## Colorectal cancer treatments
NB: heterogeneous populations

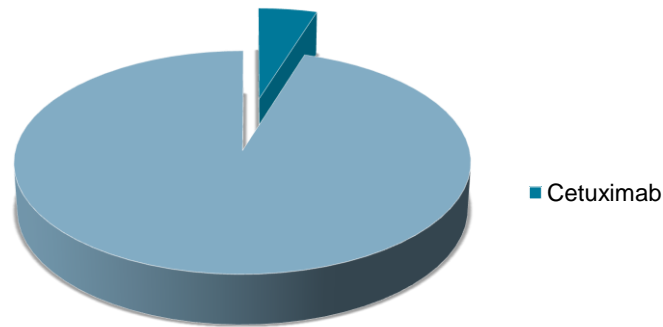**Hazard ratios for mortality**

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

.4 1 1.4

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Colorectal cancer treatments

Modelled life expectancy with and without interventions

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

0 2 4 6 8 10 12 14

■ Mean survival without intervention
■ Additional survival with intervention

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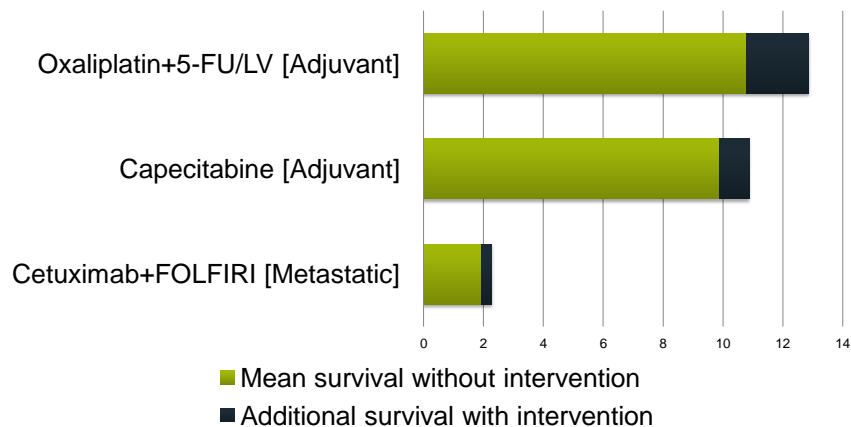
Indicated/recommended populations as a proportion of total incident colorectal cancer cases

■ Cetuximab

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Breast cancer treatments
NB: heterogeneous populations

Hazard ratios for mortality

Intervention	Comparator		HR (95% CI)
Trastuzumab	Observation		0.66 (0.57, 0.77)
Docetaxel[TAC]	FAC		0.70 (0.53, 0.93)
Anastrazole[HR +ve]	Tamoxifen		0.97 (0.83, 1.14)
Exemestane	Tamoxifen		0.83 (0.67, 1.02)
Letrozole	Tamoxifen		0.86 (0.70, 1.06)
Gemcitabine[GT]	Paclitaxel(T)		0.82 (0.67, 1.00)

.5   1   1.5

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Breast cancer treatments

Modelled life expectancy with and without interventions

Legend:
- ■ Mean survival without intervention
- ■ Additional survival with intervention
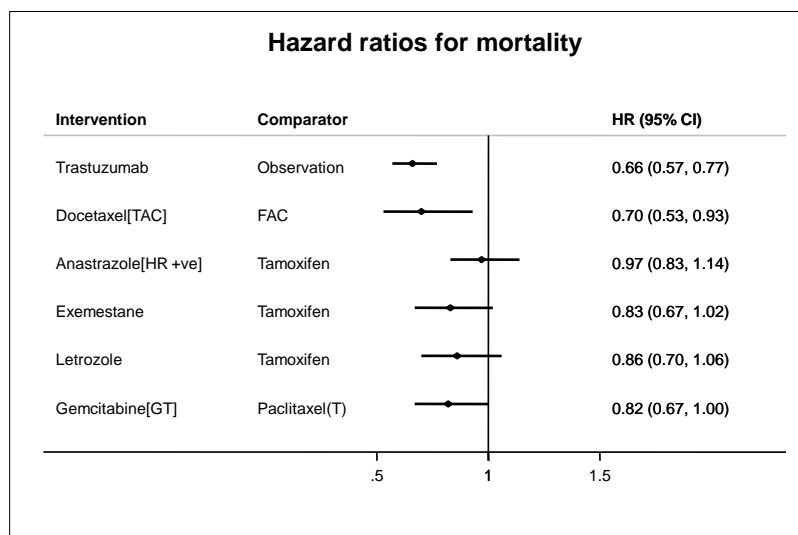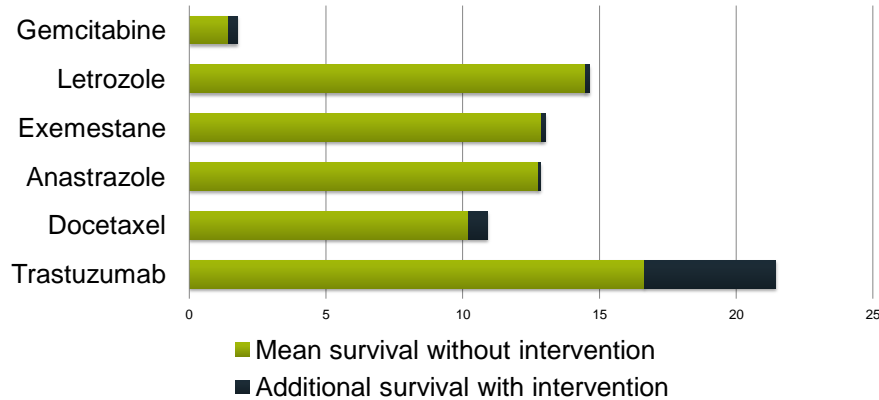
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Indicated/recommended populations as a proportion of total incident breast cancer cases

- ■ Trastuzumab
- ■ Docetaxel
- ■ Aromatase Inhibitors
- ■ Gemcitabine
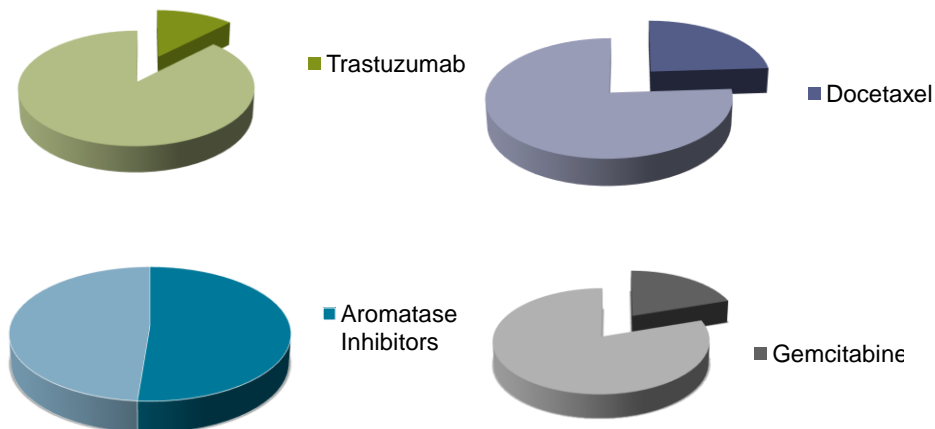
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Slim pickings, or the hint of distant promise?

- 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
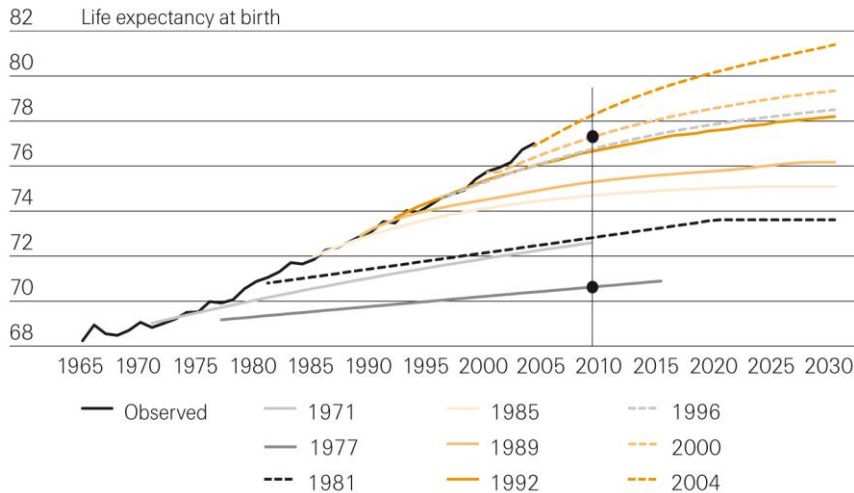
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Inference considerations and conundrums

- 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

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A window into the future:
Understanding and predicting longevity, Swiss Re, 2011

82   Life expectancy at birth

Legend:
— Observed
— 1971
— 1977
--- 1981
— 1985
— 1989
— 1992
--- 1996
--- 2000
--- 2004

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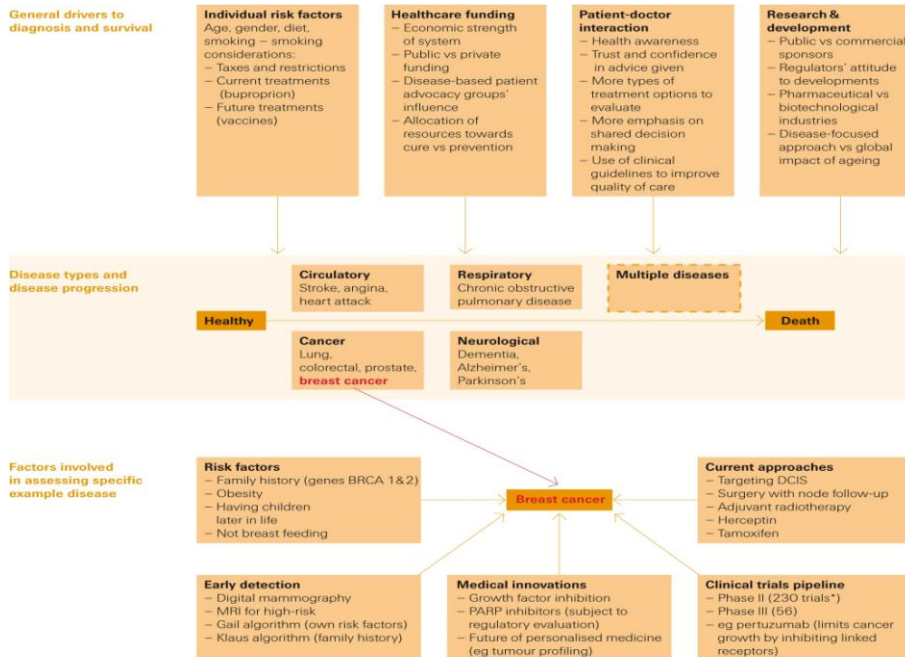
Considerations when building a forward-looking, disease-centred approach to assessing future longevity, Swiss Re, 2011

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.

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