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Investigating time lags and attribution in the translation of cancer research
A case study approach
Investigating time lags and attribution in the translation of cancer research

A case study approach

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Prepared for the Wellcome Trust, Cancer Research UK, the National Institute for Health Research and the Academy of Medical Science
In 2012, RAND Europe and the Health Economics Research Group (Brunel University) were commissioned by the Wellcome Trust, Cancer Research UK, the National Institute for Health Research and the Academy of Medical Science to conduct a study of the returns to the public/charitable investment in cancer-related research. This study built on previous work published in the 2008 ‘What’s it worth?’ report that estimated the economic returns to medical research in terms of spillover benefits and health gain. The 2008 study was extensively quoted and cited as a clear justification for the economic importance of medical research and appears to have played a role in achieving the protection of the medical science budget in the recent public expenditure cuts.

This cancer study used a similar approach to that used in the previous study, but with some methodological developments. One of the methodological developments was the inclusion of case studies to examine the validity and variability of the estimates on elapsed time between funding and health gains, and the amount of health gains that can be attributed to UK research. This report provides the full text of the five case studies conducted as well as some discussion of observations emerging across the case study set.
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Previous work has shown that medical research offers a good return on investment.

Buxton et al. (2008) estimated the economic returns to medical research in the cardiovascular and mental health fields in terms of spillover benefits and health gain, finding that every pound invested in research led to a stream of benefits equivalent to around 39 pence each year in perpetuity. The work was extensively quoted and cited as a clear justification for the economic importance of medical research and appears to have played a role in achieving the protection of the medical science budget in the recent public expenditure cuts.

This report is part of our recent study which replicated that work in cancer research, with some methodological developments including case studies.

Buxton et al. (2008) recommended that the approach should be repeated in other clinical areas to both test and refine methods and to see whether rates of return appeared to be similar. We have now completed such a study in the field of cancer research, again finding that research is economically beneficial (Glover et al., 2014). To do this, we estimated: (1) public and charitable expenditure on cancer-related research in the UK; (2) the net monetary benefit (NMB), i.e., the health benefit valued in monetary terms minus the cost of delivering that benefit, for a prioritised list of interventions; (3) the proportion of NMB attributable to UK research; (4) the elapsed time between research funding and health gain; and (5) the internal rate of return from cancer-related research investments on health benefits. One of the main methodological developments in this new study was the inclusion of case studies to investigate two of these elements: the elapsed time between research funding and health gains, and the proportion of health gains that can be attributed to UK publicly funded research.

This report contains the five detailed case studies conducted and outlines observations emerging from them.

The case studies conducted were:

- The use of guaiac-based faecal occult blood test in bowel cancer screening
- Cancer service configuration
- Smoking reduction
- The use of tamoxifen in the treatment of breast cancer
- Total mesorectal excision (TME) in rectal cancer.

The aim of the case studies was to examine the estimates of the elapsed time between funding and health gains and the fraction of health gains that can be attributed to UK research.
These estimates form part of the model used to evaluate the economic returns and were calculated for the numerical estimation based on the analysis of citations on guidelines. The case studies were used to inform the sensitivity analyses conducted around those estimates. This report also includes some observations emerging across the case study set both on these two key issues, but also on wider issues relating to the translation of research into practice.

**The case studies were selected to cover a variety of interventions.**

Case studies were purposively selected in discussion with the Steering Group (made up of representatives of the funders) to cover a range of different types of intervention (i.e., pharmaceutical, screening, surgical, prevention and service organisation) and cancer sites with the highest burden of disease (i.e., lung, breast, bowel, prostate).

**Trying to understand and estimate elapsed time between funding and health impact is difficult.**

Estimates from guideline analysis use the time difference between the date of publication of the guideline and the average date of publication of cited references and adds to this estimates for the time between awarding of funding and publication, and the time between recommendation and use. By contrast, the case studies describe the process of research translation from a qualitative point of view and as such the focus moves away from an average time lag figure for the total research spend and towards the overall elapsed time from the original research breakthrough to some measure of when the health gains might start accruing. This can provide a detailed picture of the body of research related to the intervention and the timescales involved, supporting the guidelines analysis, but means that the quantitative estimates are not directly comparable.

**There is a range of factors which contribute to the elapsed time.**

The case studies identify a range of factors influencing elapsed time, from the length of time needed to conduct randomised controlled trials (RCTs) in the field of bowel cancer screening, to the training needed for surgeons to implement TME. However, some themes do emerge across several case studies which are of interest.

**Having networks in place can support rapid research translation.**

Policy uptake after the publication of research evidence in particular appears to have been facilitated by the availability of networks in two of the case studies (bowel cancer screening and service configuration). Having the structures and networks in place means that the transfer of knowledge can happen more quickly once research evidence becomes available.

**A ‘champion’ can play an important role in the translation of research and in reducing elapsed time.**

Several case studies (tamoxifen, TME and service configuration) illustrate the role of a ‘champion’ in the translation of research and in reducing time lags, which has been observed previously (Wooding et al. 2011, 2013). In all cases, researchers played a wider role in helping to facilitate the translation of research in their particular areas, by engaging with policy and decision makers or facilitating training.

**Analysing case studies allows us to consider the wider range of inputs to attribution more carefully than analysis of guidelines.**
The analysis of guidelines to estimate the proportion of health gain from research in cancer that can be attributed to UK public research funding has some limitations. It assumes each publication cited has equal weight; neglects any work which is not cited on guidelines (eg early basic research); does not account for the fact that some of the evidence for a particular intervention might have been unnecessary; and only provides an estimate for part of the translation process with estimates for the time from funding to publication and from inclusion on guidelines to implementation needing to be supplemented. Analysing case studies addressed some of these issues by allowing us to consider the wider range of inputs more carefully.

Assigning relative importance to different pieces of research and different stages of the research process is challenging.

Although case studies offer some advantages, assigning a figure to attribution remains difficult since it is challenging to assign relative importance to different pieces of research evidence. For example, how important is the initial discovery of a drug relative to an important clinical trial of that drug, or a meta-analysis of evidence across a number of trials? Deciding the relative weighting between these different countries contributing to multi-country studies is also not necessarily straightforward.

Analysis of the case studies conducted suggests that the estimate of 17 per cent for the proportion of health gains attributable to UK publicly funded research obtained from the guidelines analysis may be a low estimate

Three out of the five case studies appear to show that a higher proportion of the research contributing to the new intervention or approach was publicly funded and conducted in the UK, with the other two not providing any clear conclusions in either direction. However, this is a very small sample and as such no generalisable conclusions about the overall level of attribution across the research field can be drawn.

The role that research evidence plays varies between the case studies.

The role of evidence, and the importance of different types of evidence differed between case studies. For the service configuration and bowel cancer screening case studies, local research which could take into account the specific context was important, perhaps due to the nature of these interventions. In the case of bowel cancer screening, having the right kind of evidence available, through the economic evaluation ‘built into’ one particular trial may have facilitated the speedy policy uptake. By contrast, in the smoking case study, the extent to which research evidence was an important driver of policy actions at all is not so clear cut, with campaigning and public opinion playing an important role in policy change.

A number of different actors can play an important role in the translation of research into practice.

The role of a ‘champion’ was illustrated in two case studies as described above, but other important actors in research translation were identified. The TME case study illustrates the role of practitioners, with surgeons playing an important role in uptake, both in terms of their willingness to engage with the new approach, and the training needed for them to use the new approach. Policy makers can also play an important role, through their level of connection with relevant researchers as described above, but also potentially through their willingness to act early, potentially before evidence is conclusive, to facilitate rapid implementation as described in the bowel cancer screening study.

Estimating the economic impact of research is challenging.
As well as some of the issues in estimating elapsed time and attribution as described above, the service configuration case study illustrates an additional challenge in the estimation of the economic impact of research. Estimates of the health benefits of a particular intervention (in terms of quality-adjusted life year (QALY) gains) used in the economic model (in Buxton et al., 2008 and Glover et al., 2014) are largely extrapolated from trial data, mainly derived from UK relevant health technology assessments. This service configuration case study shows that the gains actually realised in the NHS may differ from those observed in trials – in this particular instance suggesting a situation where trial gains may underestimate what is now being achieved, though the reverse may be true in other cases.
Acknowledgements

We would like to thank: members of the Steering Group for their advice and support, particularly Liz Allen for chairing, along with David Cox, Aoife Regan, Emma Greenwood and Rachel Quinn; Pete Burge and Steven Wooding for their helpful review of this report; and Martin Buxton and Matthew Glover for their wider input to the work including discussion of the case studies.

We would especially like to extend our thanks to those cancer experts that have reviewed and commented on the case studies in this report: Professor Peter Selby, Professor Paul Finan, Professor Jack Cuzick, Professor V. Craig Jordan, and Professor Amanda Amos. Their help in this regard has been extremely valuable, but any misunderstandings or mistakes that remain are our own.
In 2008, a team from the Health Economics Research Group (HERG, Brunel University), RAND Europe and the Office of Health Economics published a study commissioned by the Evaluation Forum (comprising the Wellcome Trust, Medical Research Council and the Academy of Medical Science) that estimated the economic returns to medical research in terms of spillover benefits and health gain (Buxton et al., 2008). It used cardiovascular research as its main exemplar, whilst demonstrating the generalisability of the approach through a limited application to mental health research. The team found that for each pound invested by the taxpayer or charity donor in cardiovascular disease and mental health research, a stream of benefits is produced equivalent to earning 39 pence and 37 pence respectively each year in perpetuity. The study provided ‘compelling evidence that investment in medical research leads to significant improvements in both health and economic prosperity’ (MRC, 2014). It was extensively quoted and cited as a clear justification for the economic importance of medical research and appears to have played a role in achieving the protection of the medical science budget in the recent public expenditure cuts.

The study also recommended that the approach should be repeated in other clinical areas to both test and refine methods and to see whether rates of return appeared to be similar. Cancer is an obvious follow-on indication: it accounts for more than a quarter of all medical research, and 15 per cent of the UK health burden (Cooksey, 2006). Improving cancer outcomes continues to be a political priority for the NHS (see, eg, Department of Health, 2011). It is hence a particularly important area in which to establish an additional estimate of the economic returns from medical research and to begin to identify ways in which these returns might be further improved.

In 2012, RAND Europe and HERG were commissioned by the Wellcome Trust, Cancer Research UK, the National Institute for Health Research and the Academy of Medical Science to conduct a study of the returns to the public and charitable investment in cancer-related research. This study used a similar approach to that used in the previous study (Buxton et al., 2008), but with some methodological developments. The results demonstrated that in cancer research there is again a clear economic benefit to public and charitable research investment, with each pound invested in research leading to a return equivalent to around 40 pence per year in perpetuity. One of the methodological developments in this study was the inclusion of case studies to examine the validity and variability of the estimates on elapsed time between funding and health gains and the amount of health gains that can be attributed to UK research. The aim of the case studies was to help to examine and analyse two key assumptions used in estimating the internal rate of return – the elapsed time and attribution – as well as to contribute to the qualitative understanding of how research investments lead to health gain. This report provides the full
text of the five case studies conducted as well as some discussion of observations emerging across the case study set.

Case studies were purposively selected in discussion with the Steering Group (made up of representatives of the funders) to cover a range of different types of intervention (ie, pharmaceutical, screening, surgical, prevention, and service organisation) and cancer sites with the highest burden of disease (ie, lung, breast, bowel, prostate). Five case studies were chosen as follows, listed in the order presented in this document:

- Case study 1: The use of guaiac-based faecal occult blood test in bowel cancer screening
- Case study 2: Service configuration
- Case study 3: Smoking reduction
- Case study 4: The use of tamoxifen in the treatment of breast cancer
- Case study 5: Total mesorectal excision (TME) in rectal cancer

The case studies were prepared through desk research, primarily document analysis and, where appropriate, the occasional informal interview. The documents investigated included clinical guidelines, patents, journal publications, and relevant web sites. The case studies have a common structure which allows comparisons to be made between them. This structure consists of the following elements:

- **Scope of the case study**: A box at the beginning of each case study outlines the scope of the material included in the case study.
- **Narrative/history**: A narrative outline of the key stages of the development of the intervention, with a focus on factors relating to attribution and elapsed time but also covering the cancer affected and the mode of action of the intervention. This section also defines the scope of the case study.
- **Summary timeline (table)**: A table listing key dates in the development of the intervention and its implementation and describing their significance.
- **Key observations for estimating the economic returns**: A summary of the key points emerging from the case study in relation to elapsed time and attribution.
- **Summary timeline (graphic)**: A diagram illustrating some of the key events in the development and implementation of the intervention.

Case studies were reviewed by an expert in the field to ensure accuracy of the information included and verify the findings in relation to attribution and elapsed time in particular. In reviewing the case studies, reviewers were asked the following questions:

- Is the overall account historically accurate? Does it miss any important key events?
- Do the account and the timelines correctly summarise the key steps in the development and implementation of the research?
- Do the account and the timelines correctly summarise the key actors (and the country from which they were operating) in the development and implementation of the research?

Where inaccuracies or omissions were identified by reviewers, the case studies were amended appropriately by the author. Case studies were analysed qualitatively, comparing the key messages and lessons drawn in each case in relation to attribution and elapsed time. The findings from the case studies
as a group were then used to see how far they might contribute to an examination of the validity and variability in estimating the elapsed time between funding and health gains and the amount of health gains that can be attributed to UK research.

In using the findings in this way to examine the elapsed time it is important to establish appropriate comparators. There are two main approaches that whilst overlapping should not be seen as direct comparators other than in exceptional circumstances.

First, in the main analysis of the value of UK cancer research (Glover et al., 2014), as in our earlier study of the value of UK research in CVD and mental health (Buxton et al., 2008), the estimate of the elapsed time used in the study is based primarily on the analysis of cited references on clinical guidelines. This approach focuses on estimating the time difference between the date of publication of the guideline and the average date of publication of cited references. To produce an estimate of elapsed time between spending on research and health gain as required for this study, it was necessary to add on to this average value estimates for the period between the awarding of funding and publication, and the period of time between recommendation and use. Using the same approach adopted in the 2008 report we estimated these two periods to total approximately seven years, giving a best estimated elapsed time between spending on cancer research and health gain of 15 years. (The combined figure in the 2008 report was 17 years).

Second, in the case studies described in this report we are exploring the body of research that contributed to an intervention, but inevitably the focus of the timeline, narrative/history and graphic in each case is chronological. This usually moves the main headline focus away from an average time lag figure for the total research spend and towards the overall elapsed time from the original research breakthrough to some measure of when the health gains might start accruing. (It can also of course provide a much richer picture of how the body of research related to the intervention built up and the timescales involved).

It is highly likely that the examples of the overall timeline in the case study approach will be longer than the average time lags in the guideline citation approach because they are measuring different things. There is of course considerable value in examining the time elapsed as set out in the case studies, but great care is needed in using the headline figures for the overall time elapsed to examine the validity of the estimates made using the first approach. This is further discussed in the final chapter.

The estimate of the proportion of health gains which can be attributed to UK charitably and publicly funded research is also calculated through analysis of guidelines, looking at the proportion of the publications referenced on a selection of guidelines which were produced in the UK, proxied by a UK address being listed. There are several limitations to this approach, as described in the final chapter, and case studies can usefully be compared to the estimate produced and used to gain a fuller understanding of the attribution of research to various sources. The analysis of guidelines in this case suggested that 17 per cent of research contributing to health gain can be attributed to UK publicly and charitably funded research.

In addition to observations on time lags and attribution, other interesting observations on the research translation process across the case studies are identified and discussed.
2. Case study 1: The use of guaiac-based faecal occult blood test in bowel cancer screening

Scope of case study

This case study focuses on the use of the guaiac-based faecal occult blood test (gFOBT) in the early detection of bowel cancer through to the establishment and rollout of the NHS’s Bowel Cancer Screening Programme. It begins in 1967, with the suggestion that a gFOBT could be used in the home for early detection of bowel cancer and finishes in 2010 when the Bowel Cancer Screening Programme in England achieved national coverage. The case study excludes more recent technologies, such as flexible sigmoidoscopy, which are currently being piloted by the NHS Bowel Cancer Screening Programme, and focuses on the impact in England.

Globally, more than a million people will develop bowel (colorectal) cancer every year with the disease specific mortality rate 33 per cent in the developed world (Parkin et al., 2005, cited by Cunningham et al., 2010). In the UK, bowel cancer is the cause of 16,000 deaths a year and is second only to lung cancer as the leading cause of death from cancer (Ferlay et al., 2010, cited by Logan et al., 2011). In recent years, in the UK and elsewhere substantial progress has been made in the early diagnosis of colorectal cancer and improved treatment resulting in increased survival rates. Between 1986–90 and 2005–2009, there has been an increase of 16 per cent in the number of women and men who survive colorectal cancer for more than five years. Key treatment advances have included chemoradiotherapy and surgery for preoperative management, surgery with adjuvant chemotherapy, including total mesorectal excision (see Case Study 5) and laparoscopic surgery, and various combination therapies for those in the advanced, metastatic, state of the disease. However, as about 75 per cent of diagnosis is in patients with no apparent risk factors other than old age, Cunningham et al. (2010) argue that ‘screening continues to offer the best prospects of a reduction in mortality rates’.

The aim of screening it to detect localised bowel cancer or premalignant adenomas (polyps) at an early stage; that is before people are experiencing any symptoms and when treatment is more likely to be effective. Several tests exist but the guaiac-based faecal occult blood test (gFOBT) is the most extensively studied and is currently used by the NHS Bowel Cancer Screening Programme. This test is the focus of this case study. The gFOBT is one of several methods that detect the presence of faecal occult blood, which is blood in the faeces that cannot be seen. The term ‘guaiac’ denotes the name of the paper surface, used in the test, which has a phenolic compound, alpha-guaiaconic acid, that is extracted from the wood resin of guaiacum trees. Screening test kits are posted out to people. Over a few days the faeces from three separate bowel movements are saved in a disposable container and a small sample smeared on the test kit, using a piece of card. Once the test is completed, the card is posted to a laboratory, where a chemical is
added to the samples on the card to check for blood. If the test is positive, the subject and GP are notified and invited to attend a clinic and have further investigations to identify the cause of the bleeding.¹

The concept of occult blood detection can be traced back to the nineteenth century, when Van Deen used gum guaiac to indicate the presence of blood (see Simon, 1985 for discussion on the history of occult blood detection, on which this section is drawn). Boas (1901) (as cited by Simon, 1985) first suggested the existence of occult blood may be an indication of bowel cancer, but it was not for a further 60 years until Greegor (1967) proposed the use of a commercially available gFOBT for home use in the early detection and screening of large bowel cancer.

Greegor asked the manufacturers of the test (Hemoccult) to make special slides that could be prepared at home and mailed to a laboratory in an ‘inoffensive’ state. In 1971 Greegor went on to develop a protocol (the ‘Greegor Screening Protocol’) of six sequential tests from three consecutive days of bowel movement after adopting a meat free, high-residue diet for four days. This protocol was endorsed by the American Cancer Society (ACS) in 1974 (Leffall, 1974).

Although subsequent studies confirmed the ability of the home tests to identify early stage (and undetectable) bowel cancer, the early endorsement of the Greegor Protocol by the ACS predates any firm evidence that bowel cancer screening was effective or cost effective. Indeed in 1975 two health economists examined the benefit of the marginal costs of detection from multiple tests and concluded that the six tests were not cost-effective (Neuhauser and Lewicki, 1975). (Interestingly this paper was widely used as a teaching resource in health economics until it was disputed on methodological grounds by Brown and Burrows in 1990). In 1985 Simon argued, in a critical review in *Gastroenterology*, that existing studies were ‘too often ill designed and superficial’ and went on to argue that ‘only controlled trials can answer the central question of whether screening decreases mortality from bowel cancer.’

Several randomised controlled trials (RCTs) followed and a Cochrane Review provided high quality evidence that the gFOBT, if offered every two years, has the potential to reduce mortality rates from bowel cancer by 16 per cent (Cunningham et al 2010). Two of the RCTs (Hardcastle et al 1996 and Kronborg et al 1996) were published in the same edition of *The Lancet* along with an editorial title *Is it time to recommend screening for colorectal cancer?* Unusually at the time the Hardcastle study included a detailed economic evaluation of the cost effectiveness of bowel cancer screening (see Whynes et al., 1998). Two years later a Cochrane Review and associated paper was published in the *BMJ* on the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. This review included six papers, of which four where RCTs. The paper and review concluded that the ‘meta-analysis of the mortality results of the four randomized controlled trials showed that those allocated to screening had a reduction in mortality from colorectal cancer of 16 per cent’ (Towler et al 1998).

Informed by this evidence the NHS’s National Screening Committee recommended the establishment of the UK Colorectal Cancer Screening Pilot to determine the feasibility of screening for colorectal cancer in the UK population using faecal occult blood testing. Pilot sites were commissioned in 1999, with recruitment in 2000. The NHS Cancer Plan published in September 2000 stated that a national bowel cancer screening programme would be introduced subject to evidence of effectiveness of the pilot, which

reported in 2003 with an associated *BMJ* paper in 2004 and a long-term follow up in 2006 (UK CRC Screening Pilot Evaluation Team, 2003; UK CCS Pilot Group, 2004; Weller et al., 2006). Based on the 2003 evaluation report of the pilot and a formal Options Appraisal that had subsequently been commissioned (Tappenden et al 2004), the Secretary of State for Health announced in October 2004 that the NHS Bowel Cancer Screening Programme would begin in April 2006. The programme offered men and women aged 60 to 69 a gFOBT test every two years. People aged 70 and over were provided with a gFOBT testing kit on request. The Bowel Cancer Screening Programme achieved national coverage in 2010, with the millionth test occurring by October 2008. Up to that point uptake was just over 50 per cent with around 2 per cent of tests being abnormal resulting in follow on investigations for 17,518 individuals, with 1,772 cancers being detected and 6,543 high risk adenomas (Logan et al., 2012). Overall these early results indicated that the screening programme in England was on course to match the 16 per cent reduction in bowel cancer mortality found in the randomised trials of gFOBT.
2.1. Summary timeline (table)

1967 Gregor proposes a test for home use that involved guaiac-impregnated paper slides. US-based researcher. No funding source acknowledge, but the guaiac slides used were supplied as Hemoccult Slides through Laboratory Diagnostics Co.

1971 Gregor proposes protocol of a meat free and high residue diet follow by six sequential tests over a three day period.


1975 Neuhauser and Lewicki publish economic assessment questioning the value of the marginal costs of the sixth test in the Gregor Protocol.

1985 Simon review paper in Gastroenterology calls for RCTs to ‘answer the central question of whether screening decreases mortality from bowel cancer’.

1975–1998 Four key RCTs (and two observational studies) identified in systematic review by Towler et al., 1998.

RCTs: Mandel et al., 1993, US-based, supported by NIH and NCI; n=46,551; Kewenter et al., 1994, Swedish, n=65,308; Hardcastle et al., 1996, UK, DH & MRC, n=152,850; Kronborg et al., 1996, Denmark, several Danish funders, n=137,485.

The Hardcastle et al., 1986 study includes a detailed economic evaluation that is reported by Whynes et al., 1998.


1998 ‘Systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult’ is published in the BMJ (Towler et al. 1998). Also published and maintained on the Cochrane Library. Identified six papers and included the four RCTs (listed above).

Key result was that ‘meta-analysis of the mortality results of the four randomized controlled trials showed that those allocated to screening had a reduction in mortality from colorectal cancer of 16 per cent’.

Largely Australian authorship with exception of Kewenter (Sweden), no funding acknowledged.

1998 The NHS National Screening Committee recommended the establishment of the UK Colorectal Cancer Screening Pilot to determine the feasibility of screening for colorectal cancer in the UK population using faecal occult blood testing. Pilot sites commissioned

2000 The NHS Cancer Plan in September 2000 stated that a national bowel cancer screening programme would be introduced subject to evidence of effectiveness of the pilot.

2003 Final evaluation report of Colorectal Cancer Screening Pilot published in Feb/May 2003. [An evaluation of the second round was published in 2006].


October 2004 Based on the final evaluation report and a formal Options Appraisal, the Secretary of State for Health announced in October 2004 that the NHS Bowel Cancer Screening Programme would begin in April 2006. The programme will offer men and women aged 60 to 69 an FOB test every two years. People aged 70 and over will be provided with an FOB testing kit on request. The Bowel Cancer Screening Programme achieved national coverage in 2010.

2011 Logan et al. publish paper title ‘Outcomes of the Bowel Cancer Screening Programme in England, after the first 1 million tests’.
2.2. Key observations for estimating the economic returns

2.2.1. The time lag is 40+ years which is longer than the average 15 years estimated from the analysis of the clinical guidelines.

This is partly explained by the fact that it takes 10 years to undertake the RCTs (albeit over a 20 year time frame). However, once there is strong evidence of an effect from a meta-analysis gFOBT is quickly adopted into national policy although it takes a further 10 years for the screening programme to be developed and rolled out. It is also interesting to note the almost instantaneous impact of the research on policy, suggesting in part that the national infrastructure of a screening programme may help to facilitate the translation of research into practice.

2.2.2. Attribution would be higher than the 17 per cent estimated from the analysis of clinical guidelines.

Of the four studies that were included in the meta-analysis that provided the key evidence for a national screening programme, one was from the UK (Hardcastle et al., 1996), suggesting one estimate for an attribution rate could be 25 per cent (ie, 1 in 4). If you look at the contribution participants of those four trials made to the meta-analysis then the rate would be higher, at 38 per cent (ie, 152,850/402,194). That said, the original idea that gFOBT could be used for national screening stems from a US-based author, Greegor.

2.2.3. Other observations of note.

The ACS endorsement and recommendation predated the formal evidence, suggesting a willingness to ‘act early’ ‘at risk’. The economic evaluation ‘built into’ Hardcastle trial perhaps facilitated the speedy policy uptake.
### 2.3. Summary timeline (graphic)

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<td>1985</td>
<td>Hardcastle, 1996 (UK)</td>
<td>Feb/May 2003 Final evaluation report of Colorectal Cancer Screening Pilot published in Feb/May 2003</td>
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<td>1995</td>
<td>Kronborg, 1996 (Denmark)</td>
<td>October 2004 Secretary of State for Health announced that the NHS Bowel Cancer Screening Programme would begin in April 2006</td>
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<td></td>
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<td>Lieberman, 1996 [Commentary in Cancer]</td>
<td>April 2006 NHS Bowel Cancer Screening Programme begins</td>
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<td></td>
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<td></td>
<td>2010 The Bowel Cancer Screening Programme achieves national coverage</td>
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2.4. Key papers and reports


2.4.1. Key web sites consulted

http://www.cancerscreening.nhs.uk/bowel/pilot-evaluation.html
http://www.cancerscreening.nhs.uk/bowel/programme-information.html
http://www.cancerscreening.nhs.uk/bowel/research.html
http://www.cancerscreening.nhs.uk/bowel/nhsbcsp-organised.html
http://en.wikipedia.org/wiki/Colorectal_cancer
http://www.bbc.co.uk/health/physical_health/conditions/in_depth/cancer/typescancer_bowel.shtml
http://appliedresearch.cancer.gov/icsn/colorectal/screening.html
http://www.screening.nhs.uk/
http://www.beatingbowelcancer.org/
3. Case Study 2: Service configuration

**Scope of case study**

This case study focuses on service configuration, which can cover a number of overlapping issues, but here we concentrate on the key issues of: the volume of surgery/concentration of services, about which there is quite a long international history of research; and multidisciplinary specialised care. The focus on specialised care developed somewhat later than the volume of surgery debate, and did so particularly around evidence-informed reforms proposed in the UK. To some extent the specialised care issue encompasses the volume of surgery as one of a number of factors along with the role of Multidisciplinary Teams (MDTs).

The case study starts with an account of the timeline of the research that examined the volume of surgery issue in a range of medical fields. We next consider surgical volume in cancer services in general. But the main focus of the case study will be on the three main cancer sites that are included in our main study’s analysis of cancer treatments, ie breast, colorectal and prostate. Input aspects of the volume of surgery debate include hospital volume and surgeon volume. Outcome aspects include perioperative mortality and long-term survival. The timeline we develop to describe research on multidisciplinary specialised care is multi-faceted, but specifically relates to cancer and again we concentrate on our three main sites. While we set out two main strands of the service configuration issue (surgical volume and multidisciplinary specialised care), they become so intertwined that this case study mostly provides a combined analysis of the two. As with the other case studies, the evidence being considered is international, but the analysis of policies and implementation mostly focuses on the UK. We report on evidence illustrating that evidence-informed service configuration has been beneficial in the UK. But, unlike other case studies, this one does not attempt overall to assess the possible extent of the health gain that might result from the implementation of the research findings; it is assumed that some of the relevant health gains would be captured in the figures for the gains from various specific treatment interventions assessed in the analysis conducted in our main study. We also acknowledge, however, that this case study illustrates an example where it is possible that our assessment of the gains underestimates the gains realised in the NHS.

Various papers in the last decade exploring the volume of surgery in cancer treatment (for example, Ihse, 2003; Gookier et al., 2010; Archampong et al., 2012; London Cancer, 2013) identified a study from the USA (Luft et al., 1979) as being a key early study showing a correlation between surgical volume and mortality. In their paper, Luft et al. included surgery in a range of fields and referred to recommendations in the early 1970s from professional groups for concentration of CVD surgery. Nevertheless, the 1979 paper is a reasonable starting point for the issues covered in this case study.

While Luft et al. identified a correlation between higher volume and better outcomes, they discussed alternative views on the direction of any causal relationship: either greater experience leads to improved results, or a referral model in which larger volumes are the result of better results. In a follow-up paper in 1980 Luft et al. produced evidence that, they claimed, suggested that the referral model of causation might be of crucial importance for some procedures. Some further studies from the USA also supported this view. This is important because the policy implications might be different for the different circumstances. Furthermore, there is diversity between countries as noted much later in a Cochrane review of colorectal cancer that stated: ‘particularly for overall 5-year survival and operative mortality,
there were differences between US and non-US data, suggesting provider variability at hospital level between different countries, making it imperative that every country or healthcare system must establish audit systems to guide changes in the service provision based on local data, and facilitate centralisation of services as required.’ (Archampong et al., 2012).

Even after accepting that the bulk of the evidence supports the idea that the causal relationship is that higher volume leads to better outcomes, the reasons behind it, and the assessment of appropriate policy responses differ. The higher volumes leading to better outcomes for individual surgeons is often associated with a ‘practice makes perfect’ type argument; in terms of larger volumes for hospitals the key factors might be the existence of MDTs and better (more extensive) post-surgery services. The most common policy response is to call for concentration of services. But some argue that such a response could threaten the viability of some smaller hospitals, and they advocate alternative responses such as better training and support for lower volume providers.

Turning to the theme of multidisciplinary specialised care, concern about figures showing higher cancer mortality figures in the UK than in many other European countries led to the appointment of an Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales. The resulting Calman-Hine report recommended that care should be concentrated in the hands of site-specialists in each relevant discipline working in MDTs (Calman-Hine, 1995). It was wide-ranging and covered more than issues of surgical volume; indeed, it did not specially refer to volume. A key paper in the UK (and probably international) context is Stiller (1994), which reviewed the evidence for a range of cancer sites. At that time it was probably the most substantial such review ever conducted. Stiller examined centralised referral and entry to cancer trials and concluded that they were ‘frequently associated with a higher survival rate, particularly for the less common cancers, and never found to be associated with a lower survival rate.’ (p. 352). This paper is the main source in the table below for many of the early studies in relation to this issue in the major cancer sites. It was the only academic paper referenced (and referenced as being ‘in press’) in the influential 1995 Calman-Hine Report. But, the Calman-Hine Report was also supported by an annex that consisted of a review conducted from the University of Leeds by Peter Selby (1995). This included key studies, some yet to be published, from Leeds and Glasgow. The review pointed out that the nature of the evidence limited the conclusions that could be drawn, but that some literature and registry studies indicated significant improvements in survival resulting from specialist care. Selby also showed that the aspects of care which were most important may vary between cancer sites, and went on to claim: ‘The data suggest that the impact of specialised care for common cancers, and probably for many cancers, can increase long term survival by 5–10 per cent, a very important clinical outcome.’ (p. 29). Crucially, Stiller (1994) and Selby (1995) provided evidence which informed, and was rapidly incorporated into the Calman-Hine report, even if much of the specific evidence was later supplemented or superseded.

A growing stream of research, especially from teams in Leeds and Glasgow, informed the policy implementation documents from the NHS’s Clinical Outcomes Group (COG), called Improving Outcomes, for each main cancer site. They are illustrated below for our key sites. This evidence-based approach to service configuration was also promoted in the Cancer Plan (DH, 2000, updated in 2007 and
2011), and implementation is further encouraged by a peer review system, supported by a database: the Cancer Quality Improvement Network System (CQUINS).

While it is important to identify, and acknowledge, the two main aspects of service configuration being considered here, it is also the case that quite often the two are brought together. For example, a full range of the arguments were set out in the background to the recent Cochrane review, ‘Workload and surgeon’s specialty for outcome after colorectal cancer surgery’ (Archampong et al., 2012). For the high-volume surgeon, they claimed the thinking is, ‘greater experience should lead to improvements in the pre- and intraoperative decision-making process, case selection and surgical techniques; for the high-volume hospital the organisation of care including multidisciplinary team work approach, local availability of other specialist services and more active involvement with research is thought to lead to better results’ (p. 5). While this review frames the discussion of the two aspects in the context of the volume of surgery, other contributions bring the two streams together in the context of specialised care. For example, Selby’s Annex to the Calman-Hine report was published in a fuller version in the Lancet (Selby et al., 1996). It states: ‘There are many elements within specialist care – including training and skills, the composition of the multidisciplinary team, the volume of work undertaken by a unit or individual, and the provision of care within teaching or non-teaching hospitals or large regional or local hospitals.’ (p. 314)

For the major cancer sites the strongest evidence reported in Calman-Hine related to breast cancer. The evidence base was also continuing to expand and new studies were rapidly incorporated into the evidence-base for policies. For example, Selby referred to an important audit of breast cancer in Scotland as ‘(Gillis et al., submitted for publication)’ (para. 6.3) and described how it showed surgeons with specialist skills had better survival outcomes. Breast cancer was the first major area in which there was publication by the NHS Centre for Reviews and Dissemination, and Nuffield Institute for Health (NHS CRD, 1996) of an Effective Health Care bulletin, which was a systematic review of a wide range of breast cancer literature commissioned to inform policy. This evidence synthesis supported an accompanying NHS policy document from the COG (Improving Outcomes in Breast Cancer, NHS, 1996). The Effective Health Care bulletin highlighted a very recent major study from Leeds by Sainsbury et al. (1995) that showed the links between volume and outcomes. It was co-authored by Bob Haward who was also Director of Yorkshire Cancer Organisation, a member of the Calman-Hine Expert Advisory Group and Chair of the COG Cancer Subgroup. This again illustrates rapid uptake of UK evidence: it was perhaps being drawn upon as far as it was reasonable to take the findings at each step in the process. Based on the evidence from the bulletin, the NHS policy document recommended that a minimum of 100 annual cases should be the threshold for a modern specialist breast cancer service. Further studies continued to strengthen the international evidence base, as reviewed by Gooiker et al. (2010), but this Dutch study said there were policy uncertainties and more research was needed. Nevertheless, Autier et al. (2010) examined changes in trends in breast cancer mortality in 30 European countries between 1989 and 2006, and, drawing, especially on Morris et al. (2008) etc, suggested one reason for the large decrease in the UK was the reorganisation of breast cancer services on the basis of Calman-Hine.

For colorectal cancer the Effective Health Care bulletin (NHS CRD, 1997) and accompanying NHS policy document (Improving Outcomes in Colorectal Cancer, NHS, 1997) were supportive of the Calman-Hine principles, but had to note that in contrast to breast cancer: ‘Evidence of a volume effect in colorectal surgery is simply not there in most studies.’ (NHS, 1997, p. 9). By 2004, the second editions of
each publication reported on a much stronger evidence base reporting a volume-outcomes link, and the updated manual reported that the studies were: ‘consistent in finding evidence that for rectal cancer at least higher patient volumes and greater specialisation among surgeons were associated with better outcomes’ (NICE, 2004, p. 52). Studies continued to be conducted, with the Cochrane review described above (Archampong et al., 2012) re-enforcing the findings.

For prostate cancer there had generally been much less evidence from the earlier periods about any volume-outcomes link. The NHS policy document Improving Outcomes in Urological Cancer: The Manual was not produced until 2002 (NICE, 2002). It was informed by an accompanying Research Evidence document prepared by the Centre for Reviews and Dissemination that had highlighted some of the complexities in the evidence: ‘Concentration and specialisation of services often accompany each other. When this is the case, it is sometimes difficult to discern whether the concentration of services to high volume providers or the specialisation of treatments to experienced professionals has the greater influence on altered clinical outcomes.’ (CRD, 2002, p. 7). The manual recommended, ‘Patients with cancers which are less common or require complex treatment should be managed by specialist multidisciplinary urological cancer teams.’(NICE, 2002, p. 29). In 2013 the web site of London Cancer described various changes that were being made to concentrate local services where specialist treatment was required. This demonstrates that the process is still continuing, but it also conducted an analysis that showed strong evidence supporting the volume-outcome relationship was continuing to be produced and further strengthening the evidence base for the policies being promoted (London Cancer, 2013).

In the timeline table and graphic below we demonstrate how, overall and for the specific sites, the evidence built up and the policies were introduced in the UK, often fairly rapidly, and then further evidence accumulated and new policy recommendations were stronger and/or covered a wider range of cancer sites. It is noticeable that there have been frequent calls for further studies to be conducted in order to strengthen or clarify the evidence base. A further issue to note when considering the timeline is that most of the studies are not trials but rely instead on analysing data from previous years, so even though some key studies have been drawn upon quite rapidly, especially initially they generally reflected practice from further back. As noted in the Cochrane review of colorectal cancer, it is important to consider that more recent colorectal cancer management has changed, for example with more complex surgery such as TME (see case study 5). This highlights the desirability of the continuing efforts to research the topic, and also why this case study discusses the evolving relationship between research and policy/practice long after the initial policies were formulated.
## 3.2. Summary timeline (table)

### SURGERY IN GENERAL

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>1979</td>
<td>Luft et al. (US) examined data for 12 surgical areas and found ‘The mortality of open-heart surgery, vascular surgery, transurethral resection of the prostate, and coronary bypass decreased with increasing number of operations.’</td>
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<td>1980</td>
<td>Luft et al (US): discussed range of possible reasons for volume/outcomes link; claimed that a simultaneous equation model suggested that the referral model of causation may be of crucial importance for some procedures.</td>
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<td>1984</td>
<td>Flood et al (US) x 2: First paper showed for a range of surgical areas including bowel operations with cancer diagnosis, strong and consistent evidence that high volume is associated with better outcomes as measured by hospital mortality. Second paper included a range of other variables related to both to volume and outcome. Taken together the findings supported concentration of specific services. An editorial from Donabedian highlighted importance of the study but said more research was needed to show in detail the relationship between outcome and organisational characteristics.</td>
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<td>1986</td>
<td>Kelly and Hellinge (US): ‘The findings confirm the inverse relationship found in other studies between patient mortality and the total volume of specific surgical procedures performed in the hospital...However, there is no statistical relationship between the volume of services provided by individual surgeons and outcomes, suggesting that the volume-outcome relationship reflects hospital rather than physician characteristics.’ (p. 785). Again colon rectum cancer one of the areas looked at.</td>
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<td>1991</td>
<td>Burns and Wholey (US): A general study that included large bowel resection – found hospital volume increased mortality, but physician volume decreased mortality. But Effective Health Care bulletin (NHS CDR, 1997) suggested it did not adjust adequately for case mix.</td>
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### CANCER SURGERY/TREATMENT IN GENERAL

<table>
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<th>Year</th>
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<tr>
<td>1994 (August)</td>
<td>Stiller (UK) review: ‘Centralised referral or entry to trials was frequently associated with a higher survival rate, particularly for the less common cancers, and never found to be associated with a lower survival rate.’ (p. 352). Various comments in this review are used in the sections below to describe some of the early papers relevant for the three cancer sites being considered, but studies of individual clinicians were not included in his main analysis.</td>
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<tr>
<td>1995 (April)</td>
<td>Calman-Hine (Report by Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales) recommended that care should be concentrated in the hands of site-specialists in each relevant discipline working in MDTs. It covered much more than issues of surgical volume, and did not explicitly refer to volume, but some of the supporting evidence did refer to the volume/outcomes issue. The bibliography to the main report cites a few reports, and just one paper described as ‘in press’, but eventually published before the report. This was Stiller (1994), described above. An annex to the report by Selby, dated March 1995, pointed out that the nature of the evidence limits the conclusions that can be drawn from it, but suggested ‘The literature, supplemented by registry studies, indicates significant improvements in survival a result of specialist care for a number of cancers both common, moderately common and rare.’ (p.</td>
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Selby drew on a range of studies to draw this conclusion, and referenced the work of the Glasgow team, including a paper by Junor et al. (1994) on the management of ovarian cancer (in that paper Junor et al concluded: ‘The new finding that in a common cancer management by a multidisciplinary team at a joint clinic directly affects survival requires urgent attention.’ p. 363). Selby also described work from Leeds that was yet to be published (see below). The aspects of specialist care that are most important may differ: colorectal cancers may be critically dependent on the technical skill of surgeon; breast cancer outcomes may depend more on the mobilisation of a broad experience of physicians and surgeons. In breast not all studies confirmed the impact from specialised care but none has ever shown a disadvantage from specialised care. ‘The data suggest that the impact of specialised care for common cancers, and probably for many cancers, can increase long term survival by 5–10 per cent.’ (p. 29).

1996 Selby et al. (UK). This paper in the *Lancet* was co-authored by Gillis (from Glasgow) and Haward (from Leeds), updated Selby’s review in Calman-Hine and presented the evidence to support the report’s ‘view that specialisation in cancer care will improve outcomes.’ (p. 313). As noted above, it set out the various elements that constituted specialist care, including the composition of the MDT and the volume of work undertaken by a unit or individual. A table in the article set out in detail the evidence from the Yorkshire study (Sainbury et al., 1995 – see below) about the reduced mortality from breast cancer for patients managed by surgeons who had an annual caseload of more than 30 patients. This study was mentioned but could not be fully reported in the 1995 annex.

1998 Begg et al. (US) examined 30-day post-operative mortality in a range of cancer sites. ‘[The] data support the hypothesis that when complex surgical oncologic procedures are provided by surgical teams in hospitals with specialty expertise, mortality rates are lower.’ (p. 1747)

2000 Hillner et al. systematic review. Identified papers mostly from US and UK. Separately reported on complex surgery, low-risk surgery, and non-surgical treatments. Volume-outcome relations found for more complex surgical procedures, fewer studies on low risk.

2000 *NHS Cancer Plan* (DH, England): covered many issues but a key aspect was improving treatment. It stated: ‘The 1995 Calman/Hine report and subsequent evidence-based *Improving Outcomes* guidance began this process but progress needs to be much faster and more consistent across the country….For common cancers, such as breast cancer, patients treated by specialist teams are more likely to survive…. Progress has been made in establishing specialist teams for the most common cancers’ (paras. 6.4, 6.8, 6.9).

2003 Ihse (Sweden, but presidential address to the European Surgical Association). Reviewed key aspects of the literature from various countries on the volume-outcome relationship, going back to Luft et al. (1979) and concluded: ‘It is high time for us to pay regard to the higher-volume-better outcome association for cancer surgery and cancer treatment.’ (p. 780).

2007 *Cancer Reform Strategy* (DH, England): continued to promote the *Improving Outcomes* Guidance and noted that such guidance now covered the vast majority of all cancers: ‘Implementation of this guidance, which involves the establishment of multidisciplinary teams and reconfiguration of some complex services is now well advanced for many cancers’ (p. 115). It also referred to the role of peer review in identifying progress and challenges, and that information about peer review was available on the CQUINS web site.

quality of treatment has already improved significantly, with more widespread and rapid access to the latest forms of surgery, radiotherapy and drugs as well as the establishment of local and specialist multidisciplinary teams (MDTs) across the country. However, there is more to do.’ (p. 55). The strategy again highlighted the role of peer review: ‘findings from the National Cancer Peer Review Programme for breast, lung, upper GI, urology and gynaecological cancers show that there has been an improvement in the quality of multidisciplinary teams (MDTs), with greater compliance with peer review measures.’ (p. 82).

**BREAST CANCER**

1982 Ebeling et al. (Germany; former GDR): survival for breast cancer diagnosed in 1975–6 significantly higher at cancer centres than other hospitals.

1990 Karjalainen (Finland): survival of patients diagnosed in Finland 1970–81 higher if treated in a district with a university hospital with modern facilities.

1992 Basnett (UK): significantly higher risk of relapse and death at non-teaching hospitals in NE Thames compared with teaching centres.

1994 Stiller (UK): listed five breast cancer studies in total, including the three above. They supported Stiller’s conclusion that centralised referral and entry to cancer trials were, ‘frequently associated with a higher survival rate...never found to be associated with a lower survival rate.’ (p. 352)

1995 Selby (UK): Described various studies, and concluded: *Not all studies have confirmed the impact of “specialised care” in breast cancer (Bofetta et al., 1993) but none has ever shown a disadvantage from specialised treatment.*’ (p. 28 Emphasis added). Highlighted the results of ‘An important audit of breast cancer’. This was the still to be published study by Gillis and Hole below. NB: See above for Selby’s conclusions about the improvements in survival as a result of specialist care, but that in breast cancer it may be due to the mobilisation of a broad band of experience. Outcomes possibly linked to better radiology treatment.

1995 Sainsbury et al. (UK): the large study conducted in Yorkshire showed a volume/outcomes link as mentioned above.

1996 Gillis & Hole (Scotland) reported improved outcomes from specialist surgeons. They studies patients treated between 1980 and 1988 and reported after five years there was a 17 per cent reduction in the risk of death for patients treated by specialist surgeons.

1996 NHS CRD: *Effective Health Care* bulletin (UK): Included five studies in a meta analysis of studies focusing on specialisation, of which two from UK, and concluded they ‘point to the likely improvement in effectiveness associated with specialist treatment by multidisciplinary teams.’ (p. 11) It also describes some studies examining the link between volume and outcomes and highlighted the Sainsbury et al. (1995) study from Yorkshire.

1996 NHS: *Improving Outcomes in Breast Cancer* (England): this drew on the *Effective Health Care* bulletin and called for implementation of Calman-Hine and also recommended a minimum of 100 cases as the threshold for a modern specialist breast service.

1998 Roohan et al. (US): high volume leads to better outcomes. Has since been cited over 200 times.

2000 European Society of Mastology (EUSOMA): published a position paper, *The Requirements of a specialist breast unit*, which set out how in the UK the Calman-Hine recommendations were
being implemented first in breast cancer. It highlighted the importance multidisciplinary specialist breast units, and stated 'A Unit must be of sufficient size to have more than 150, newly diagnosed cases of primary breast cancer…each year.’ (p. 2289).

2003 Mikeljevic et al. (UK): study confirmed with long-term follow up the importance of surgeon workload in predicting outcomes, as shown in Sainsbury et al. (1995 –above).

2008 Morris et al. (UK): Leeds study of data from Yorkshire showed that while the extent of implementation of Calman-Hine had been variable, ‘on the basis of limited clinical and organisational information available, its recommendations appear to be associated with improvements in processes and outcomes of care for breast cancer patients.’ (p. 284)

2010 Gooiker et al systematic review: part of an initiative from the Dutch Cancer Society. It starts by stating that since Sainsbury, 1995, and Gillis & Hole, 1996, the question of whether or not breast cancer treatment should be centralised in high volume breast units, ‘dominates the debate on the quality of care in many western countries.’ (p. S27). Twelve good quality studies included in meta-analysis: ‘showed a significant association between high volume providers and an improved survival. The association is the most robust for surgeon volume’. Only included studies for which data collection started after 1988 (because surgical and clinical care has considerably changed). This ruled out the reviews in Stiller, Selby and also in the Effective Health Care bulletin. Three studies were from the UK but in terms of patient numbers by the far the biggest studies from the USA. The conclusion: ‘Minimal volume standards alone thus seem an inadequate basis for centralization. Additional quality criteria should be formulated to direct centralization initiatives. For this purpose more research is needed to identify essential structural or organisational characteristics and high leverage care processes that lead to the better outcomes. This kind of research can have direct implications for quality improvement programs.’(p. 534)

2010 Autier et al. (France, but about Europe): examined changes in breast cancer mortality in 30 European countries between 1989–2006. UK saw one of largest decreases and had: ‘high screening coverage of women aged 50–64 after 1995, a rapid and general use of reasonably priced tamoxifen and adjunctive chemotherapy by UK doctors, and the reorganisation of breast cancer services on the basis of the Calman-Hine and Campbell evaluation reports’ (p. 7). Three of the four references supporting this came from the Leeds team, including Morris 2008.

**COLORECTAL CANCER**

1989 Hakama et al. (Finland): analysed records of patients diagnosed 1970–81. University hospitals approx. 10 per cent better survival rate than general hospitals.

1990 Mohner and Sislow (Germany: GDR): patients diagnosed 1976–80 treated at centres seeing at least 12 cases per year had higher five-year survival rates; statistical significance not quoted.

1991 McArdle and Hole (UK, Scotland): 1974–9 data showed four-fold variation in survival and complications. Funded by Cancer Research Campaign. Various interpreted. Hilner et al.: the findings were ‘based on a surgeon’s specialty volume and interest in colorectal disease’. Stiller did not include it in main analysis, said variation appeared not to be volume related.

1992 Kingston et al. (UK): Operative mortality and five-year survival similar for teaching hospital and for district general hospitals.

1992 Pickering et al. (UK): significant variation in survival in 10 districts – no attempt to relate these
to the presence of a university hospital in one district, or service provision in general.

1992 Launoy (France): lower survival rate for women if lived in rural areas, but place of treatment had no effect, poor prognosis attributed to delay in diagnosis

1994 Stiller (UK, review cited in Calman-Hine): included above papers, but McArdle and Hole separately listed, because it focused on individual surgeons.

1995 Selby (UK, review as Calman-Hine Annex): included all the studies listed above apart from Pickering et al., but also showed Kingston et al. had compared declared specialists working in district general and teaching hospital, and claimed that their study suggested that high quality specialist services could be successfully established in district hospitals when specific commitments to them are made.

1997 NHS CRD: Effective Health Care bulletin: ‘There is contradictory evidence that specialisation and increased patient throughput improves outcomes.’ (pp. 4–5). In addition to several of the specific studies referred above, it also drew on the colorectal data from three of the general papers cited above (Flood et al., 1984; Kelly et al., 1986; Burns and Wholey, 1991). The review also drew on two additional UK studies of surgical practices (The consultant surgeons and pathologists of the Lothian and Borders Health Board, 1995; Darby et al., 1992) to claim: ‘There is some evidence that volume of activity and specialisation may be associated with better surgical technique or practice.’ (p. 5).

1997 NHS: Improving Outcomes in Urological Cancers (COG, England): Forward: referred to the recommendation that a minimum of 100 cases should be the threshold for a modern specialist breast service, but, ‘There is not the same body of evidence on which to base an equivalent recommendation in colorectal cancer. Evidence of a volume effect in colorectal surgery is simply not there in most studies.’ (p. 9).

2004 CRD: Effective Health Care bulletin: (update, UK): Identified a much greater body of evidence that had accumulated since their previous review published in 1997. Six systematic reviews (one of which was the draft of an unpublished UK study on which they were able to draw: Harding et al.) and 33 more recent primary studies (including some from the UK) ‘were consistent in showing evidence that for rectal cancer at least, higher patient volumes and greater specialisation among surgeons were associated with much better outcomes; lower surgical complication rates; decreased local recurrence, lower colostomy rates, and improved survival.’ (p. 4).

2004 NICE: Improving Outcomes in Colorectal Cancers: Manual Update: Based on the stronger evidence was able to make much stronger recommendations: ‘Each surgeon in the MDT should carry out a minimum of 20 colorectal resections with curative intent per annum. Sub-specialisation should be specifically encouraged among surgeons who treat patients with rectal cancer.’ (p. 44).

2006 Morris et al. (UK): Examined how far Calman-Hine recommendations for MDTs and surgical site specialisation had been implemented by 2000, and if changes were associated with improved outcomes. While they reported that for the period they were considering not all within the health service subscribed to the volume-outcomes theory, they nevertheless stated: ‘This study provides some of the first formal evidence to demonstrate that the Calman-Hine report’s recommendations have been implemented and that these changes have improved NHS cancer care.’ (p. 984). They identified the difficulty of analysis because of ‘the risk of collinearity among crucial explanatory factors.’ p. 983). They suggested, ‘Surgical specialisation was linked to
changes in practice, while teams were associated with an improvement in survival.’ They concluded the data suggest ‘complete adherence to the Calman-Hine principles may improve care for colorectal cancer patients.’ (p. 983).

2012 Cochrane review (Archampong et al.): Workload and surgeon’s specialty for colorectal cancer surgery. ‘The results confirm clearly the presence of a volume-outcome relationship in colorectal cancer, based on hospital and surgeon caseload, and specialisation.’ But differences between US and non-US data are noted, as are the lack of RCTs, which means the included studies are largely non-randomised cohort studies and observational studies. Searched: January 1990 to September 2011. ‘We chose 1990 as the study cut-off point to capture the effects of volume and outcome in the context of modern colorectal cancer management, as this has changed dramatically over the years.’ In total the review identified 54 observational studies. Eleven UK (20 per cent); earliest from any country Carter (1995) was from UK; did not include any of the studies used by Selby or Stiller, stating, eg, that the McArdle and Hole (1991) study had a study period of 1974–1979, but used a later one by McArdle (2004).

PROSTATE CANCER

1991 Diamond et al. (US): A survey of men treated in 1978 showed overall survival was significantly better at radiotherapy centres with a large number of patients per physicist. This seems to be the only evidence from the Stiller review that supported a volume/outcomes link, and it was related to radiotherapy.

1999 Yao and Lu-Yao (US): Included data on 100,000 patients from Medicare claims database. Outcomes better with high volume.

2002 CRD: Improving Outcomes in Urological Cancer: The Research Evidence (UK). Review focused on two systematic reviews on volume and outcomes that both included prostate cancer. It also included six additional primary studies. Conclusion: ‘a concentration of activity to a small number of professionals usually leads to an increase in the effectiveness of that intervention.’ (p. 11).

2002 NICE: Improving Outcomes in Urological Cancers: The Manual: Based on the evidence was able to make strong recommendations highlighting the Calman-Hine report and stating ‘Whilst there are honourable exceptions, urological cancer services in general have lagged behind in adopting these principles, although there are encouraging signs that this has begun to change.’ (p. 3) It went on to state that prostate cancer patients ‘for whom surgery is being considered should be treated by specialist multidisciplinary urological cancer teams, normally based at cancer centres…Radical prostatectomy should not be carried out by teams which carry out fewer than 50 radical operations (prostatecomies and cystectomies) for prostate or bladed cancers per year.’ (p. 66).

2010 Hanchananale et al. (England): studied radical prostatectomy (RP) practice in England and ‘showed a significant inverse correlation between provider volume (hospital and surgeon) and outcome (in-house mortality and hospital stay) for RP in England; thus, supporting the recommendations for centralization of care for complex radical procedures, including RP.’

2012 Trinh et el. (US): Hospital volume and surgical volume strongly correlated with postoperative outcomes following RP. Decision-curve analysis suggests hospital volume matters more.
The London Cancer web site reports on current campaign in North and East London to concentrate services: [http://www.londoncancer.org](http://www.londoncancer.org) In October 2013 London Cancer (North and East) published a report, *Specialist Services Reconfiguration: A case for change in specialist cancer services*, that included an appendix, *Specialist urological cancer centres. The clinical evidence*. This summarised ‘the clinical evidence base that supports the case for change being made for urological cancer services in north central and north east London....it does show that there is a broad evidence base in support of the changes to services that are being proposed, that demonstrates improved outcomes related to both higher surgeon as well as higher hospital volumes.’ p. 125). In their recommendation for a reconfiguration of specialist urological cancer services in urological cancer, London Cancer drew on the review of the evidence and stated: ‘A large team is required to deliver surgical excellence. A single specialist centre would make it easier to ensure that patients receive care from health professionals with specialist expertise. This is because we could more easily sustain a critical mass of health professionals with specialist expertise to look after patients during and after their surgery and to have joint appointments with or rotate through local hospitals.’ (p. 40).
3.4. Key observations for estimating the economic returns

3.4.1. Time lags

It is difficult to identify a single time lag because there have been an evolving series of policy documents in which the general move towards recommendations of concentration of services, or provision of treatment by multidisciplinary teams of site-specialists, have been strengthened as the evidence has strengthened. Overall, however, the time lags, in particular in relation to the publication of key research papers and their adoption in the policies promoting multidisciplinary teams of site-specialists, appear to be shorter than the period applied in our main calculations of the value of the research. In this case study we noted on several occasions that key local UK evidence was drawn on extremely quickly to inform policy recommendations. Examples include: the referencing of Stiller’s review by the Calman-Hine report as being ‘in press’ (which clearly indicates this groundbreaking review was made available to Calman-Hine prior to publication); and Selby’s inclusion in his Annex to Calman-Hine of very recent studies from Glasgow and studies by his colleagues in Leeds that had not yet been published. Furthermore, none of the six systematic reviews or 33 primary studies included in the 2004 update of the colorectal Effective Health Care bulletin had been available for the 1997 original version.

3.4.2. Attribution

In order to decide how much of the benefit of the health research should be attributed to UK research we have to attempt to assess the contribution made by UK research. As with the time lags, the proportion of UK studies referenced on major policy documents has again varied as the various documents have developed over the last 18 years. Especially in the early UK policy developments of multidisciplinary specialised care there are several reasons for believing that UK studies played a key role in their formulation and subsequent promotion. In addition to the importance of the review by the UK-based Stiller on Calman-Hine, we have noted the importance in Selby’s review for Calman-Hine of recent Glasgow studies, and the then yet-to-be-published Leeds study. Then the Leeds study (Sainsbury, 1995) was highlighted in the 1996 Effective Health Care bulletin on breast cancer. Probably a major contributing factor in the rapid adoption of key UK studies was the dual role of Haward and Selby in both research and in informing policy, as set out above. Looking at some of the more recent systematic reviews of the volume/outcomes link, UK papers constituted 20 per cent of the papers on the 2012 Colorectal Cochrane review and 25 per cent of the studies (but a lower proportion of patients) on the 2010 breast cancer review (Gooiker et al). Finally, it is worth repeating the comments in the Cochrane review for the volume/outcomes issue in colorectal cancer about it being ‘imperative that every country or healthcare system must establish audit systems to guide changes in the service provision based on local data, and facilitate centralisation of services as required.’ (Archampong et al., 2012).

3.4.3. Other observations of note

This case study highlights the complexity of trying to identify the impact made by research. It also differs from other case studies: it covers cancer care in general as well as focusing on all three cancer sites (breast, colorectal, prostate) featured in the analysis elsewhere in this report; the analysis of time lags and level of attribution are complicated by the evolving relationship between the evidence and the policy.
Furthermore, in our quantitative estimates of the return to cancer research we have not attempted to estimate a specific additional QALY gain from evidence-informed service configuration per se, but have assumed that in principle the health gain from this and all other supportive service changes (including diagnostics and imaging) should be captured in the estimates of the gains from specific interventions. In practice our estimates of QALY gains are mainly derived from UK relevant health technology assessments that extrapolate from trial data, which may not provide a perfect estimate of the gain when the interventions are used in routine NHS practice. The specific estimates of health gain as reported in this case illustrate an example where it is possible that our assessment of the gains underestimates the gains realised in the NHS, but it is impossible to know whether overall our data over or underestimates the actual gains realised in the NHS.
3.5. Summary timeline (graphic)

Research: 1979 onwards

- Luft, 1979 (US): surgery in general
- 5 breast papers 1982-92
- 4 colorectal papers 1989-92
- 3 prostate papers 1984-92

UK policy/implementation: 1995 onwards

- Stiller, 1994 (UK): review of all cancer
- Calman-Hine, 1995 report: encouraged multidisciplinary specialised care (Selby evidence review)
- Selby in Calman-Hine: ‘specialised care for common cancers, and probably for many cancers, can increase long-term survival by 5-10%’. Selby, 1996: review in Lancet. Message reinforced in NHS Cancer Plan (2000) but studies claimed implementation was slow, partly because of claimed doubts about the evidence: further studies continued to strengthen the evidence implementation supported by evidence-based peer review process. The Cancer Plan was updated in 2007 and 2011, with further promotion of the implementation of MDTs, and the role of peer review highlighted.

Breast: Sainsbury, 1995 (UK): key study - volume / outcome link
- Breast: Effective Health Care Bulletin and NHS Improving Outcomes 1996: treatment by teams treating 100+
- 12 papers (all since 2003: only post-1988 data used)

Breast: Gooiker, 2010 systematic review: volume / outcomes link;
- Breast: Autier, 2010: decreased UK mortality in part linked to Calman-Hine

- Colorectal: Revised Effective Health Care Bulletin & NHS Manual 2004: higher volumes & specialisation linked to better outcomes

- Colorectal: Cochrane review 2010: evidence to support volume / outcomes link

Prostate: NHS NICE Manual 2002: recommended 'dedicated specialist services' with 50+ cases
- Prostate: London Cancer 2013: review demonstrates improved outcomes related to higher hospital and surgeon volumes

Health gain: mid-1990s onwards?

- 54 post-1990 papers, but most key ones post-mid 1990s
3.6. Key papers and reports


Centre for Reviews and Dissemination (2004). The management of colorectal cancers. Effective Health Care, 8(3).


Investigating time lags and attribution in the translation of cancer research: A case study approach


Rand Europe


4. Case study 3: Smoking reduction

**Scope of case study**
This case study looks at the history of smoking reduction. It begins with the recognition of the harmful effects of smoking and runs through to the present day looking at a range of interventions used to reduce smoking and hence the associated harms. While the case study includes research evidence internationally, it focuses on intervention in the UK. This is mostly restricted to national level policies, campaigns and activities, as it was not possible to capture everything that has taken place locally or regionally. Unlike our other case studies, this document is not looking at one definable intervention, since there are numerous approaches to reducing smoking and they are not easily separable. This means that different ‘interventions’ are intertwined in the timeline table. These are classified into different categories and colour coded in the timeline table as indicated in the key. It has been necessary to make a number of decisions around the focus of the case study in order to keep the scope manageable. These include:
- Interventions that are commercially developed have not been included (eg drugs, stop smoking aids) – other case studies look at commercially developed products and so they were not considered a priority in this instance
- Evidence on harms other than cancer (eg heart disease, respiratory problems, smoking in pregnancy, etc) has not been included, given the overall focus of the study
Evidence on effectiveness of the various ‘interventions’ is rarely included, as in an attempt to constrain the scope, the case study focus is on evidence of harms and measures taken to reduce smoking. In some instances, the evidence on effectiveness is either not specific to smoking/public health (eg on effects of taxation on consumer behaviour) or only emerged following the implementation of an ‘intervention’ as its effectiveness was assessed. In this latter case, effectiveness evidence is likely to have had little/no effect on the time lag.
An important aspect of this case study is awareness raising – eg campaigns, media coverage, information provision. This does not fit easily into the study’s structure for analysing time lags and attribution. Campaigns can be classed as interventions, but such a classification is less clear for events such as a TV documentary on the tobacco industry or a statement by a lobbying group

Although writers had speculated about a link between tobacco and cancer since the 1850s, it was not until 1912 that Isaac Adler first proposed that smoking (as opposed to tobacco dust) might be a cause of lung cancer. The number of deaths from lung cancer increased dramatically in the first half of the twentieth century, leading to the MRC organising a conference in 1947 to examine possible causes. The suggestion at this conference that tobacco, and in particular cigarette smoking, might be significant led to the MRC funding a case control study to look at the link between smoking and lung cancer (Doll & Hill, 1950). This study, along with four US studies published the same year, all concluded that cigarette smoking was likely a causal factor in the development of lung cancer.

Building on these studies, and realising that a different kind of evidence was needed to make a conclusive case, Doll and Hill began a prospective cohort study of 40,000 British doctors, tracking their smoking habits and investigating whether it was possible to predict lung cancer risk. The study’s first findings were
published in 1956, and even at this early stage the authors were able to conclude a death rate from cancer that was 20 times higher in smokers than in non-smokers. At the same time, evidence was also beginning to build on the nature of tobacco, with the discovery of carcinogens in tobacco smoke and evidence on the effects of tar in causing tumour growth in animals. In 1957, both the MRC and the US Surgeon General declared a causal link between cigarette smoking and cancer, and in the following years, influential reports from the US Surgeon General and the Royal College of Physicians summarised the evidence and recommended a variety of restrictions on sales and marketing.

Throughout the 1960s and 1970s, a range of advertising restrictions were introduced (with a UK ban on TV advertising of cigarettes enforced in 1965) and various anti-smoking campaigns implemented, focused both on lobbying for smoke-free environments (for which public support was growing) and on encouraging people to stop smoking. During this period the evidence on smoking harms had also continued to build, both from the British Doctors Study’s ongoing analysis and more widely, with an increasing emphasis on the potential effects of environmental tobacco smoke. The first epidemiological evidence linking passive smoking to lung cancer was published in 1981, and in 1986 a number of reports concluded a causal link, leading to proposals for further restrictions on smoking in public places (eg Foggatt, 1988). As part of the UK government’s 1994 action plan to reduce smoking, a new Scientific Committee on Smoking and Health was launched. The committee published a review of the evidence on passive smoking in 1998, concluding that it is a cause of lung cancer, and in the years that followed a number of reports called for a ban on smoking in public places (including from the British Medical Association and the Chief Medical Officer). In 2004 the Scottish First Minister announced that Scotland would implement a total ban on smoking in workplaces and public places, while the Department of Health released a white paper proposing similar legislation for the majority of workplaces and public places in England and Wales. A similar announcement for Northern Ireland was made the following year. In 2006 Scotland became the first UK country to implement smokefree legislation, with Northern Ireland, England and Wales following in 2007.

At the same time as evidence was mounting on the effects of passive smoking, there was also an increase in the availability of smoking cessation services to individuals (initially through organisations such as ASH and QUIT, then through the NHS from 1998) and moves to further restrict tobacco advertising. In 1990 the European Parliament voted in favour of a total ban on advertising, which led to a European Commission proposal for a ban in 1991 and the eventual adoption of an EU directive banning advertising and sponsorship in member states in 1998. This directive was overturned by the European Court of Justice three years later as its implications were deemed beyond the EU’s powers, but a more restricted directive replaced it in 2002. In the UK, the 1992 Smee report summarised the evidence on the effects of tobacco advertising on consumption and the 1994 action plan to reduce smoking included measures to restrict advertising. In 1996 Guernsey became the first government in the British Isles to agree a complete ban on advertising, before a similar bill was passed in the UK parliament in 2002. Most recently, the UK government launched a public consultation on plain packaging of cigarettes (2012), with a survey suggesting that 62 per cent of adults in England are in favour.
4.1. Summary timeline (table)

Key – colours represent different categories of ‘intervention’

<table>
<thead>
<tr>
<th>Taxation</th>
<th>Legislation:</th>
<th>Public health campaigns</th>
<th>Smoking cessation support</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Advertising restriction</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sales restriction</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Smokefree legislation</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Period/date</th>
<th>Study/Event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1761</td>
<td>John Hill, an English physician, reports a case of nasal snuff causing cancer of the nose – the next case is not documented until 2007.</td>
<td>(Jacobs, 1855; Shew, 1854)</td>
</tr>
<tr>
<td>1850s</td>
<td>Writers first link tobacco to cancer, particularly of the mouth and face.</td>
<td>Source: (Proctor, 2012)</td>
</tr>
<tr>
<td>1898</td>
<td>Hermann Rottmann, a medical student, in Würzburg proposed that tobacco dust— not smoke— might be causing the elevated incidence of lung tumours among German tobacco workers</td>
<td></td>
</tr>
<tr>
<td>1912</td>
<td>Isaac Adler first links smoking with lung cancer (rather than tobacco dust), but states that this is only a possible cause and notes that there is not sufficient evidence (Adler, 1912).</td>
<td></td>
</tr>
<tr>
<td>1939</td>
<td>Müller (1939) publishes first case control study, comparing retrospectively smoking behaviour of patients who had died of lung cancer with healthy controls. He concluded that 'the extraordinary rise in tobacco use' was 'the single most important cause of the rising incidence of lung cancer'.</td>
<td>Details in English in Proctor (2000) and Doll (1998).</td>
</tr>
<tr>
<td>1944</td>
<td>Schairer &amp; Schöningen (1944) support Müller’s findings with a larger sample and comparison stomach</td>
<td>Details in Doll (1998)</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
<td>Reference/Source</td>
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<tr>
<td>1947</td>
<td>MRC conference on possible causes of increase in deaths from lung cancer. It was hypothesised that tobacco, particularly when smoked in the form of cigarettes, might be responsible. This led directly to MRC-supported Doll and Hill (1950) study.</td>
<td><a href="http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Smoking/index.htm">MRC website</a></td>
</tr>
<tr>
<td>1947</td>
<td>A 43 per cent increase in cigarette tax in the UK leads to 14 per cent reduction in cigarette consumption among men.</td>
<td><a href="http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Smoking/index.htm">ASH document</a></td>
</tr>
<tr>
<td>1948</td>
<td>Wassink (1948) supports Muller’s and Schairer &amp; Schoningen’s findings, demonstrating a relationship between smoking and lung cancer in the Netherlands.</td>
<td><a href="http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Smoking/index.htm">Wassink, 1948</a></td>
</tr>
<tr>
<td>1950</td>
<td>Five key papers published, all describing case control studies showing a link between smoking and lung cancer: Doll and Hill (1950) in the UK; and Wynder and Graham, Schrek et al., Levin et al., and Mills and Porter in the US. The first two were particularly influential.</td>
<td>Doll &amp; Hill (1950), Levin, et al., 1950, Wynder &amp; Graham, 1950, Mills &amp; Porter, 1950, Schrek, et al., 1950</td>
</tr>
<tr>
<td>1951</td>
<td>British Doctors Study begins – 40,000 doctors born between 1900 and 1930 tracked (Doll &amp; Hill).</td>
<td>Start of data collection (Oct 1951), Detailed in Doll and Peto (1976)</td>
</tr>
<tr>
<td>1953</td>
<td>Ernst L. Wynder finds that painting cigarette tar on the backs of mice creates tumours. This is the first biological link between smoking and cancer.</td>
<td>Wynder, et al., 1953</td>
</tr>
<tr>
<td>1954</td>
<td>Reader's Digest publishes an article entitled ‘The cigarette controversy’ documenting the evidence on the association between smoking and lung cancer.</td>
<td><a href="http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Smoking/index.htm">Reader's Digest</a></td>
</tr>
<tr>
<td>1955</td>
<td>Cooper and Lindsey (1955) demonstrate existence of carcinogens in cigarette smoke</td>
<td><a href="http://www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Smoking/index.htm">Cooper &amp; Lindsey, 1955</a></td>
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<tr>
<td>Mid-1950s</td>
<td>In the US, individuals begin to sue tobacco companies for damages.</td>
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<tr>
<td>1956</td>
<td>Doll and Hill publish first results of the British Doctors Study, demonstrating a death rate from lung cancer 20 times higher in those that smoke than those that don’t (Doll &amp; Hill, 1956).</td>
<td>(Doll &amp; Hill, 1956)</td>
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<td>Year</td>
<td>Event</td>
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<tr>
<td>1957</td>
<td>MRC statement that there is a causal relationship between tobacco smoke and cancer (Medical Research Council, 1957)</td>
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<tr>
<td>1957</td>
<td>US Surgeon General declares that the official position of the US Public Health Service is that a causal relationship exists between smoking and lung cancer.</td>
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<td>1958</td>
<td>First health authority smoking withdrawal clinic opened in Salford.</td>
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<td>April 1959</td>
<td>RCP sets up committee 'to report on the question of smoking and atmospheric pollution in relation to carcinoma of the lung and other diseases'.</td>
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<tr>
<td>1960</td>
<td>Tobacco advertising has increased, primarily driven by cigarette marketing. In 1960, £11m spent on advertising. (Royal College of Physicians, 1962)</td>
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<tr>
<td>1962</td>
<td>Three-quarters of men and half of women in Britain smoke. (Royal College of Physicians, 1962)</td>
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<tr>
<td>1962</td>
<td>Influential RCP report ‘Smoking and Health’ summarises evidence on smoking causing lung cancer. It recommends advertising restrictions, increased taxation among other things. (Royal College of Physicians, 1962)</td>
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<td>1962</td>
<td>Tobacco Advisory Committee (representing manufacturers) agrees to implement code of advertising practice to make cigarettes seem less glamorous.</td>
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<td>1964</td>
<td>Influential report published by the US Surgeon General on smoking harms. Over 7,000 papers were reviewed between 1962 and 1964. The report estimated the increased mortality rate and increased risk of lung cancer for smokers compared with non-smokers. (Advisory Committee to the Surgeon General of the Public Health Service, 1964)</td>
<td></td>
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<tr>
<td>1965</td>
<td>Japanese prospective cohort study on passive smoking begins.</td>
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<tr>
<td>1965</td>
<td>UK government bans cigarette advertising on TV.</td>
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<tr>
<td>1967</td>
<td>First report on effects of environmental tobacco smoke on children’s health (Cameron, 1967).</td>
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<tr>
<td>1969</td>
<td>\textit{Radio Times} bans cigarette advertising.</td>
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<tr>
<td>1969</td>
<td>Health Education Council (set up in 1968) launches its first anti-smoking campaign, highlighting risk of lung cancer.</td>
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</tbody>
</table>
### Timeline of Events

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
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</thead>
<tbody>
<tr>
<td>1970</td>
<td>WHO report on ‘the limitation of smoking’ presented to 23rd World Health Assembly, calling for an end to cigarette advertising and promotion among other recommendations.</td>
</tr>
<tr>
<td>1971</td>
<td>Second RCP report, ‘Smoking and Health Now’, published, endorsing 1970 WHO report. ASH report claims caused a permanent 5 per cent drop in cigarette consumption and that a clear socioeconomic divide had emerged whereby professional classes stopped smoking and other did not.</td>
</tr>
<tr>
<td>1971</td>
<td>Action on Smoking and Health (ASH) set up by the RCP as a campaigning public health charity to eliminate harm caused by tobacco.</td>
</tr>
<tr>
<td>1971</td>
<td>ASH campaigning leads to an increase in provision of non-smoking accommodation on London transport.</td>
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<tr>
<td>1971</td>
<td>First voluntary agreement between government and industry, including warnings on packs and scientific committee established to explore less dangerous forms of smoking. A series of such agreements followed.</td>
</tr>
<tr>
<td>1974</td>
<td>ASH publishes a report calling for more support for smoking cessation clinics. ASH reports no action from health authorities.</td>
</tr>
<tr>
<td>1975</td>
<td>Responsibility for Code of Advertising Practice of cigarettes moves from industry to Advertising Standards Authority and it agrees to develop a stricter code.</td>
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<tr>
<td>1975</td>
<td>Gallup poll indicates that two TV documentaries in successive weeks result in 160,000 people (5 per cent of audience) giving up.</td>
</tr>
<tr>
<td>1976</td>
<td>BBC smoking cessation campaign ‘Stop smoking with Nationwide’ runs for several months.</td>
</tr>
<tr>
<td>1976</td>
<td>Public opinion: DHSS and NOP poll shows that 70 per cent of the population – a majority of both smokers and non-smokers – favoured further restrictions on smoking in all public places</td>
</tr>
<tr>
<td>1976</td>
<td>Cigarette taxation increased by 3.5p</td>
</tr>
<tr>
<td>1976</td>
<td>Doll and Peto (1976) publish 20 year follow-up and conclude that between a half and a third of smokers will die because of their smoking.</td>
</tr>
<tr>
<td>1977</td>
<td>HEC launches a TV campaign focusing on the rights of non-smokers and smoking by women.</td>
</tr>
<tr>
<td>1977</td>
<td>New voluntary agreement with industry limits marketing and introduction of high tar brands, and...</td>
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</table>
Investigating time lags and attribution in the translation of cancer research: A case study approach

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Third RCP ‘Smoking or Health’ report, summarises evidence and makes strongest call yet for government action.</td>
<td>(Royal College of Physicians, 1977)</td>
</tr>
<tr>
<td>1978</td>
<td>Independent Broadcasting Authority publishes Code of Advertising which terms cigarettes ‘unacceptable products’ not to be advertised on radio.</td>
<td></td>
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<tr>
<td>1979</td>
<td>WHO report ‘Controlling the smoking epidemic’ reviews recent evidence and highlights the risks of passive smoking, as well as socioeconomic effects of smoking.</td>
<td>(WHO Expert Committee on Smoking Control, 1979)</td>
</tr>
<tr>
<td>1980</td>
<td>BBC <em>Panorama</em> reports on tobacco industry, highlighting its refusal to acknowledge harms.</td>
<td></td>
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<tr>
<td>1980</td>
<td>BBC <em>Horizon</em> highlights less well known effects of smoking and advantages of giving up.</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>The majority of UK people do not smoke but smoking is now highly related to socioeconomic position, ie inequalities.</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Cigarette tax increased by 14p (per pack of 20), the biggest percentage increase since 1947</td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>US Surgeon General’s report declares cigarette smoking the major cause of cancer mortality in the US and highlights that cessation appears to reduce cancer risk.</td>
<td>(US Department of Health and Human Services, 1982)</td>
</tr>
<tr>
<td>1982</td>
<td>British Medical Association asks the government to ban all forms of tobacco advertising</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Fourth RCP report, ‘Health or Smoking’?, examines health risks of passive smoking, concluding that more than 100,000 people die each year from smoking-related illness in the UK and calling for an end to tobacco advertising and promotion.</td>
<td>(Royal College of Physicians, 1983)</td>
</tr>
<tr>
<td>1984</td>
<td>National No Smoking Day launched in the UK to take place in March every year.</td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td><em>The Smoke Ring</em> by campaigning journalist Peter Taylor is published, discussing the politics of the tobacco</td>
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</tbody>
</table>
industry. It is publicised by a BBC *Panorama* programme aired the same day.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1985</td>
<td>London Regional Transport bans smoking in underground trains and stations, following a fire at Oxford Circus station, possibly caused by a cigarette.</td>
</tr>
<tr>
<td>1985</td>
<td>HEC TV advert campaign highlights that smoking is killing almost as many women as breast cancer.</td>
</tr>
<tr>
<td>1985</td>
<td>DHSS issues guidelines asking health authorities to introduce smoking policies in all health premises.</td>
</tr>
<tr>
<td>1985</td>
<td>UK case control study finds, among other things, reduced lung cancer risk among ‘long-term ex-smokers’. (Alderson, et al., 1985)</td>
</tr>
<tr>
<td>1985</td>
<td>ASH Scotland produces the second edition of ‘The Smoking Epidemic’, which reports numbers of tobacco-related deaths in each parliamentary constituency.</td>
</tr>
<tr>
<td>1986</td>
<td>Protection of Children (Tobacco) Act passes, making it illegal to sell any tobacco product to under-16s (previously only applied to loose tobacco).</td>
</tr>
<tr>
<td>1986</td>
<td>British Medical Association publishes ‘Great Expectorations’, exploring tobacco industry marketing</td>
</tr>
<tr>
<td>1986</td>
<td><em>BMJ</em> article concluding that passive smoking is a cause of lung cancer. The authors combined data from 13 previous studies, which individually were too small to generate conclusive results. (Wald, et al., 1986)</td>
</tr>
<tr>
<td>1986</td>
<td>Britain has highest death rate from lung cancer in the world (WHO).</td>
</tr>
<tr>
<td>1987</td>
<td>Independent Television ceases transmission of tobacco-sponsored sport.</td>
</tr>
<tr>
<td>1987</td>
<td>Launch of European Commission’s ‘Europe Against Cancer’, a three-year campaign to raise awareness of risky behavior.</td>
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<tr>
<td>Year</td>
<td>Event</td>
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</tr>
<tr>
<td>1988</td>
<td>Less than one-third of UK adults smoke, but decline has slowed.</td>
</tr>
<tr>
<td>1988</td>
<td>Independent Scientific Committee on Smoking and Health publishes the Froggatt Report. Among its conclusions it highlights a 10–30 per cent increased risk of developing lung cancer for non-smokers exposed to other people’s smoke. Recommends that workplaces and public places should be non-smoking where separate provision for non-smokers is not possible. (Froggatt, 1988)</td>
</tr>
<tr>
<td>1988</td>
<td>In the US, a court awards damages against a tobacco company for a lung cancer death.</td>
</tr>
<tr>
<td>1990</td>
<td>Parents Against Tobacco launched to campaign for legislation to protect children from tobacco. It is a coalition of MPs, TV personalities, activists and the public.</td>
</tr>
<tr>
<td>1990</td>
<td>Telephone advice and counselling service launched by QUIT for people trying to stop smoking.</td>
</tr>
<tr>
<td>1990</td>
<td>European parliament votes in favour of banning tobacco advertising.</td>
</tr>
<tr>
<td>1991</td>
<td>16p (per pack of 20) increase in cigarette tax</td>
</tr>
<tr>
<td>1991</td>
<td>European Commissioners call for advertising ban and a major campaign is launched in the UK, led by Doctors for Tobacco Law (29 organisations representing almost all of the UK’s doctors). First activity was a demonstration held outside Rothmans’ AGM.</td>
</tr>
<tr>
<td>1991</td>
<td>For the first time health warnings are legally required on tobacco packaging, in line with EC requirements.</td>
</tr>
<tr>
<td>1991</td>
<td>EC directive making TV advertising illegal comes into force.</td>
</tr>
<tr>
<td>1991</td>
<td>‘From the Billboard to the Playground’ highlights evidence on effects of tobacco advertising on children.</td>
</tr>
<tr>
<td>Year</td>
<td>Event Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
</tr>
<tr>
<td>1991</td>
<td>Health Education Authority publishes ‘The Smoking Epidemic’, a survey of deaths from tobacco-related disease and details of costs to the NHS.</td>
</tr>
<tr>
<td>1992</td>
<td>MEPs vote in favour of banning tobacco advertising.</td>
</tr>
<tr>
<td>1992</td>
<td>Fifth RCP report, on ‘Smoking and the Young’.</td>
</tr>
<tr>
<td>1992</td>
<td>Children and Young Persons (Protection from Tobacco) Act comes into force, tightening previous legislation including banning sales of single cigarettes.</td>
</tr>
<tr>
<td>1992</td>
<td>13p (per pack of 20) increase in tobacco duty</td>
</tr>
<tr>
<td>1992</td>
<td>The Smee Report on effect of tobacco advertising on consumption, including the effect of advertising bans.</td>
</tr>
<tr>
<td>1993</td>
<td>HEA publishes ‘The Smoking Epidemic: a Prescription for Change’, which puts the annual cost of smoking in terms of GP consultations, prescriptions, and inpatient and outpatient visits at £610m to the NHS in England and Wales.</td>
</tr>
<tr>
<td>1993</td>
<td>‘Quitting is Winning’ anti-smoking campaign launched in London, targeting parents who smoke.</td>
</tr>
<tr>
<td>1994</td>
<td>Government action plan to reduce smoking, outlining action on: price; increasing awareness of risks and supporting people to give up; advertising controls; protection from passive smoking; and improving scientific understanding. A new Scientific Committee on Tobacco and Health is launched.</td>
</tr>
<tr>
<td>1994</td>
<td>More than 50 organisations make a joint submission to the Chancellor of the Exchequer, supporting regular tax increases to control tobacco consumption.</td>
</tr>
<tr>
<td>1994</td>
<td>Update on the British Doctors Study published, concluding that around half of all smokers will die from smoking-related causes.</td>
</tr>
<tr>
<td>1994</td>
<td>Government launches three year £13.5m national anti-smoking campaign in England aimed at adults.</td>
</tr>
<tr>
<td>1995</td>
<td>HEA launches ‘Put smoking out of fashion’ campaign aimed at models and modelling agencies.</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
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<tr>
<td>------</td>
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</tr>
<tr>
<td>1996</td>
<td>Government launches three-year campaign aimed at teenagers.</td>
</tr>
<tr>
<td>1996</td>
<td>Guernsey’s State Parliament becomes first government in British Isles to impose a complete ban on tobacco advertising, coming into force in 1997.</td>
</tr>
<tr>
<td>1997</td>
<td>New Labour government announces its commitment to ban tobacco advertising, and Health Secretary announces that tobacco advertising of sport will be banned. An Anti-smoking summit is held to discuss ways to reduce smoking.</td>
</tr>
<tr>
<td>1997</td>
<td>MINTEL survey suggests a rise in number of smokers in the UK for the first time in 20 years. Contrary to earlier trends, the increase appears to be in the highest socioeconomic groups. Similarly, an ONS survey reveals a 1 per cent increase in smoking prevalence in the 11–15 age group, and the 1996 General Household Survey finds a rise in prevalence among adults for the first time since smoking data was first collected by the government in 1972.</td>
</tr>
<tr>
<td>1997</td>
<td>European Council of Health Ministers votes to ban tobacco advertising throughout the EU.</td>
</tr>
<tr>
<td>1998</td>
<td>Government-appointed Scientific Committee on Tobacco and Health publishes its review on the evidence on passive smoking, concluding that it is a cause of lung cancer. (UKDH, 1998)</td>
</tr>
<tr>
<td>1998</td>
<td>EP votes in favour of EU Directive to ban tobacco advertising and sponsorship, and it is formally adopted by member states.</td>
</tr>
<tr>
<td>1998</td>
<td>Gro Harlem Brundtland, newly elected director general of the WHO, calls for worldwide ban on tobacco advertising. WHO sets a target of reducing smoking in Europe to under 20 per cent.</td>
</tr>
<tr>
<td>1998</td>
<td>White paper on first ever national comprehensive tobacco control strategy includes targets to reduce smoking prevalence, launch local NHS smoking cessation services, ban tobacco advertising and promotion, action against tobacco smuggling, increase tobacco taxation by 5 per cent in real terms each year, media campaigns, tougher enforcement on under age sales, and support further restrict smoking in the workplace but only through a voluntary charter.</td>
</tr>
</tbody>
</table>
1999  First smoking cessation services established in English NHS.

1999  World Health Assembly backs a resolution to begin work on a new Framework Convention on Tobacco Control (FCTC).

2000  Evidence from UK trends shows that smoking cessation can greatly reduce lung cancer risk, even among those smoking well into middle age. (Peto, et al., 2000)

2000  House of Commons Health Committee report on tobacco industry concludes that in almost every area it is under-regulated or poorly regulated, and calls for establishment of a Tobacco Regulation Authority.

2000  UK introduces entitlement to receive behavioural support from trained advisor plus nicotine replacement therapy or bupropion on NHS prescription, local cessation services expanded to have national coverage.


2001  European Court of Justice overturns EU directive on tobacco advertising, ruling that this is beyond the EU’s powers. A new, more limited directive is published that would ban press and radio advertising, as well as sponsorship of sports events taking place in more than one EU country.

2002  CRUK launches draft code of practice urging universities and research organisations to reject tobacco industry funding, while itself committing to not funding any institution which also receives industry money.

2002  Bill to ban tobacco advertising, which had begun as a private member’s bill in the House of Lords, is passed in Parliament.

2002  EU Directive on tobacco advertising is adopted.

2002  British Medical Association report calls for ban on smoking in public places because of effects of passive smoking. See Gulland (2002)

2003  First phase of Tobacco Advertising and Promotion Act 2002 is implemented, banning advertising on billboards, in print media, direct mail, internet advertising and new promotions.


2003  CMO Liam Donaldson challenges the government to ban smoking in public places in his 2002 Annual
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Ireland implements smokefree legislation covering all workplaces, including bars and restaurants. Subsequent studies show its success in terms of the respiratory health of bar workers (Allwright, et al., 2005), and a decline in reported smoking in all venues and increased support among the public for bans (Fong, et al., 2006).</td>
</tr>
<tr>
<td>2004</td>
<td>British Heart Foundation (BHF) anti-smoking campaign showing fat oozing out of a smoker’s artery. BHF reports that the campaign is effective in increasing calls to NHS smoking helpline and visits to web site.</td>
</tr>
<tr>
<td>2004</td>
<td>Follow-up results from the British Doctors Study show that, on average, smoking lowered life expectancy by 10 years. Around half of those who smoked were killed by their habit. Stopping smoking at ages 30, 40, 50 and 60 increased life expectancy by around ten, nine, six and three years, respectively. (Doll, et al., 2004)</td>
</tr>
<tr>
<td>2004</td>
<td>Government adviser Derek Wanless publishes ‘Securing Good Health for the Whole Population’, which recommends banning smoking in work places among other things. This is echoed by the Chief Medical Officer in his 2003 annual report, which concludes that this would bring a net benefit to society of £2.3–2.7 billion annually. (Wanless, 2004)</td>
</tr>
<tr>
<td>2004</td>
<td>A government white paper follows proposing a ban in the majority of workplaces and public places (but short of a total ban).</td>
</tr>
<tr>
<td>2004</td>
<td>Scottish First Minister announces that Scotland will introduce a total ban on smoking in workplaces and public places.</td>
</tr>
<tr>
<td>2004</td>
<td>GP contract revised to include the Quality and Outcomes Framework (QOF) where points (and funding) are awarded for the delivery of clinical services against set standards including smoking cessation advice.</td>
</tr>
<tr>
<td>2005</td>
<td>WHO Framework Convention on Tobacco Control (FCTC) reaches the level of ratifications necessary (40) for entry into force, 27 Feb 2005.</td>
</tr>
<tr>
<td>2005</td>
<td>Cochrane review of individual behavioural counselling for smoking cessation. (Lancaster &amp; Stead, 2005a)</td>
</tr>
<tr>
<td>2005</td>
<td>Cochrane review of self-help interventions for smoking cessation. (Lancaster &amp; Stead, 2005b)</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>2005</td>
<td>Special supplement of <em>Addiction</em> on effectiveness of the English cessation services.</td>
</tr>
<tr>
<td>2005</td>
<td>Scottish Parliament passes Smoking, Health and Social Care (Scotland) Bill to ban smoking in all workplaces and public places.</td>
</tr>
<tr>
<td>2005</td>
<td>Final phase of Tobacco Advertising and Promotion Act 2002 is implemented, banning tobacco sponsorship of global sports. EU directive banning cross-border advertising and sponsorship comes into effect at the same time (July).</td>
</tr>
<tr>
<td>2005</td>
<td>Northern Ireland Minister announces that smoking will be banned in all workplaces by April 2007.</td>
</tr>
<tr>
<td>2006</td>
<td>NICE public health intervention guidance PH1: Brief interventions and referral for smoking cessation in primary care and other settings.</td>
</tr>
<tr>
<td>March 2006</td>
<td>Scotland implements smokefree legislation.</td>
</tr>
<tr>
<td>July 2006</td>
<td>Government issues proposals to raise minimum age for purchase of tobacco to 18 (from 16).</td>
</tr>
<tr>
<td>2007</td>
<td>NICE PH intervention guidance PH15: Workplace health promotion: how to help employees to stop smoking.</td>
</tr>
<tr>
<td>March 2007</td>
<td>Chancellor announces that VAT on stop smoking aids will be reduced to 5 per cent.</td>
</tr>
<tr>
<td>2007</td>
<td>Wales and Northern Ireland (in April) and England (in July) implement smokefree legislation.</td>
</tr>
<tr>
<td>Oct 2007</td>
<td>Legal age for purchase of tobacco increases to 18.</td>
</tr>
<tr>
<td>July 2008</td>
<td>ONS Survey: 80 per cent of Britons support smokefree law.</td>
</tr>
<tr>
<td>2008</td>
<td>NICE public health guidance 10 on smoking cessation services.</td>
</tr>
<tr>
<td>2008</td>
<td>Cochrane review of school-based programmes for preventing smoking.</td>
</tr>
<tr>
<td>2009</td>
<td>General Household Survey 2007 reveals lowest ever number of smokers and a record 59 per cent who have never smoked.</td>
</tr>
<tr>
<td>Sept 2009</td>
<td>New tobacco control measures to restrict sales to young people voted through in both Scotland and Westminster. Includes banning vending machines and point of sale display.</td>
</tr>
</tbody>
</table>
### Investigating time lags and attribution in the translation of cancer research: A case study approach

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>NICE public health guidance 23 on school-based interventions to prevent smoking.</td>
<td></td>
</tr>
<tr>
<td>March 2010</td>
<td>ASH cost-benefit analysis of increasing tobacco tax suggests that a 5 per cent increase would decrease numbers of smokers by 190,000 and lead to economic benefits of over £270m. A Policy Exchange report also argues for a 5 per cent rise in tobacco duty. (ASH, 2010)</td>
<td></td>
</tr>
<tr>
<td>March 2010</td>
<td>Chancellor raises tobacco duty by 1 per cent above inflation and commits to increase it by 2 per cent above inflation between 2011 and 2014.</td>
<td></td>
</tr>
<tr>
<td>Oct 2010</td>
<td>Association of Public Health Observatories launches Local Tobacco Control Profiles for England – web-based tool to provide data on the extent of tobacco use, tobacco related harm, and measures being taken to reduce harm at a local level. It is intended for local authorities.</td>
<td><a href="http://www.tobaccoprofiles.info/">http://www.tobaccoprofiles.info/</a></td>
</tr>
<tr>
<td>Dec 2010</td>
<td>Government launches Public Health white paper and commits to consultation on plain packaging of tobacco products.</td>
<td></td>
</tr>
<tr>
<td>March 2011</td>
<td>Government launches Tobacco Plan for England, committing to reducing adult prevalence to 18.5 per cent by 2015.</td>
<td>(Department of Health, 2011)</td>
</tr>
<tr>
<td>2012</td>
<td>Chancellor raises tobacco duty by 5 per cent above inflation.</td>
<td></td>
</tr>
<tr>
<td>April-Aug</td>
<td>Public consultation on plain packaging, with more than 200,000 responses. YouGov find 62 per cent of adults in England are in favour.</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>DH launches ‘Stoptober’, the first mass smoking cessation attempt.</td>
<td></td>
</tr>
<tr>
<td>Oct 2012</td>
<td>DH launches £2.7m nine-week media campaign showing a tumour growing on a cigarette.</td>
<td><a href="http://www.who.int/fctc/ten_fctc/en/index.html">http://www.who.int/fctc/ten_fctc/en/index.html</a></td>
</tr>
<tr>
<td>2012</td>
<td>WHO FCTC current membership of 176 countries, covering 90 per cent of the world’s population.</td>
<td><a href="http://www.who.int/fctc/ten_fctc/en/index.html">http://www.who.int/fctc/ten_fctc/en/index.html</a></td>
</tr>
<tr>
<td>2013</td>
<td>Scottish government’s new tobacco control strategy ‘Creating a Tobacco-free Scotland’ sets target of reducing adult smoking to &lt;5 per cent by 2034.</td>
<td></td>
</tr>
</tbody>
</table>
4.2. Key observations for estimating the economic returns

4.2.1. Time lags

- Overall, the time lag seems substantially longer than the 17 years estimated from the analysis of clinical guidelines in another strand of this study, but individual parts of the story may be similar to this timeframe. For example:
  - First epidemiological evidence on passive smoking published in the early 1980s, smokefree legislation proposed in the early 2000s.
  - Key evidence on harms published in 1950, ban on TV advertising enforced in 1965.
- It seems likely that industry lobbying and denial of harms delayed interventions, both by questioning evidence (eg on causality) and obstructing the passage of legislation.
- Many interventions were phased in, so the ‘end-points’ for time lags are difficult to define – at what point can we consider that they have become ‘standard practice’ and result in health gain? (eg advertising restrictions, public smoking bans in some locations).

4.2.2. Attribution to UK research

- Much of the very early work on harms was carried out in Germany, but one of five key case control studies was from the UK (others US) and the British Doctors Study was influential from 1956 onwards.
- Regular RCP ‘Smoking and Health’ reports reviewing/summarising evidence seem to have been influential.

4.2.3. Other points of note

- It is unclear how much policy changes were driven directly by research evidence and how much by campaigning and public support – there were many influential actors other than researchers and implementers.
4.3. Summary timeline (graphic)

<table>
<thead>
<tr>
<th>Research on harms (1912–present)</th>
<th>Interventions (1960s–present)</th>
<th>Health gain (c1970 onwards?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler, 1912 (US)</td>
<td>1960 – five key case control studies (one UK, four US)</td>
<td>British Doctors Study (Doll &amp; Hill) (UK)</td>
</tr>
<tr>
<td>Muller, 1939 (Germany)</td>
<td>1965 – TV advertising ban</td>
<td>Evidence of harm from passive smoking</td>
</tr>
<tr>
<td>1939</td>
<td>2002 – total advertising ban</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>Sales restrictions</td>
<td>1908 – sales to under-16s banned</td>
</tr>
<tr>
<td>1908</td>
<td>1960s – Smokefree legislation</td>
<td>2002 – BMA recommends ban in public places</td>
</tr>
<tr>
<td>1981</td>
<td></td>
<td>2007 – minimum age raised to 18</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td>2006/7 – whole UK implements</td>
</tr>
</tbody>
</table>
4.4. Key papers and reports

Adler, I. (1912). Primary malignant growths of the lungs and bronchi. Longmans, Green, and Co.


Froggatt, P. (1988). Fourth report of the independent scientific committee on smoking & health, HMSO.


Investigating time lags and attribution in the translation of cancer research: A case study approach

5. Case study 4: The use of tamoxifen in the treatment of breast cancer

Scope of the case study
This case study covers the story of tamoxifen from its initial development in the early 1960s as a potential contraceptive to its widespread adoption as a treatment for both advanced and early breast cancer and as a preventative amongst certain groups of high risk women. The case study begins by providing context, outlining information on the prevalence of breast cancer and how tamoxifen works. It then provides historical background, describing the development of anti-oestrogens from the first reported use of the removal of ovaries as a treatment for breast cancer in 1896, to the development of the first non-steroidal anti-oestrogens in the late 1950s. The key focus of the case study is on the development and implementation of tamoxifen treatment from its discovery in 1962, concluding with the publication of NICE guidance recommending the use of tamoxifen as a preventive treatment amongst women with a high risk of breast cancer in 2013. It is not a complete story of every step in the development of tamoxifen and may not cover every important study conducted in detail. Rather, the aim of the case study is to highlight the key steps in tamoxifen’s progress to widespread usage, with a particular emphasis on factors which affected the time taken from discovery to implementation, and evidence around where the research was conducted that supported this process. The case study focuses on the implementation of tamoxifen treatment in the UK but covers research conducted internationally.

Breast cancer is the most common cancer in the UK, with more than 49,900 people diagnosed in 2010 (ONS, ISD Scotland, WCISU and Northern Ireland Cancer Registry data referenced by CRUK website, 2013). It is also the second most common cause of death from cancer in women in the UK after lung cancer, causing around 11,600 deaths in 2010 (ibid.). Worldwide, it is estimated that more than 1.38 million women were diagnosed with breast cancer in 2008 (Ferlay et al., 2010). However, survival rates in the UK have been improving, largely as a result of faster diagnosis due to improvements in treatment, raised awareness and the NHS Screening Programme. This is reflected in UK five-year survival rates, which increased by 33 percentage points between 1971–1975 and 2005–2009 (CRUK website, 2013). One important treatment which has been rolled out over that time period is tamoxifen, which is now widely used in the treatment of breast cancer.

Tamoxifen is an anti-hormone therapy for breast cancer that acts by blocking the action of the hormone oestrogen. Many breast cancers are termed hormone receptor positive, meaning that they are stimulated to grow by the hormones oestrogen and progesterone. Cancers which are oestrogen receptor (ER) positive are most commonly treated by tamoxifen. Tamoxifen blocks the oestrogen receptor, preventing the oestrogen molecule stimulating cancer growth. Treatment with tamoxifen can reduce the risk of cancer
recurring after surgery, or developing in the other breast. Around three quarters of breast cancers are ER positive and hence can benefit from this kind of anti-hormone therapy.

The first clue to the role of oestrogen in breast cancer came in the late 1800s, when Dr George Beatson found that he could extend the lives of women with breast cancer by surgically removing their ovaries (Beatson, 1896). This work was based on observations of veterinary practice where similar procedures were commonplace. However, the development of anti-oestrogens, such as tamoxifen, did not come until over 50 years later. Interestingly, this did not come out of a cancer research programme. Instead the first non-steroidal anti-oestrogens were developed and tested in 1957 by Merrell and were intended for use as contraceptives. Research into tamoxifen in Merrell was discontinued shortly afterwards due to safety concerns but this area was explored subsequently by Dr Arthur L. Walpole, then head of the fertility control programme for ICI, and colleagues, and in 1962, ICI filed a patent for tamoxifen, developed as a potentially safer contraceptive. However, though tamoxifen was an effective postcoital contraceptive in rats, it was found to induce ovulation rather than reduce fertility in humans.

It was another eight years before the first clinical trial took place testing tamoxifen as a breast cancer treatment, and around this time ICI started to consider what role tamoxifen could take in their portfolio given it had proved ineffective in its planned role as a contraceptive. By 1972 ICI had considered numerous applications for tamoxifen and stopped the development programme as market prospects were not promising. Crucial in preventing ICI from dropping tamoxifen was Arthur Walpole, who despite working in the fertility control program at ICI, had a long interest in cancer research. In 1973 he convinced ICI to market Tamoxifen in the UK for breast cancer treatment, and it was approved for clinical use in the UK in that year (Jordan, 2003).

Initially, tamoxifen was only used in cases of advanced breast cancer. However, a number of clinical trials were conducted in Europe and the US to investigate its wider use in breast cancer (for example, Baum et al., 1983, Ingle et al., 1981). Many studies demonstrated that tamoxifen could be used as an adjuvant treatment2 in early breast cancer, and by 1984 tamoxifen was the adjuvant endocrine treatment of choice for breast cancer according to the US National Cancer Institute (Jordan, 2003). Its use as an adjuvant treatment for breast cancer was similarly widespread in the UK. The Early Breast Cancer Trialists Collaborative Group in the UK played an important role in demonstrating the effectiveness of tamoxifen, publishing a meta-analysis of the evidence for its use in early breast cancer in 1988 (EBCTCG, 1988), and later, in 1998, showing that tamoxifen was effective in the treatment of premenopausal women, widening its usage even further (EBCTCG, 1998).

Initially, tamoxifen was typically given for a period of one year after primary treatment, as it was known to be effective over that time period in advanced breast cancer (Ingle et al., 1981) and it was feared that longer use could lead to drug resistance (Jordan, 2003). There were also concerns that since tamoxifen was classified as an anti-oestrogen, long-term therapy would increase the risk of osteoporosis and coronary heart disease. Although initial concerns around these side effects were put to rest (Jordan et al., 1987,

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2 Adjuvant treatments are additional treatments given to support the primary therapy (e.g. surgery or chemotherapy). The term typically refers to treatments that are given once the primary therapy has proved effective to remove any remaining cancer cells and to reduce the risk of relapse.
Love et al., 1981, 1982), further concerns emerged around the mid-1980s when tamoxifen was found to enhance the growth of endometrial cancer in the laboratory (Satyaswaroop, 1984; Gottardis, 1988). The stimulation of endometrial cancer was also shown to occur in humans, with tamoxifen causing a fourfold increase in the (small) risk of endometrial cancer in post-menopausal women (Fisher et al., 1994; Fornander et al., 1989). In 1990, tamoxifen was also found to produce liver tumours in rats (Greaves et al., 1993), but this finding has not been replicated in humans. It is interesting to note that, according to Jordan (1995), ‘if rat liver tumours had been noted in the early 1970s, drug development in this area would have stopped, as there was no successor [ie alternative] to tamoxifen’.

The suggestion tamoxifen could not only be used to treat cancer, but could also act as a preventative came as early as 1976 (Jordan, 1976), with further support on the basis of existing research and clinical experience of the use of tamoxifen in 1991 (Nayfield et al., 1991). This was reinforced in 1998 by a US trial of 13,388 high-risk women which found a 50 per cent reduction in invasive breast cancer (Fisher et al., 1998). However, it wasn’t until 2013 that NICE recommended the use of tamoxifen as a preventive treatment in women who have a family history of breast cancer (NICE, 2013). This was largely based on evidence from two high quality RCTs conducted in 2005 and 2007 (Fisher, et al., 2005 and Cuzick, et al., 2007), the first of which was conducted in the US, and the second in Australia and the UK (with Cancer Research UK funding).

An interesting side note to the tamoxifen story is the issue of patenting. In 1962, ICI submitted a patent application for tamoxifen in the UK which was published in 1965 as UK Patent GB1013907. However in the US, ICI was repeatedly denied patent protection due to the primacy of Merrell’s patents on anti-oestrogens. This did not prevent ICI from releasing the drug to the US market, or tamoxifen being approved in the US for the treatment of advanced breast cancer in post-menopausal women in 1977. The US patent was finally approved in 1985 through court of appeals, after over a decade of clinical development advancing with no assurance of exclusivity in the US market.
### 5.1. Summary timeline (table)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1876</td>
<td>Beatson studies lactation in sheep and establishes causal link with removal of ovaries (already known by cow farmers!). Continues studies in rabbits in 1878 (Beatson, 1896).</td>
</tr>
<tr>
<td>1896</td>
<td>Beatson reports ‘curing’ patient by removing ovaries (Beatson, 1896). Boyd (1900) also supports role of oestrogen withdrawal on breast tumours.</td>
</tr>
<tr>
<td>1936</td>
<td>Antoine Lacassagne speculates that if increased sensitivity to oestrogen was responsible for the hereditary susceptibility to breast cancer, then perhaps an antagonist of oestrogen accumulation could prevent the disease (Jordan, 2003).</td>
</tr>
<tr>
<td>1957</td>
<td>The first non-steroidal anti-oestrogen: Merrell cardiovascular programme tests ethamoxytriphetol as part of an endocrinology programme evaluating synthetic oestrogens and discovers that it is in fact anti-oestrogenic. It was investigated as a contraceptive in rat models, shortly followed by clomiphene. Ethamoxytriphetol proved too toxic and clomiphene was found to have the opposite effect in humans. Numerous applications, but experimental treatments for breast cancer stopped due to extensive side effects and toxicity concerns (see below) (Patent US 2914563 A).</td>
</tr>
<tr>
<td>1958</td>
<td>The initial report of the anti-oestrogen actions of a non-steroidal compound. The compound was, unlike tamoxifien, anti-oestrogenic in all species tested (Lerner et al., 1958).</td>
</tr>
<tr>
<td>1962</td>
<td>Legal issues around the toxicity and subsequent market-withdrawal of Merrell-developed triparanol (lipid-lowering agent) in 1962 result in Merrell avoiding long-term treatments using agents believed to increase circulating levels of desmosterol (including anti-oestrogens), which can cause cataract formation. However, short-term treatment to induce ovulation (clomiphene) was considered safe, and this became their focus.</td>
</tr>
<tr>
<td>1962</td>
<td>Failure of Merrell to market non-steroidal anti-oestrogens as contraceptives attracted the attention of Arthur Walpole and his colleagues Michael J. K. Harper—a reproductive endocrinologist — and Dora M. Richardson — a synthetic organic chemist—at ICI Pharmaceuticals Division. Tamoxifen is discovered by Richardson in 1962.</td>
</tr>
<tr>
<td>1962</td>
<td>ICI file patent for tamoxifen, developed as a potentially safer anti-fertility agent (than, for example, triparanol).</td>
</tr>
<tr>
<td>1962</td>
<td>A pioneering study which showed the target site-specific action of radiolabelled oestradiol injected into immature rats (Jensen and Jacobsen, 1962).</td>
</tr>
<tr>
<td>1965</td>
<td>ICI patent published in the UK, GB1013907.</td>
</tr>
</tbody>
</table>
| 1967 | First detailed report of the antifertility activity of tamoxifen in rats. The anti-oestrogen lowered circulating cholesterol but did not increase demosterol (Harper et
1970s
Enthusiasm for chemotherapy in the treatment of breast cancer. Tamoxifen not considered breakthrough. Focus on tamoxifen in reproductive endocrinology instead.

1971
The first clinical trial testing tamoxifen as a breast cancer treatment carried out at the Christie Hospital in Manchester (Cole et al., 1971). Showed that tamoxifen had equivalent efficacy to historical results of standard endocrine therapy, but fewer side effects.

1972
ICI consider numerous applications for tamoxifen and stop development programme as market prospects were not promising.

1973
Walpole convinces ICI to market in the UK for breast cancer treatment.

1973
Approved for clinical use in the UK.

1976
Publication demonstrates that tamoxifen could not only be used to treat mammary cancer, but could also act as a preventative (Jordan, 1976).

1977
Approved in US for advanced breast cancer in post-menopausal women, but patent protection repeatedly denied due to perceived primacy of Merrell patents.

1977
The first study to show that tamoxifen, with a low affinity for the oestrogen receptor, was converted into anti-oestrogenic metabolites with high affinity. The publication of these data was delayed for more than a year to secure patent protection for the metabolites (tamoxifen did not have patent protection in the US at the time). (Jordan et al., 1977).

1980
The first study to demonstrate, in the lab, that long-term anti-oestrogen therapy and a strategy of oestrogen blockade was the best way to treat patients with receptor-positive disease (Jordan and Allen, 1980).

1983
Publication of clinical report demonstrating that extended adjuvant tamoxifen therapy saved lives (Baum et al., 1983).

1983
Early clinical work published looking at the use of tamoxifen as an adjuvant treatment in early breast cancer. (NATO, 1983).

1984
NCI state tamoxifen is the adjuvant endocrine treatment of choice for breast cancer (Jordan, 2003).

1984
ICI US patent application denied.

1985
First human prevention data based on contralateral tumours in the adjuvant trials (Cuzick and Baum, 1985).

1985
US patent approved through court of appeals, after over a decade of clinical development advancing with no assurance of exclusivity. This may also illustrate the perceived lack of importance of the drug in the pharmaceutical industry (Jordan, 2003). Patent granted with precedence to the patent dating back to 1965.
1987 The first report that both tamoxifen and raloxifene would maintain bone density selectively, despite the fact that both prevented mammary cancer in rats (Jordan et al., 1987).

1988 The first study to illustrate the target site-specificity of tamoxifen in endometrial and breast cancer. The authors suggested screening of women who were taking adjuvant tamoxifen (Gottardis et al., 1988).

1989 First pilot trial in breast cancer prevention in 3,000 high-risk women (Powles et al., 1989) – underpowered to show significant effect.

1989 US trial of 13,388 high-risk women showed 50 per cent reduction in invasive breast cancer (Fisher et al., 1989).

1990 Study starts which finds that tamoxifen produces liver tumours in rats (Greaves et al., 1993) (no significant increase in liver cancer has been reported in humans, but Jordan notes that had rat effects been established in early 1970s, development would have stopped – Jordan, 1995).

1991 Publication makes first suggestion that tamoxifen has potential as a chemopreventive agent for breast cancer, based on aspects of its pharmacology, and existing laboratory research and clinical experience (Nayfield et al., 1991).

1992 The first prospective randomised study to demonstrate that tamoxifen had the potential to increase bone density in postmenopausal patients is published (Love et al., 1992).


1998 First prospective randomised trial of high-risk pre and post-menopausal women to show that tamoxifen reduced the risk of breast cancer. (Fisher et al., 1998).

1999 Clinical proof of the concept proposed in 1990 that women taking a selective oestrogen-receptor modulator to present or treat osteoporosis would have a reduced incidence of breast cancer (Cummings et al., 1999).

2000 Study showing that long-term tamoxifen users have a worse prognosis of endometrial cancers, and questioning the widespread use of tamoxifen as a preventive agent against breast cancer in healthy women (Bergman et al., 2000).

2001 Study comparing use of tamoxifen over ten rather than five years (Fisher et al., 2001).

2001 Global sales of tamoxifen reach $1,024m.

2002 US patent expiry.

2002 First evidence on prevention from the International Breast Cancer Intervention Study (IBIS) published (Cuzick et al., 2002).

2003 Review of existing trial data published showing that tamoxifen can reduce the risk of...
ER-positive breast cancer (Cuzick et al., 2003).

2005 Important evidence published on the use of tamoxifen for the prevention of breast cancer cited on NICE guidance. (Fisher et al., 2005).

2007 Further importance evidence based on research conducted partially in the UK on the use of tamoxifen for the prevention of breast cancer published. The work is cited as important on NICE guidance. (Cuzick, et al., 2007).

2013 Meta-analysis of nine prevention trials published showing that incidence of invasive oestrogen (ER)-positive breast cancer was reduced both during tamoxifen treatment and for at least five years after completion (Cuzick et al., 2013).

2013 NICE recommends the use of tamoxifen as a preventive treatment in women who have a family history of breast cancer.
5.2. Key observations for estimating the economic returns

5.2.1. Time lags

Time lags are difficult to accurately measure as there is no one point of implementation. However, they appear to be of a similar scale to the average 15 years estimated from the analysis of the clinical guidelines.

Tamoxifen was approved for clinical use in the UK in 1973, 11 years after discovery. It became the standard for adjuvant treatment in the 1980s, around 20 years after discovery, and 15 years after the first trial in breast cancer. The time lags to use of tamoxifen as a preventative in high-risk women are even more difficult to pin down. The first evidence for its use in this form was published in 1976, but it was not included in NICE guidance for use in this manner until 2013, a time lag of 37 years. But the first clear evidence of effectiveness in prevention comes from a clinical trial conducted in 2005, which only gives a time lag of eight years to inclusion in guidelines in 2013.

A ‘champion’ may have had a significant impact on the time lag.

Arthur Walpole, as well as being involved in the development of tamoxifen, was also instrumental in keeping the drug in development at ICI and also in moving the focus for its use to cancer. He also played an important role in its release to the UK market. Without his influence, it is likely the time lags observed would have been greater, and it is possible that tamoxifen would not have been developed further for use in breast cancer.

5.2.2. Attribution

Attribution is likely to be higher than the 17 per cent estimated from the analysis of clinical guidelines.

The inclusion of tamoxifen in clinical guidelines as a preventative was based largely on two key studies, one of which was a joint study between the UK and Australia, with the UK portion being funded by CRUK. The case is more complex in terms of tamoxifen’s use in advanced breast cancer and as adjuvant therapy for early breast cancer. However, several important studies took place in the UK, including the first clinical trial of tamoxifen, and the work of the Early Breast Cancer Trialists Collaborative Group.

Although the drug was produced in industry, public funding played an important role in the large-scale trials needed to prove effectiveness.

The drug was developed by ICI in the UK but most of the trials were conducted through public funding, largely in the US and UK.

The development of tamoxifen shows the importance of interaction between different research fields.

Tamoxifen was initially developed as an antifertility drug, but found its application in cancer. Equally, although it is used largely as a cancer drug, it has had an impact on treatments for osteoporosis. This illustrates the potential for cross over between research fields and the way in which that is accounted for in quantitative approaches which focus on one field only.
5.3. Summary timeline (graphic)

- **Idea (1962)**
  - Discovery (fertility use intended). ICI file patent which is rejected.

- **Research into effectiveness (1970-present)**
  - First clinical trial in breast cancer (Cole et al., 1971), UK.
  - Walpole convinces ICI to market for breast cancer. Approved for use in UK.
  - Evidence for use as preventative (Jordan, 1976), US.
  - Publication of clinical report demonstrating that extended adjuvant tamoxifen therapy saved lives (Baum, 1983), UK.
  - Publication suggests that tamoxifen could be used preventatively (Nayfield et al., 1991), US.

- **Health gain (1973 onwards)**
  - Clinical evidence for preventative use (Cummings et al., 1999), US.
  - US trial of 13,388 high-risk women showed 50% reduction in invasive breast cancer (Gail et al., 1989).

- **Clinical guidance (mid 2000s-present)**
  - US patent in effect after long battle to put in place.
  - NICE recommends the use of tamoxifen as a preventive treatment in women who have a family history of breast cancer (2013).
5.4. Key papers and reports


Investigating time lags and attribution in the translation of cancer research: A case study approach


5.4.1. *Key web sites consulted*

http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/cancerstats-key-facts-on-breast-cancer

http://scienceblog.cancerresearchuk.org/2012/10/15/high-impact-science-tamoxifen-the-start-of-something-big/


6. Case study 5: Total mesorectal excision (TME) in rectal cancer

**Scope of case study**

This case study focuses on the development of total mesorectal excision (TME) as a new technique in rectal cancer surgery through to its acceptance as the ‘gold standard’ in the UK for middle and lower third rectal cancers. It begins with questions being raised about high local recurrence rates following ‘traditional’ procedures and ends with the adoption of TME as the new standard procedure for middle and lower third rectal cancers. At this point the research focus shifted from building evidence on the effectiveness of the technique to efforts to optimise its use.

Globally more than a million people develop bowel (colorectal) cancer every year, with the disease-specific mortality rate 33 percent in the developed world (Parkin et al., 2005, cited by Cunningham et al., 2010). In the UK, bowel cancer is the cause of 16,000 deaths a year and is second only to lung cancer as the leading cause of death from cancer (Ferlay et al., 2010, cited by Logan et al., 2011).

The past four decades have seen a steady increase in the five year survival rate in England and Wales (CRUK data), due to both improvements in treatment and earlier diagnosis. Between 1986–90 and 2005–09, the relative survival rate increased by 16 percentage points. With the exception of very early tumours, for which local excision may be sufficient, radical surgery is the mainstay of treatment for bowel cancer.

Prior to the past 30 years, abdominoperineal (AP) resection or anterior resection (AR) were the standard surgical techniques, but both produced poor outcomes in terms of local recurrence and overall survival. In the late 1970s, Bill Heald at North Hampshire Hospital in Basingstoke challenged the existing practice and refined these techniques to develop total mesorectal excision (TME), suggesting that recurrence was often due to incomplete removal of cancerous cells. TME involves the removal of the entire mesorectum and lymph nodes. His early use of the technique appeared to support this supposition, as did evidence from Quirke et al. (1986), who championed the importance of circumferential resection margin in addition to precisely controlled surgical technique.

In 1993 the Norwegian Rectal Cancer Group noted that recurrence rates were high and suggested that this was primarily due to surgeon performance. Comparing this with the improved outcomes reported for TME, they took the decision to make TME the standard treatment in every hospital in Norway. This involved a large-scale training programme, which was supervised by Heald himself. During the period 1978–1997 Heald undertook 125 television workshop demonstrations in 17 countries, as well as documenting over 500 procedures he carried out himself – again he was able to demonstrate better survival following TME than standard procedures.

In the early 2000s, results were published from some of the large-scale European trials that had begun in the 1990s. Major studies in Sweden and the Netherlands, as well as the national programme in Norway,
showed better outcomes for TME and highlighted the importance of standardised, quality-controlled surgery. They also demonstrated that the kind of intensive training programme first rolled out in Norway (but replicated soon after in other countries) can be an effective way of ensuring the uptake of new techniques as standard clinical practice.

In the UK, the 2004 update of the NICE guideline for rectal cancer recommended TME and that every multidisciplinary team should be trained in its use. Much of the research since has focused on optimisation of the technique, through the use of robotic or laparoscopic TME and its use alongside other treatment options, such as preoperative radiotherapy.
6.1. Summary timeline (table)

1908–1982 Standard procedures abdominoperineal (AP) resection, largely replaced by anterior resection (AR) – outcomes were poor (recurrence and damage to surrounding tissue).

1978 Heald (North Hampshire Hospital, Basingstoke) questioned traditional procedures and began developing TME in an effort to reduce recurrence (Heald, 1979).

1982 Heald et al. (1982) suggest that recurrence is due to incomplete removal of cancerous cells and provide evidence for the effectiveness of TME in preventing recurrence.

1986 Heald & Ryall (1986) publish further results on their ongoing study.

1986 Quirke et al. (1986) report that pelvic recurrence was a direct consequence of inadequate mesorectal excision leaving regional disease. Quirke and colleagues go on to document the importance of circumferential resection margin (CRM) status in assessing prognosis (recurrence being lower in instances where there is no tumour involvement in the CRM), and its use as an indicator of quality of surgery (see, for example, Birbeck, et al., 2002).

1993 Concern among Norwegian surgical community that recurrence too high and recognition growing across Europe that this is due primarily to surgeon performance. Norwegian Rectal Cancer Group decides that TME should be standard treatment nationally. Every hospital in Norway took part in the project. Training in TME was organised, supervised by Heald. Additionally, rectal resections were removed from the general surgery curriculum to ensure they were performed only by specialists. A study was launched to audit and assess the effects of the policy change.

1993 Randomised trial shows that preoperative radiotherapy reduces relapse (Frykholm, et al., 1993).

1994–1997 Having noted Heald & Ryall’s (1986) success rate, the Stockholm Colorectal Cancer Study Group investigated the surgical techniques involved and set up a programme of surgical workshops to introduce TME to surgeons in Stockholm. There were three 3–4 day workshops of live surgery by video, histopathology sessions, discussions on surgical technique, and assisting in theatre. A study was set up to assess the effectiveness of the teaching initiative.

1996–1999 The Dutch ColoRectal Cancer Group introduces a nationwide training programme for TME. More than 200 surgeons are trained and participate in a trial comparing to a previous trial using conventional surgery.

1996 The Dutch ColoRectal Cancer Group begins an RCT of TME with adjuvant preoperative radiotherapy (previous studies had not used standardised surgery) (Kapiteijn, et al., 1999).
1996 Royal College of Surgeons recommends TME.

1998 Norwegian prospective study on introduction of TME reports first results and highlights importance of comprehensive training in the technique – while the level of complications associated with the TME group was deemed an ‘acceptable risk’, it decreased with experience over time (Carlsen, et al., 1998).

1998 Heald et al. (1998) publish results of more than 500 TME operations carried out by Heald between 1978 and 1997, demonstrating better survival than for standard procedures. During the time of the study, Heald undertook 125 television workshop demonstration operations in 17 countries.

1999 Tripartite Consensus Conference in Washington, DC, clarified terminology by defining the ‘complete excision of visceral mesorectal tissue to the level of the levators’ as TME – several names had been used in previous years. The American Society of Colon and Rectal Surgeons, the Colorectal Surgical Society of Australia and The Association of Coloproctology of Great Britain and Ireland convened the meeting to clarify a wide set of terms, with the aim of ensuring that data and results could be accurately compared internationally.

2000 Results of the Stockholm group’s study show a significant reduction in recurrence among patients treated by TME, suggesting that the teaching initiative was effective (Martling, et al., 2000).

2001 Dutch ColoRectal Cancer Group publishes results of its randomised trial of TME plus preoperative radiotherapy, demonstrating that this reduces the risk of recurrence more than TME alone (Kapiteijn, et al., 2001).

2002 Norwegian audit reveals a successful national policy change with a ‘centrifugal spread of competence’. Better outcomes were found following TME and it was demonstrated that surgery alone could be effective (ie without necessarily needing adjuvant therapy) (Wibe, et al., 2002).

2002 Dutch trial results show improved outcomes following training in and implementation of TME, which has become the standard treatment in the Netherlands. Authors emphasise standardisation of treatment and quality control of surgery (Kapiteijn, et al., 2002).

2004 NICE’s updated colorectal cancer guideline recommends TME and that every MDT should be trained in all aspects of the technique.


2006 Cochrane review of LTME vs open TME concludes that there are short-term benefits to LTME for some patients. No differences in longer-term cancer outcomes were found, but evidence from large RCTs is needed (Breukink, et al., 2006).

2008 Cochrane review of long-term outcomes of LTME concludes similar outcomes to
open TME for colon surgery. Upper rectum laparoscopic surgery is feasible, but further RCTs needed (Kuhry, et al., 2008).

2010

LTME not widely used because of technical complexity and long learning curve. Robotic Tumour-Specific Mesorectal Excisions proposed as an alternative that may assist surgeons. Evidence supports feasibility, but more studies are needed on outcomes (Pigazzi, et al., 2010).
6.2. Key observations for estimating the economic returns

6.2.1. Time lags

- In the UK, the time lag from the initial idea to acceptance as standard practice (recommendation in the NICE guideline) was 26 years. However, in other countries uptake was much faster (eg Norway – around 15 years).
- It is also worth noting that although the initial idea emerged in the late 1970s, there was likely little research investment in the development of the technique until the bigger trials started in the 1990s. This may mean that the lag between the largest amount of funding and the adoption of the technique as standard practice may be much shorter.

6.2.2. Attribution to UK research

- Heald, who initially developed the technique and was active in both building the evidence base and disseminating skills and knowledge, was based in the UK. Quirke and colleagues are also UK-based.
- However, much of the evidence from large scale trials came from other European countries, albeit with the involvement of Heald in many cases.

6.2.3. Other points of note

- TME needs highly skilled surgeons and is expensive – Heald (1998) suggests this has led to low uptake in the US.
- Uptake in Europe appears largely to have been driven by surgeons. However, it has also been suggested that there was some resistance among UK surgeons to the new technique.
- Apparent importance of a ‘champion’ ie Heald in dissemination of new knowledge and techniques.
- Importance of standardisation and training – and willingness of pioneers to do the teaching.
- Surgeons 'believed' TME to be better than traditional surgery, even before extensive evidence was available. This prevented RCTs in some cases, due to delivery of apparently inferior care being considered unethical.
6.3. Summary timeline (graphic)
6.4. Key papers and reports


7. Discussion and observations

Although only five case studies were conducted, and as such it is not possible to draw generalizable conclusions from the analysis of this set of case studies, it is possible to identify some interesting observations from the case studies which may warrant further investigation. Observations are discussed in three sections: those relating to time lags; those related to attribution; and other observations of note.

7.1. Time lags

Analysis of the case studies confirms the complexity inherent in trying to understand and estimate elapsed time. As noted in the Introduction, the validity of the estimate of 15 years for the average time between the funding of the cancer research and the generation of health gains cannot be explored by making a direct comparison with the overall time elapsed from the original research breakthrough to the implementation of the intervention. The latter period is measuring something different and would normally be expected to be longer than the average time estimated at 15 years.

The case studies describe a range of factors that contribute to the time lag. For bowel cancer screening, it is noted that it just takes a long time (c. 10 years) to conduct RCTs in this area. However, contrastingly, once a meta-analysis in this area was published, the impact on policy was almost instantaneous, perhaps facilitated by the national infrastructure in place with a national screening programme. The concept of locality is particularly important in the case of the service configuration case study, where it is noted that key local evidence was drawn on very quickly to inform policy recommendations. One of the crucial elements here was the network connecting policy and research. For example, policy documents reference research as ‘in press’, meaning that work must have been sent to (and/or known by) the relevant policy makers in advance of publication. These types of close relationships have facilitated rapid uptake of research and reduced time lags in this example. As with the national screening programme, having the structures and networks in place means that the transfer of knowledge can happen more quickly.

Both the tamoxifen and TME case studies raise the importance of a ‘champion’ in the translation of research and in reducing time lags. The potential importance of a ‘champion’ has been raised previously
(Wooding et al. 2011, 2013). In tamoxifen, Arthur Walpole played an important role in ensuring that ICI continued to pursue research in tamoxifen and in pushing for it to be licensed for use in the UK market, both of which had an impact on the time lag. In the case of the TME case study Heald played the role of champion. Not only was his research instrumental, he also acted to ensure implementation, being involved in Norway in extensive training activities. This was also seen to some extent in the case of service configuration, with the dual role of Haward and Selby in both research and in informing policy being an important factor in the rapid adoption of key UK studies.

Also important to note is the sometimes lengthy process from policy statement to roll out of a particular intervention. This appears to depend on the type of intervention. For bowel cancer screening, development and roll out takes 10 years. Implementation in the case of TME requires time for training in the appropriate techniques. For smoking reduction, this is significantly quicker, since interventions are typically legal, such as smoking bans, rather than medical.

### Summary of findings from case studies relating to the elapsed time

<table>
<thead>
<tr>
<th>Case study</th>
<th>Summary of findings relating to the elapsed time</th>
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<tbody>
<tr>
<td>Bowel cancer screening</td>
<td><strong>The elapsed time is 40+ years</strong>&lt;br&gt;This is partly explained by the fact that it takes 10 years to undertake the RCTs (albeit over a 20-year time frame). However, once there is strong evidence from a meta-analysis, gFOBT is quickly adopted into national policy although it takes a further 10 years for the screening programme to be developed and rolled out.</td>
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<tr>
<td>Service configuration</td>
<td><strong>The elapsed time between key research studies being conducted and being used was in many cases quite short.</strong>&lt;br&gt;It is difficult to identify a single time because there have been an evolving series of policy documents in which the general move towards recommendations of concentration of services, or provision of treatment by site-specialists, have been strengthened as the evidence has strengthened. Key local UK evidence was drawn on extremely quickly to inform policy recommendations.</td>
</tr>
<tr>
<td>Smoking reduction</td>
<td><strong>Elapsed time seems to vary considerably for different components</strong>&lt;br&gt;First epidemiological evidence on passive smoking occurred in early the 1980s, with smokefree legislation proposed in early 2000s. Key evidence on harms published in 1950, with ban on TV advertising in 1965. However it is likely that industry lobbying and denial of harms delayed interventions, both by challenging evidence (eg on causality) and obstructing legislation.</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td><strong>The overall elapsed time appears to vary depending on the point of implementation considered.</strong>&lt;br&gt;Elapsed time is difficult to measure as there is no one point of implementation. Tamoxifen was approved for clinical use in the UK in 1973, 11 years after discovery. It became the standard for</td>
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adjuvant treatment in the 1980s, around 20 years after discovery, and 15 years after the first trial in breast cancer. The time lags to use of tamoxifen as a preventative in high-risk women are even more difficult to pin down. The first evidence for its use in this form was published in 1976, but it was not included in NICE guidance for use in this manner until 2013, a lag of 37 years.

<table>
<thead>
<tr>
<th>Total Mesorectal Excision</th>
<th>In the UK, the elapsed time from the initial idea to acceptance as standard practice (recommendation in the NICE guideline) was 26 years.</th>
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<td></td>
<td>In other countries uptake was much faster (e.g., Norway—around 15 years). It is also worth noting that although the initial idea emerged in the late 1970s, there was little research investment in the development of the technique until the bigger trials started in the 1990s. This may mean that the time between the largest amount of funding and the adoption of the technique as standard practice may be shorter.</td>
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7.2. Attribution

The parallel analysis of guidelines (Glover et al., 2014), estimated that 17 per cent of research cited on clinical guidelines results from publicly funded work conducted in the UK, although this differed between specific guidelines. This approach clearly has some limitations as a measure of the proportion of health gain from research in cancer that can be attributed to UK public research funding. Firstly, it assumes that each publication cited on a guideline has equal weight. Perhaps more importantly, it neglects any work which is not cited on guidelines which will typically include all basic research in the area and much of the early clinical work, all of which might have been crucial in the development of an intervention. It will typically, for example, exclude the discovery of a particular drug, device, or other intervention. It is also likely to exclude the development of any techniques that might have been critical in the development and testing of the intervention. Another limitation is that this approach doesn’t account for the fact that some of the evidence for a particular intervention might have been unnecessary. It may be that one or more of the later trials would not have been necessary to prove the effectiveness of an intervention if a systematic review had been conducted at the appropriate point (and indeed additional trials may have been conducted even after a systematic review has shown that it was not necessary). In this case, evidence may be cited in guidelines without which the intervention may still have been included. Overall, this approach places excessive weight on systematic reviews and clinical trials, which may be important but are not the only types of research that contribute to changes in policy and practice.

Analysing case studies allows us to consider the wider range of inputs more carefully, but doesn’t make assigning a figure to attribution any easier. Indeed, it might make it more difficult, but also strengthens the analysis. Assigning relative importance to different pieces of research and different stages of the research process is challenging. For example, how important is the initial discovery of a drug relative to an important clinical trial of that drug, or a meta-analysis of evidence across a number of trials? Although it is possible to identify which pieces of research were conducted in the UK, attribution remains challenging. Even identifying where research was conducted can offer some challenges. Many large-scale trials cover multiple countries and have multiple funding sources. Deciding the relative weighting between these countries is not necessarily straightforward. However, attempts have been made by authors to look at the extent to which particular developments can be attributed to UK publicly funded research.
Analysis of the case studies conducted suggested that the estimate of 17 per cent obtained from the guidelines may be a low estimate. For bowel cancer screening, for example, 25 per cent of the RCTs crucial in adoption were conducted in the UK (including 38 per cent of the patients forming part of those crucial trials). TME was developed in the UK, although its efficacy was confirmed in large-scale studies elsewhere. For changes in service configuration, local research taking into account the specific context was understandably important. In the important reviews by Selby and Stiller, UK specific evidence was particularly influential. Looking at some of the more recent systematic reviews of the volume/outcomes link, UK papers constituted 20 per cent of the papers on the 2012 Colorectal Cochrane review and 25 per cent of the studies (but a lower proportion of patients) on the 2010 breast cancer review.

In the case of smoking, attribution is harder, not least because it is difficult to tell the extent to which research evidence plays a role in the timing and nature of the public health interventions introduced. It seems that wider factors such as political will, public opinion, and industry lobbying may have been equally, if not more important in the decision to introduce policy changes, though of course these factors will have themselves been influenced by the availability of research evidence around smoking harms. Given it is particularly challenging to establish which pieces of research were most influential here, the challenge of attribution is increased. Nonetheless, it is possible to identify some key pieces of research and their origins. Much of the very early work on harms was carried out in Germany, but one of five key case control studies was from the UK (with the others from the US) and the British Doctors Study was influential from 1956 onwards. Equally, regular reports by the Royal College of Physicians entitled ‘Smoking and Health’ which reviewed and summarised the evidence around smoking harms seem to have been influential. However, putting a value on the proportion of research attributable to UK funding in this case is challenging.

For tamoxifen, the relative weighting of the attribution between industry and publicly funded research also becomes important. The drug was discovered in the UK but by ICI. However, the large-scale trials needed to show effectiveness were conducted using public funds, largely in the UK and the US. Considering its preventative use, one of the two key studies which led to inclusion in NICE guidance in 2013 was conducted jointly between the UK and Australia. Evidence around its use in other contexts is less clear, though the first clinical trial was conducted in the UK. In the case of tamoxifen, it is also interesting to note the interconnectedness of different research fields when considering attribution. Tamoxifen was initially developed as an antifertility drug, but found its application in cancer. Equally, although it is used largely as a cancer drug, it has had an impact on treatments for osteoporosis. So although the publicly funded research on the drug is largely cancer related, the benefits of the drug extend beyond those health benefits due to reduction in breast cancer. This illustrates the challenges of looking at research within one particular field.

**Summary of findings from case studies relating to the rate of attribution**

<table>
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<th>Case study</th>
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<tbody>
<tr>
<td>Bowel cancer screening</td>
<td>Attribution is higher than the estimated 17 per cent. Of the four studies included in the meta-analysis that provided the key evidence for a national screening programme, one was from the UK, suggesting one estimate attribution could be 25 per</td>
</tr>
</tbody>
</table>
cent (ie 1 in 4). If you look at the contribution participants of those four trials made to the meta-analysis then the rate would be higher at 38 per cent (ie 152,850/402,194). That said the original idea that gFOBT could be used for screening stems from a US-based author, Greegor.

Service configuration  
**Attribution is higher than the estimated 17 per cent.**

Especially in the early UK policy developments of multidisciplinary specialised care there are several reasons for believing that UK studies played a key role in their formulation and subsequent promotion. Looking at recent systematic reviews, UK papers constituted 20 per cent of the papers on the 2012 Colorectal Cochrane review and 25 per cent of the studies on the 2010 breast cancer review, but on the latter review the proportion of UK patients in the overall total was much lower than 25 per cent because of the large size of some of the US studies.

Smoking reduction  
**Attribution is difficult to estimate but UK research played important role.**

Much of the initial work on harms was done in Germany, but one of five key case control studies was from the UK (others US) and the British Doctors Study was influential from 1956 onwards. The regular RCP ‘Smoking and Health’ reports reviewing/summarising evidence seem to have been influential.

Tamoxifen  
**Attribution is higher than the estimated 17 per cent.**

Although the drug was developed in industry, public funding played an important role in the large-scale trials needed to assess effectiveness. The inclusion of tamoxifen in clinical guidelines as a preventative was based largely on two key studies, one of which was a joint study between the UK and Australia. The case is more complex in terms of tamoxifen’s use in advanced breast cancer and as adjuvant therapy for early breast cancer. Several important studies took place in the UK, including the first clinical trial of tamoxifen.

Total Mesorectal Excision  
**Attribution is difficult to determine. A UK research developed the technique and played an important role in adoption, but many of the large-scale trials took place in other countries.**

Heald, who initially developed the technique and was active in both building the evidence base and disseminating skills and knowledge, was based in the UK. However, much of the evidence from large-scale trials came from other European countries, albeit with the involvement of Heald in many cases.

### 7.3. Other observations

Looking across the case study set uncovers some interesting observations about the roles of different types of evidence in changes in policy and practice. One interesting observation from the case studies, especially for changes in service configuration and bowel cancer screening, was the importance of local research to take into account the specific context. This was particularly crucial for service configuration where the existing system and context is crucial in establishing the intervention needed. Even where this is not the case, it does seem that local evidence is more influential. This could be due to a propensity of those preparing guidelines to be aware of, and to hence cite, work conducted by colleagues. However, it could
equally reflect the need to demonstrate that an intervention is not only effective, but also cost-effective in the context of the NHS in order to be accepted onto guidelines. Evidencing the cost-effectiveness, in particular, is difficult to do based on data from outside the UK, and may even have local variations within the UK. The detailed analysis of the papers cited on one guideline in the 2008 report (Buxton et al., 2008) showed that all four papers cited in the section on cost data came from the UK.

As well as local evidence, there is a suggestion that careful construction of a study to include the right evidence needed for policy uptake could be valuable. For example, in the case of bowel cancer screening, the economic evaluation ‘built into’ the Hardcastle trial may have facilitated the speedy policy uptake. However, in the case of the smoking case study, the extent to which research evidence was an important driver of policy actions needs careful analysis. There were many influential actors outside the research system and campaigning and public support were also very important in the introduction of the public health interventions used. Evidence around smoking harms would have influenced these factors, by creating public awareness of harms for example, but the direct link between research evidence and policy action is less clear-cut. This is perhaps because these types of public health actions are not mediated by a guidelines committee or other analysis of data, but rather are subject to the political will of the serving government.

The case study set also illustrates the importance of a range of different actors in the translation of research into practice. One example that occurs in several case studies, and has emerged from other research in this area, is the importance of a ‘champion’ in furthering a particular intervention. This is described in relation to time lags above, but in some cases it could be argued that their influence runs deeper than that. The counterfactual is hard to investigate, but without Heald, who not only pioneered total mesorectal excision, but also provided much of the early evidence for its effectiveness and personally undertook 125 television workshop demonstrations in 17 countries, as well as documenting over 500 procedures he carried out himself, would TME be so widely used? Similarly, without Walpole, it may be that tamoxifen would have been dropped by ICI and never marketed in the UK or elsewhere.

The role of practitioners is also prominent in the case of TME. While it has been suggested that there was some resistance among UK surgeons to the new technique, there is also a suggestion that other surgeons may have to some extent impeded research efforts in their desire to use this approach. Such surgeons ‘believed’ TME to be better than traditional surgery, even before extensive evidence was available. This might have prevented RCTs in some cases, since the delivery of care which some considered inferior could be interpreted as being unethical. Training is also important in this context. The technique requires highly skilled surgeons, who need to be trained and as such is expensive. According to Heald (1998), this might have been the cause of low uptake in the US. This also links to the service configuration case study because the higher the skills required, the stronger the case might become for concentration of services on high volume providers.

Also important is the role of policy makers as actors in the translation of research. One example of this is the willingness of the ACS to act early, at risk, in recommending bowel cancer screening before the formal evidence was available. This acts to reduce time lags perhaps, but it requires judgment on whether the risk involved is worth taking. Perhaps less controversial are the advantages of interconnectedness between researchers and policy makers illustrated by the service configuration case study, where for example a
policy document references research as ‘in press’, indicating that it had been communicated early to the relevant policy makers, enabling them to act on it more quickly. This also demonstrates the disadvantages of the sometimes lengthy delays at the publication stage.

The service configuration case study in particular illustrates one of the challenges of estimating the impact of research. In practice our estimates of the health benefits of a particular intervention (in terms of QALY gains) are largely extrapolated from trial data, mainly derived from UK relevant health technology assessments. This particular case illustrates that the gains actually realised in the NHS may differ from those observed in trials. This instance suggests a situation where trial gains may underestimate what is now being achieved, but in other cases reality may be less favourable than trials suggest.
References


