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How to improve cancer survival

Explaining England's relatively poor rates

Key points

- The government has announced its intention to focus the NHS on improving health outcomes, including specifically committing to improve our cancer survival rates in relation to other countries. This paper explains the existing differences in cancer survival between countries and makes some recommendations for policy-makers, commissioners and providers in England.
- Cancer survival rates in England are improving overall. However, the most up-to-date international comparisons show that England still has worse cancer survival rates than many countries, including Canada, Australia, Sweden and Norway. We appear to be closing the gap with the higher-performing countries in breast cancer, but the gap has not narrowed for colorectal and ovarian cancer and has widened slightly for lung cancer.
- A range of factors contribute to international differences in cancer survival, including: more advanced stage at diagnosis; delays in diagnosis and treatment; and treatment variation and co-morbidity, particularly in older people. Overall, the most plausible drivers for improved survival appear to be diagnosis at an early stage, including through effective screening programmes, access to optimal treatment and improvements in the management of older people.
- In England, the NHS and public health need to work together to diagnose more cancers at an earlier stage, and GPs need to use information about their referral rates and use of diagnostics to understand how their performance compares with others. Reducing variation in access to major surgery for cancer is needed, as is understanding and addressing inequalities in the management of older people with cancer.
- High-quality data collection, analysis and research remain important for monitoring progress and identifying which initiatives will be most effective at improving outcomes.
- Over the long term, the health system can and should be held to account for cancer survival performance. However, other outcome and process indicators are needed to monitor current performance.

Introduction

The government has outlined a framework to focus the NHS on improving health outcomes and the NHS Commissioning Board will be held to account for progress (Department of Health 2010a). The new cancer outcomes strategy, published in January, makes the following commitment:

> *Our aspiration is that England should achieve cancer outcomes which are comparable with the best in the world.*
>
> (Department of Health 2011)

This paper explores what is needed to achieve this goal in relation to survival. It sets out recent trends in cancer survival in England and discusses how and why these differ from similar countries in Europe and elsewhere. It then reviews the potential implications of this for policy and service delivery.

This review demonstrates how difficult it is to determine the drivers of health outcomes, how complex those drivers are and how much the drivers interact with and influence each other.

Current available evidence provides some good indications of where the NHS needs to focus to improve cancer outcomes, but more evidence is needed to be more certain about where to focus and what improvements and initiatives will work in practice. Some of this evidence will come from the International Cancer Benchmarking Partnership (ICBP), a partnership of policy-makers, researchers and clinicians across six countries, initiated by the Department of Health and managed by Cancer Research UK. ICBP is studying differences in survival rates between countries and identifying the most important opportunities for improvement (Cancer Research UK 2011b).

Although this paper focuses on cancer survival, it is important to stress that survival is not the only important outcome, nor is it the only important marker of the quality of our cancer services. Table 1 below presents four main measures of cancer outcome and some of their different uses.

Beyond outcome measures, measures of patient experience and of the quality of care are also important. Although survival rates are improving, many people continue to die from cancer, so the quality of their end-of-life care is important, as is the quality of care and life during and after treatment for those who survive cancer.

Table 1 Measures of cancer outcome

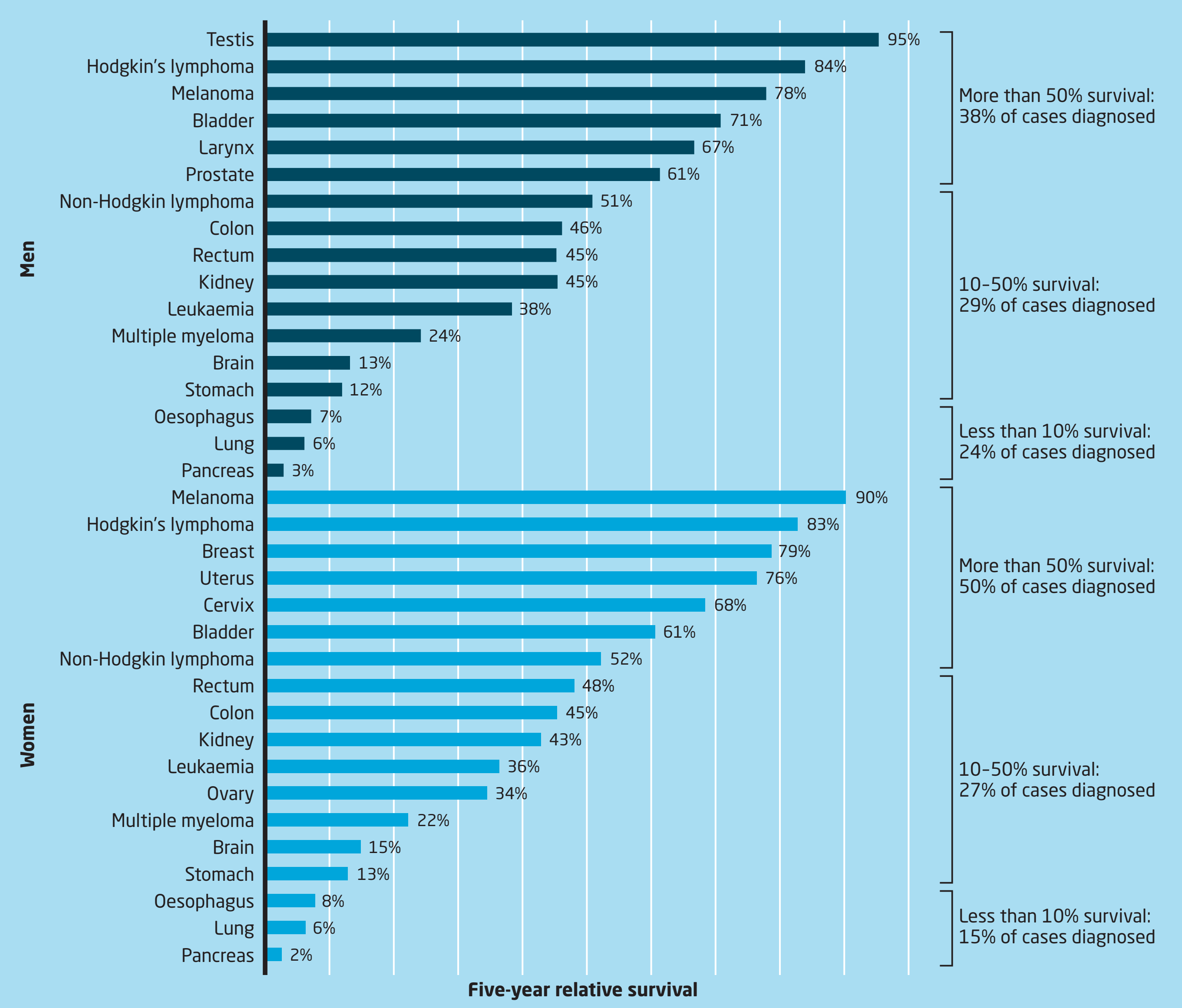
Measure	Simple definition	Examples of use
Incidence	New cases of cancer	■ Planning services ■ Monitoring the impact of strategies to prevent cancer
Survival	Proportion of people surviving after a given interval (such as one year or five years) 'Relative' survival is the definition most typically used that adjusts for other, non-cancer related, causes of death	■ Monitoring the performance of the health system in treating cancer
Mortality	Deaths from cancer	■ Reflection of both incidence and survival
Prevalence	Number of patients alive who have had a diagnosis of cancer at some point	■ Understanding size of population affected by cancer, including long-term survivors of cancer

Cancer survival rates in England

Overall cancer survival rates in England are improving. There is also some evidence that the rate of overall improvement in cancer survival has accelerated slightly between 2004 and 2007, the most recent period for which data is calculable. This might reflect the national policy focus on cancer since the NHS Cancer Plan was published in 2000 (Rachet *et al* 2009). However, survival rates are significantly different between tumour types. Figure 1 below shows recent relative five-year survival rate estimates and demonstrates clearly that although survival rates are high for breast and skin cancer, survival rates for lung, pancreatic and oesophageal cancer are very low.

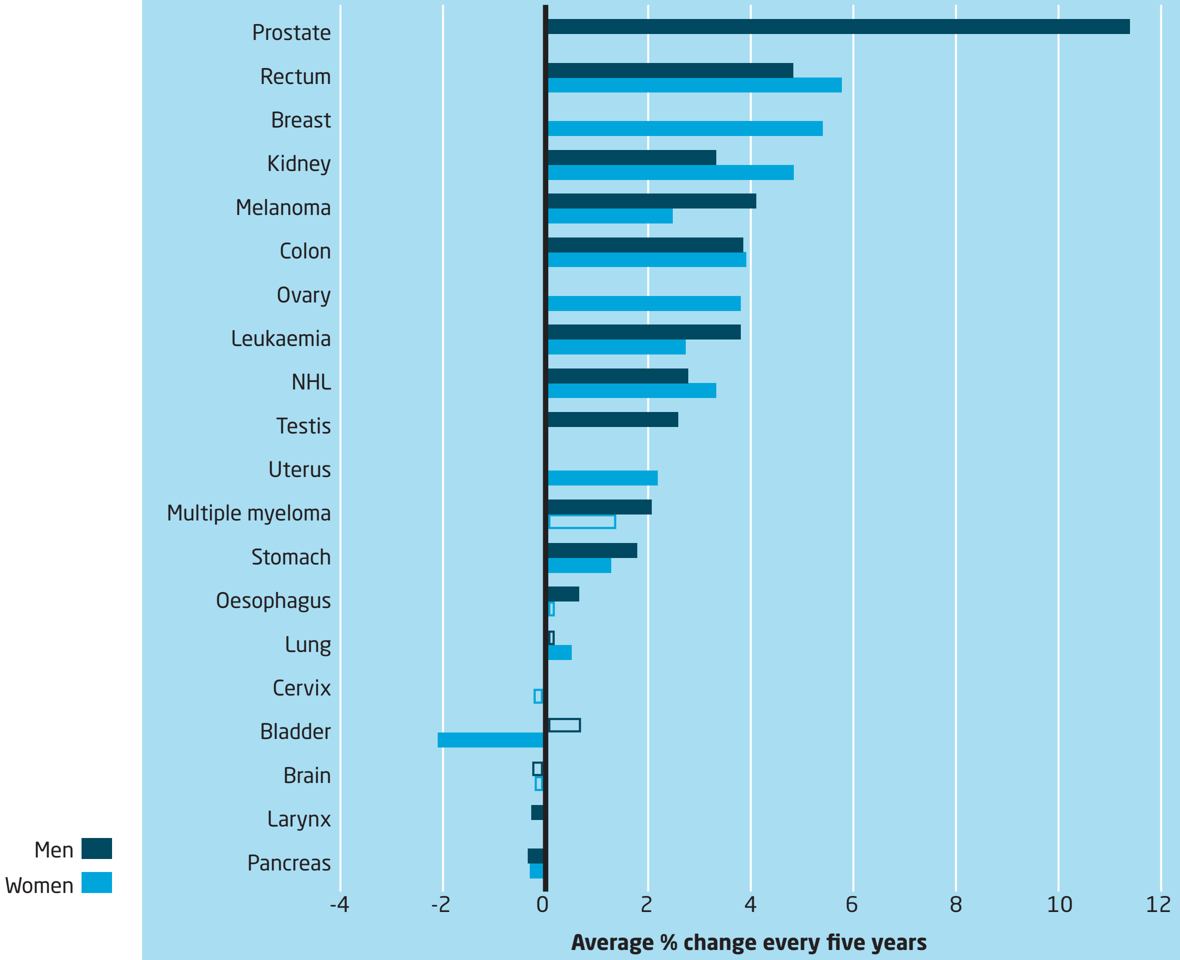
Similar variations exist when looking at survival trends over time. Figure 2 overleaf depicts trends in five-year survival and shows that, although survival rates are improving for most cancers, for some cancers survival rates are static or even declining slightly. The variation in trends between cancers is the result of a number of factors, including differences in screening, diagnostic tests, treatments and improvements in the quality and organisation of treatment.

Figure 1 Relative five-year survival estimates based on survival probabilities observed during 2000/1, by gender and type of cancer, England and Wales



Source: Cancer Research UK 2009

Figure 2 Average change (%) in five-year relative survival, by gender and type of cancer, adults diagnosed in England and Wales, 1986–99



Source: Cancer Research UK 2011a

Note: Unshaded boxes show changes that were not statistically significant

Survival rates in England vary between different geographical areas, socio-economic groups, ages and ethnic backgrounds; this partly reflects differences in incidence and mortality rates (National Cancer Intelligence Network 2010a).

- There is a consistent north–south differentiation in cancer survival, which has lessened slightly in the past 10 years (Office for National Statistics 2010).
- For most cancers, survival is worse for deprived groups and this gap has tended to increase as survival rates have increased overall, with the exception of breast cancer in women and a few other cancers (Rachet *et al* 2008).
- Cancer survival decreases with age (National Cancer Intelligence Network 2010a).
- Data on the ethnicity of patients is incomplete. However, we do know that cancer incidence varies by ethnic group.
  - Black people have higher rates of prostate cancer, stomach cancer and multiple myeloma than other ethnic groups.
  - Many other non-white ethnic groups have reduced rates of cancer (National Cancer Intelligence Network 2009).
  - Breast cancer survival is worse among black and Asian women (Jack *et al* 2009).

Factors that explain variation in survival within England may also be important in explaining international differences and are explored later in this paper.

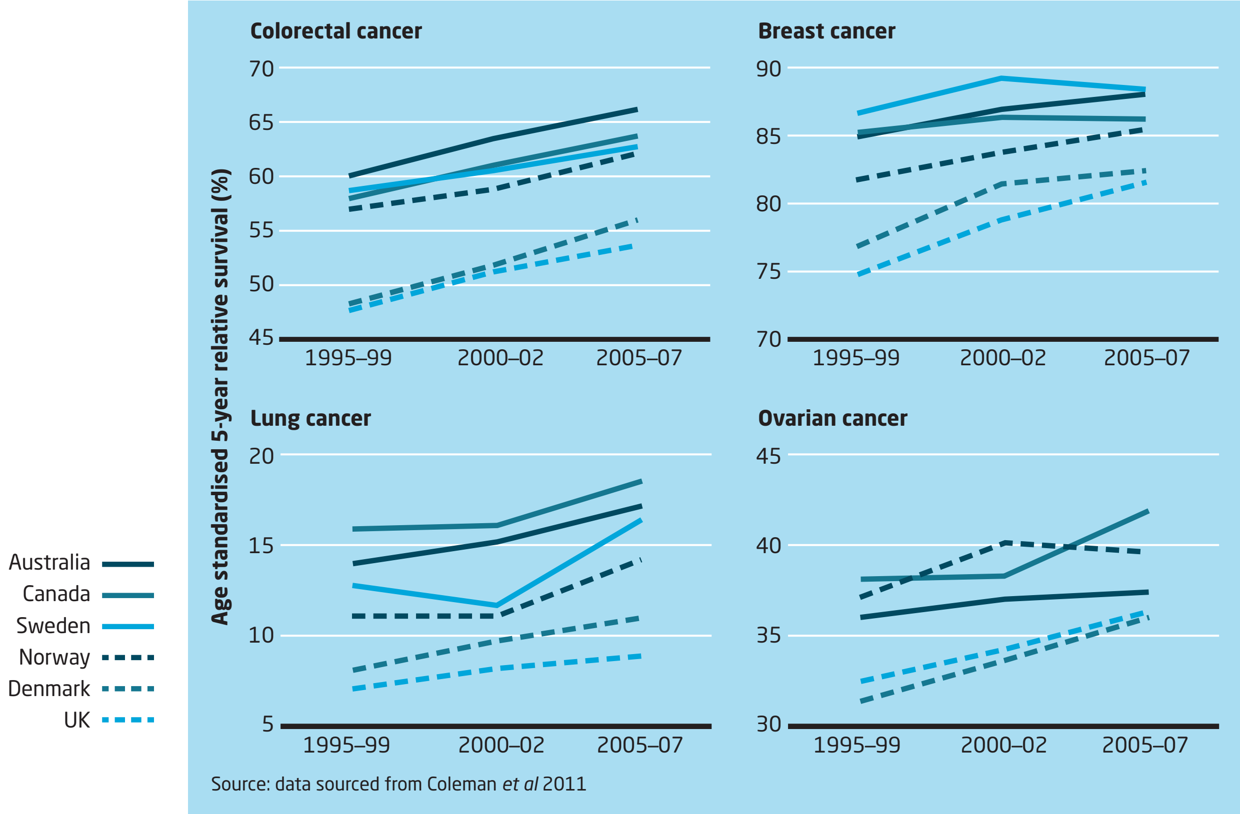
How we compare with other countries

An international comparison of cancer survival rates undertaken by the ICBP was published in *The Lancet* in January 2011 (Coleman *et al* 2011). The study compares relative survival between 1995 and 2007 for breast, colorectal, lung and ovarian cancer in six countries:

- two states of Australia
- four provinces of Canada
- two regions of Sweden
- Norway
- Denmark
- three nations of the UK – England, Wales and Northern Ireland.

Figure 3 below demonstrates that although survival has improved in all four cancers in all countries, survival is persistently lower in the UK nations and Denmark. This is particularly the case in the first year after diagnosis and among older patients (Coleman *et al* 2011).

Figure 3 Age-standardised five-year relative survival trends, by cancer and by country

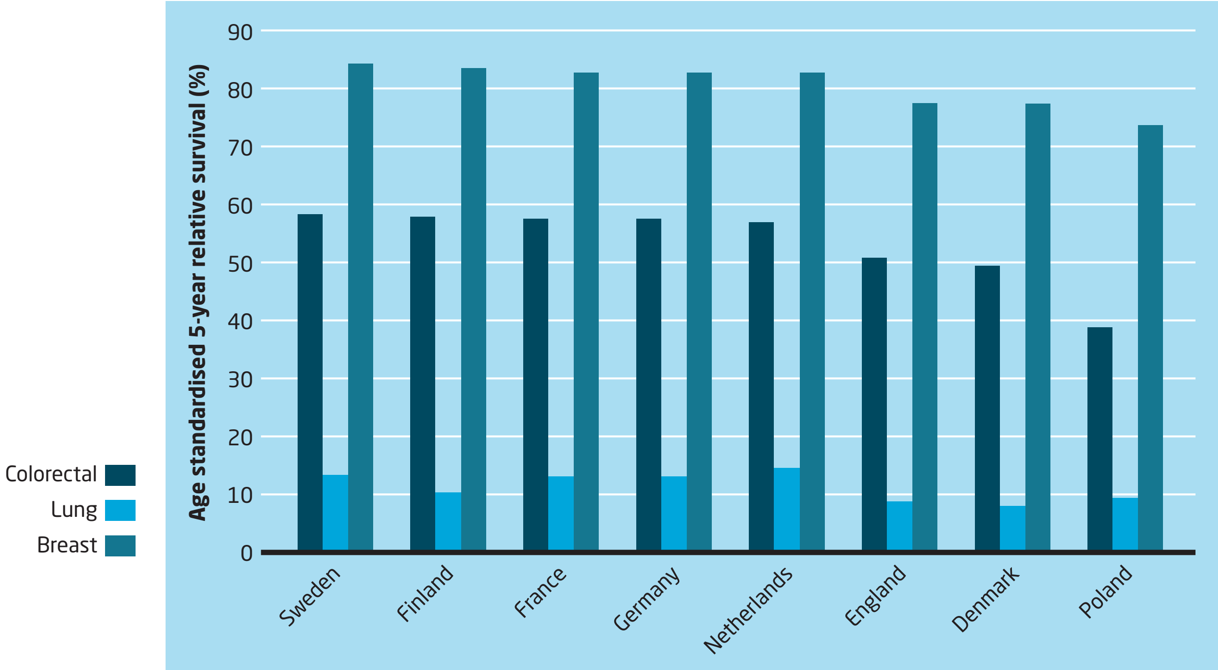


Source: data sourced from Coleman *et al* 2011

The graphs indicate that, while the UK nations have narrowed the gap somewhat for breast cancer, the gap has not narrowed for colorectal cancer, is a mixed picture for ovarian cancer and has widened slightly for lung cancer (Coleman *et al* 2011).

These findings broadly echo those of EUROCARE – a research project on the survival of European patients with cancer. The most recent EUROCARE study, covering patients diagnosed between 1995 and 1999 (Berrino *et al* 2007) and 2000 and 2002 (Verdecchia *et al* 2007), showed that survival for many cancers is lower in England than Sweden, Finland, France, Germany and the Netherlands (see Figure 4 overleaf).

Figure 4 Five-year age-adjusted relative survival for colorectal, lung and breast cancer for European adults diagnosed in 1995–99, selected countries, EUROCARE-4 study



Source: data sourced from Berrino *et al* 2007

How reliable are these conclusions?

The validity of international cancer survival comparisons and the use of survival as a measure of performance improvement in health care have been debated over the years.

The EUROCARE studies have been subject to some criticism due to the variation between countries in the coverage of cancer registry information (Wilkinson 2009). For example, cancer data from Germany amounts to only 1 per cent of the population and cancer data from France equates to only 10–15 per cent, whereas coverage is virtually complete in England and Scandinavia. Consequently, the ICBP studies compare only countries or parts of countries with comprehensive cancer registry data.

Further methodological issues arise because of differences in the quality and practices of different registries and hospitals, such as:

- differences in how well registries record and collect complete follow-up data on all patients with cancer
- how tumours are defined and recorded
- how complete data is on the date of diagnosis.

(Woodman *et al* 2001; Berrino 2003)

In order to minimise these problems, a large range of data quality checks were carried out by Coleman *et al* (2011).

A separate issue is that, although this paper presents only differences in survival, there is a need to contextualise studies of survival with data on incidence and mortality (Beral and Peto 2010; Autier and Boniol 2011). Coleman *et al* (2011) have undertaken this work.

Finally, the time it takes to calculate survival is an issue – survival data refers to treatment in the years preceding and takes time to collect and analyse. The EUROCARE-4 studies cannot be used to judge recent performance of the NHS since they relate to patients diagnosed in the 1990s and very early in the following decade. Coleman *et al* (2011) provide the most up-to-date survival comparison. They used a well-established method called period analysis, which is also used to calculate life expectancy, to predict five-year survival for patients diagnosed between 2005 and 2007.

Despite these issues, there is robust evidence that England has worse survival rates than other comparable countries. Can we explain these differences? Although many epidemiological analyses put forward possible explanations for this – with varying degrees of evidence to support them – and several studies have looked in detail at one or a small number of possible factors, there is no comprehensive study of explanatory factors. The EUROCARE studies contain only a limited amount of data that could explain the differences identified. The ICBP aims to provide new data that will provide robust insights into what is driving the differences. Meantime, in the next section of this paper, we summarise a range of existing studies and offer some possible explanations for the differences.

Analysis: explaining international differences in cancer survival rates

To date, the major studies attempting to explain cancer survival differences have focused on four main areas:

- stage at diagnosis and diagnostic delay
- treatment factors
- patient factors, including age and co-morbidities
- tumour biology and physiological/biological factors.

These groups of factors are outlined in Figure 5 below. All these factors relate to and influence each other. For example, both stage at diagnosis and the presence of co-morbidities will affect whether patients can be treated with surgery.

Figure 5 Possible drivers of international variation in cancer survival

Stage at diagnosis and delay	**Treatment with curative intent**	**Patient factors**	**Tumour and physiological/ biological factors**
■ Stage at diagnosis ■ Patient delay ■ Doctor delay ■ System delay	■ Surgery ■ Radiotherapy ■ Cancer drugs ■ Co-ordination of treatment	■ Co-morbidity and fitness ■ Age ■ Health-related behaviours ■ Social and economic determinants of health	

Many studies have found evidence to suggest that combinations of some or all of these factors explain survival differences (Gatta *et al* 2000; Sant *et al* 2003). For example, a study comparing the management and survival of all patients with lung cancer diagnosed in 2000 in Teesside in England and Varese in Italy found significant differences in outcome: three-year survival in Teesside was half that in Varese (7 per cent versus 14 per cent) (Imperatori *et al* 2006). Researchers identified patient factors, stage at diagnosis and treatment factors as contributory causes to this difference in outcome. English patients were older and had significantly more risk factors, such as smoking, higher co-morbidity and poorer performance status. Fewer English patients were diagnosed with pathological proof, which is probably reflective of cancers being diagnosed at a later stage. The rate of potentially operable cancers was lower in Teesside; the actual surgery rate was less than one third of that in Varese (7 per cent compared to 24 per cent). This may reflect factors such as co-morbidity and poorer lung function and performance status, but it may also reflect differences in clinical decision-making and age bias.

Although these factors are inter-related, taking each group of factors in turn, it is possible to identify the extent of their role in explaining international survival differences. Each group of factors is explored using two fundamental questions:

- To what extent does the factor affect survival outcomes at population level?
- What evidence exists that the factor explains international differences in survival?

Future research planned through the ICBP is identified and will add to our understanding.

Stage at diagnosis and diagnostic delay

When a cancer is diagnosed it is given a particular 'stage' to denote how far it has developed, grown or spread. Cancer is a progressive disease, moving from early to more advanced stages over time, so the stage at diagnosis is related to survival. Table 2 below shows how five-year survival rates vary by stage for several cancers.

Table 2 Five-year survival by stage for colorectal, breast, lung, melanoma and prostate cancer

Cancer type	Stage	Five-year survival (per cent)
Colorectal cancer	Stage A	93
	Stage B	77
	Stage C	47
	Stage D	7
	Unknown	25
Breast cancer	Stage I	90
	Stage II	70
	Stage III	50
	Stage IV	13
Lung cancer	Stage I	42
	Stage II	23
	Stage III	10
	Stage IV	2
	Unknown	5
Melanoma	Stage 1	97
	Stage 2	76
	Stage 3	58
	Stage 4	15
	Unknown	56
Prostate cancer	Localised	94
	Locally advanced and metastatic	28

Sources: data sourced from Department of Health 2010b; Cancer Research UK 2011c

Whether patients attend screening, or how quickly patients experience symptoms and seek help from the health system, and then how quickly they progress through primary and secondary care to diagnosis and treatment, are therefore logically important factors in determining outcomes.

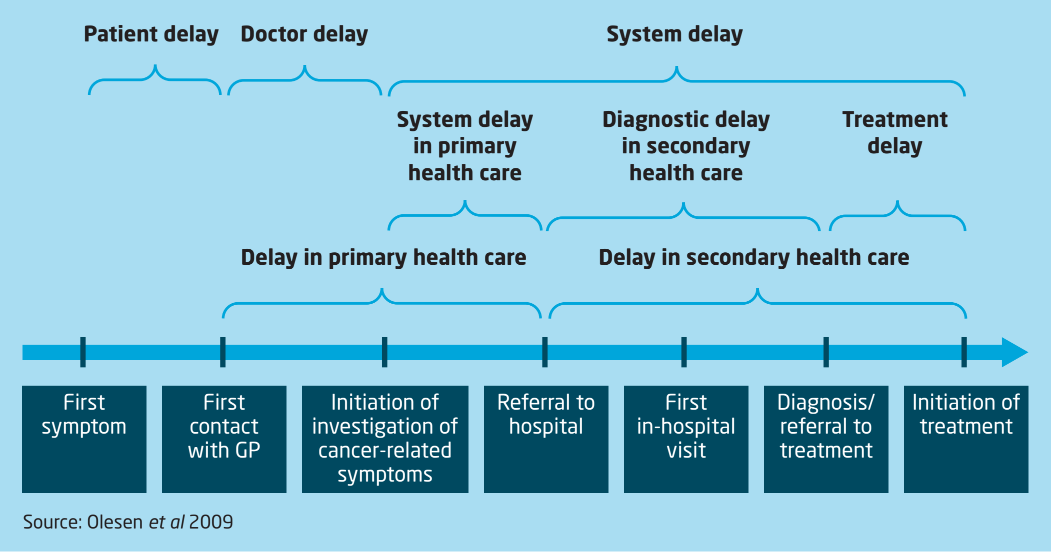
Cancers detected through screening

Outcomes can be improved for cancers that can be detected through screening by implementing high-quality screening programmes that have a good uptake and cover large numbers of the population (Barratt *et al* 2002). Breast, cervical and bowel cancers have national screening programmes that help detect cancers early and, in some cases, detect early changes that could go on to become cancer. In 2007, the breast screening programme detected 21 per cent of all breast cancers diagnosed that year and the cervical cancer screening programme detected 14 per cent of all cervical cancers (National Cancer Intelligence Network 2010b). Patients diagnosed through screening have better overall outcomes than those diagnosed through other routes (National Cancer Intelligence Network 2010b). International comparisons of cancer screening generally indicate that England has high-quality cancer screening programmes; however, there is considerable regional variation in screening uptake (Weller and Campbell 2009).

Cancers detected as a result of symptoms

A team of researchers in Denmark looking into delay in the diagnosis and treatment of cancers producing symptoms developed a categorisation of delay (see Figure 6).

Figure 6 Categorisation of delay



Source: Olesen *et al* 2009

Patient delay occurs if patients do not recognise signs and symptoms of cancer as suspicious or they do but delay seeking help from a health professional. Doctor delay occurs if there are delays in recognising potential cancer-related symptoms, investigating them and referring the patient on for specialist assessment. System delays occur if there are unnecessary waits for investigation or assessment and between the decision to treat and the time that treatment starts.

Evidence of the effect of delay on outcomes is strongest for breast cancer (Richards *et al* 1999; Neal 2009). However, other have found no relationship or even an inverse relationship (Richards *et al* 1999; Skaug *et al* 2011; Thompson *et al* 2011; Terhaar sive Droste *et al* 2010; Brazda *et al* 2010).

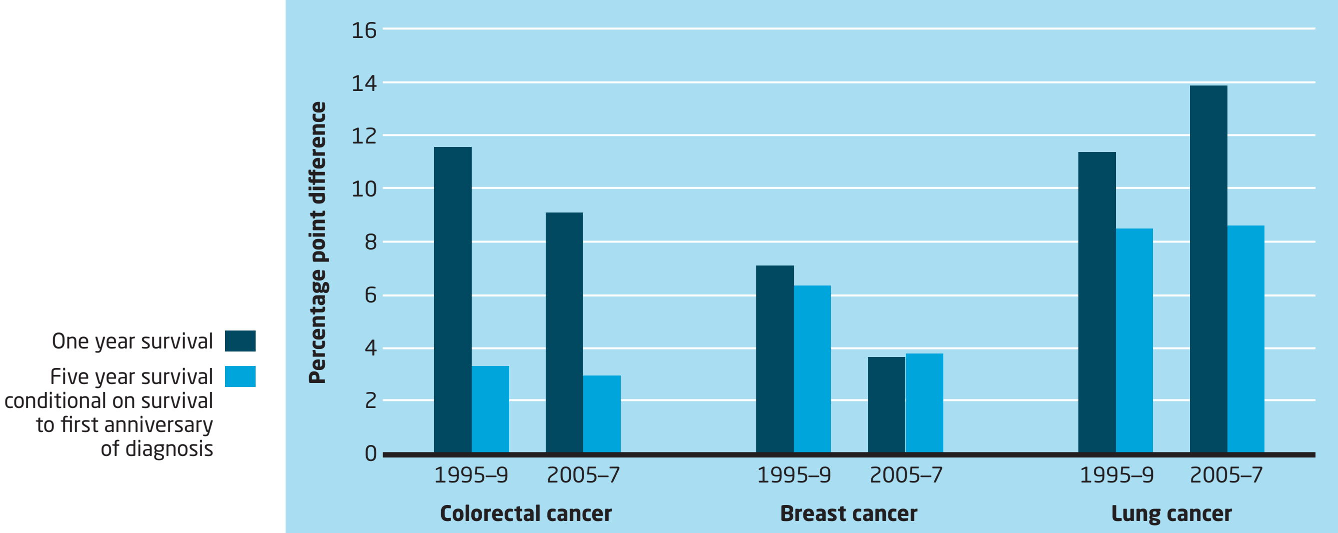
Cancer is a progressive disease, so presumably delays can affect outcomes. However, there is a lack of extensive, unambiguous evidence that this is the case. This may be due to a genuinely weak relationship between delay and survival in at least some relatively slow-progressing cancers. However, Neal (2009) and others suggest it is due to the many methodological challenges that affect research on delays, such as:

- variations between studies of definitions of different time periods in the cancer pathway
- variations between studies of methods of measuring delay
- variations between studies of measures of outcome
- an inability to apply the findings of one cancer to others due to the different behaviours of different cancers
- some patients presenting with obvious severe symptoms and who are extremely ill, so the GP refers quickly but is unable to save the patient, resulting in a poor outcome. Including these patients in crude overall analyses of the relationship between delay and outcomes can result in researchers falsely finding a weak relationship.

There is strong evidence that stage at diagnosis and delay in accessing care explain some of the difference between England and other countries. Some of this evidence comes from epidemiological studies that show that survival differences between England/UK and other countries tend to be greatest in the period up to a year after diagnosis (Coleman *et al* 2011; Coleman 1999; Thomson and Forman 2009; Gatta *et al* 2000; Holmberg *et al* 2010). For example, one study that compared survival rates for all cancers in the UK with those in the Nordic countries showed that the UK's one-year survival rates are 10.8 per cent lower. When comparing patients who were not diagnosed late by excluding those people who die within a year, the UK's five-year rates were only 3.6 per cent lower. This suggests that late diagnosis could explain much of the overall difference (Sant *et al* 2009; Møller *et al* 2009). Recent ICBP analysis also demonstrates this.

Figure 7 below compares one-year survival and conditional five-year survival in England and Sweden in the mid 1990s and a decade later. It shows less of a survival difference for colorectal and lung cancer for five-year survival, conditional on survival to the first anniversary of diagnosis, than for one-year survival.

Figure 7 Differences in one-year survival and five-year survival conditional on survival to the first anniversary of diagnosis between England and Sweden, 1995–7 and 2005–7, colorectal, breast and lung



Source: data sourced from Coleman *et al* 2011

These studies did not explore the stage of cancer, but several studies that have included this information found countries with poorer survival rates had more late-stage cancers (Folkesson *et al* 2009; Ciccolallo *et al* 2005). Registry-based studies about stages of cancer that have not found a link between stage and survival differences often acknowledge that the stage data may have been unreliable (Samson *et al* 2009; Woods *et al* 2009). A future ICBP study will look in detail at the stage data available from registries.

Some studies have taken the analysis of stage differences further and have looked into patients' clinical records. They have collected precise or proxy stage data and have sometimes included other variables, such as resection rates for surgery and other treatment information. Studies in colorectal cancer (Gatta *et al* 2000), breast cancer (Sant *et al* 2003; Jensen *et al* 2004) and gastric cancer (Bouvier *et al* 2010) have found a significant correlation between stage of cancer and survival. All studies found that the stage data was not as thorough as it could be and that unexplained variation remained, despite allowing for stage. This suggests that other factors also play a role, so the ICBP will add data from clinical records to the registry data already collected to undertake further analysis.

International comparisons of time intervals would help to determine if differences in diagnostic delay contribute to international survival differences. Evidence of long delays and late presentation exists in countries with relatively poor survival rates as well as better-performing countries, such as Sweden (Lövgren *et al* 2008) and the USA (*The Lancet* 2010). The ICBP hopes to address this knowledge gap by measuring time intervals to diagnosis and treatment in a number of countries.

It is important to explore what factors influence the patient, doctor and system delays that explain some of the international differences in survival. Studies have identified a range of delay factors, many of which were recently presented in a report of two worldwide systematic reviews of the evidence that included GP surveys, patient surveys, practice case studies and audits, cohort studies and reviews (Macleod *et al* 2009). Although defined differently in different studies, many of these factors are inter-related and are loosely grouped in the box overleaf. All of these factors have underlying causes and some fall within the control of individual patients and GPs and some do not.

The contribution of each of these different factors to overall delay is currently unclear and there are very few international comparisons of these factors. In terms of doctor delay, one study failed to find significant differences in the referral decisions of GPs between countries (Jiwa *et al* 2008). Two ICBP studies will further investigate international differences in public awareness and beliefs about cancer and international differences in GP attitudes, decision-making and primary care systems.

Factors found to influence delay in the diagnosis of cancers producing symptoms

Patient factors: Age, gender, socio-economic status, education, ethnicity and patients' attitudes and beliefs about cancer and cancer symptoms (Macleod *et al* 2009; Waller *et al* 2009).

Presentation complexity: Confounding effects of existing disease and co-morbidity (Macdonald *et al* 2006; Bjerager *et al* 2006), atypical presentations (Mitchell *et al* 2009) and patients presenting multiple problems in short GP consultations (Jiwa *et al* 2004).

Multiple presentation: Failure to link previous presentations together or lack of continuity of care (Mitchell *et al* 2009).

Knowledge: Lack of physician exposure to the malignancy, lack of knowledge of associated signs and symptoms and failure to follow referral guidelines (Abel *et al* 2008; Bird 2002; Daly and Collins 2007; Mitchell *et al* 2009).

Examination: Inadequate examination (Mitchell *et al* 2008; Weingart *et al* 2009) and reliance on patient symptoms to prompt referral as opposed to signs and screening (Abel *et al* 2008).

Misdiagnosis: Failure to consider cancer in the differential diagnosis, diagnosis other than cancer given and treatment for non-cancer causes (Macdonald *et al* 2006; Mitchell *et al* 2008; Evans *et al* 2007; Mitchell *et al* 2009).

Investigation: Inaccurate investigations, poor application and interpretation of tests, long waiting times for investigations, lack of direct GP access to investigations and non-investigation of symptoms (Mitchell *et al* 2008; Macdonald *et al* 2006; Bjerager *et al* 2006; Daly and Collins 2007 ; Evans *et al* 2007; Barrett *et al* 2006; Trickett *et al* 2004; Mitchell *et al* 2009).

Follow up: Failure to follow up the patient in a timely manner or lack of an explicit follow-up appointment (Bird 2002; Bjerager *et al* 2006; Evans *et al* 2007; Mitchell *et al* 2009).

Referral guidelines: Failure to follow referral guidelines (Webb and Khanna 2006; Flashman *et al* 2004; Duvvi *et al* 2006; Chohan *et al* 2005; Mitchell *et al* 2008) or inaccuracy of the guidelines themselves (Allgar and Neal 2006; Khattak *et al* 2006; McKie *et al* 2008; Eccersley *et al* 2003).

Co-ordination with secondary care: Poor communication with hospital services (Daly and Collins 2007; Mitchell *et al* 2009).

(Source: adapted from Foot *et al* 2010)

Treatment factors

Differences in outcomes may be attributable to differences in the proportion of patients treated with the intention of a cure and the effectiveness of the treatment provided. Treatment factors can be divided into four main groups:

- surgery
- radiotherapy
- cancer drugs
- overall co-ordination of treatment.

Surgery

Surgery is the main cancer treatment for solid tumours. Use of surgery to treat breast and colorectal cancer has been shown to vary significantly between European countries and appears to be linked to differences in survival (Allemani *et al* 2010; Gatta *et al* 2010). A study comparing lung cancer outcomes in Scotland and British Columbia found that surgery was performed nearly twice as often in British Columbia than Scotland, and that this may explain survival differences (Erridge *et al* 2009). A European study of the quality of surgery for gastric cancers (as measured by the 30-day post-operative mortality rate) found that, although quality of surgery provided a limited explanation for five-year survival differences, the age of the patients and the stage at diagnosis were more significant factors (Lepage *et al* 2010).

However, it is important to understand whether variation in treatment is clinically justified. Different rates of surgery may be related to a range of other factors, such as lifestyle differences, prevalence of co-morbidities, population genetics or cancer biology (Woods *et al* 2009; Imperatori *et al* 2006; Erridge *et al* 2009; Holmberg *et al* 2010).

Some studies have tried to explore the degree to which differences in surgery rates are necessary differences due to co-morbidities or differences due to other factors, such as age bias or different clinician attitudes. The issue of co-morbidities and age bias is covered later in this paper. One study surveyed cancer clinicians from four European countries with different survival rates (Connolly *et al* 2003), but did not find significant differences in how aggressive cancer specialists and surgeons were in treating lung cancer.

There is a substantial literature for several types of cancer and other conditions supporting the case for treatment in centralised specialist centres, particularly for complex surgery (Chowdhury *et al* 2007). Improved outcomes may be due to:

- better training of surgeons
- a higher caseload per surgeon leading to surgeons developing greater experience and expertise
- the availability of specialist support, such as nursing and intensive care
- superior equipment in large hospitals.

On balance, the weight of evidence suggests that larger units are more likely to produce better outcomes than smaller ones. However, systematic reviews of this literature are sometimes cautious about drawing clear conclusions because many of the studies suffer from methodological problems and definitions of outcomes vary (Monash Institute of Health Services Research 2006).

Very few studies involve international comparisons of the degree of specialisation. One comparison between the Nordic countries and Scotland found survival from rectal cancer to be lower in Denmark, Finland and Iceland than in Norway, Sweden and Scotland and suggested that the relatively large number of centres involved in treating rectal cancer in Denmark at the time may have resulted in lower-quality surgery and less use of radiotherapy (Folkesson *et al* 2009).

Overall, it is not clear from the available evidence whether the observed treatment differences between England and other countries are due to under treatment. However, large variations in treatment rates within England do exist. For example, the most recent National Lung Cancer Audit found the rate of surgery was four times higher in some parts of the country than others (NHS Information Centre 2009). This suggests there is scope to improve outcomes by increasing treatment rates in those parts of the country where they are low (National Cancer Intelligence Network 2011). However, as noted earlier, these low rates may be partly explained by differences in co-morbidity and other patient factors, so the precise scope for improvement remains unclear. Further work from the ICBP will collect information on treatment differences between countries.

Radiotherapy

Radiotherapy is shown in clinical trials to have a significant, if relatively modest, overall impact on five-year mortality rates (Early Breast Cancer Trialists' Collaborative Group 2005). The optimal proportion of patients with cancer that should receive radiotherapy will vary by tumour type and stage, but overall it is generally thought to be around 52 per cent (Delaney *et al* 2005). In 2005, the radiotherapy access rate in England was only 38.2 per cent (Williams *et al* 2007), so there is scope to improve outcomes by increasing access to radiotherapy. Considerable work is underway to increase England's radiotherapy capacity and expand the use of complex radiotherapy treatments (Department of Health 2007). This shortfall in radiotherapy is not unique to England and is also a problem in some high-survival countries, such as Australia (Delaney *et al* 2005) and Canada (CPAC 2010), while radiotherapy access rates are closer to the optimal rate in Sweden (Lindholm *et al* 2003). There is limited evidence to explain the role of radiotherapy in international differences in outcomes, but the ICBP is working on treatment differences between countries and will provide new evidence.

Cancer drugs

New cancer drugs have contributed to improving outcomes for many cancers, including breast cancer, many childhood cancers, testicular cancer and Hodgkin's disease. However, there is evidence of international variation in cancer drug usage. A recent report for the Department of Health found that the UK's uptake of some cancer drugs was low. Usage of recently launched cancer drugs was less than half the international average, but use of hormonal agents, such as the breast cancer drugs tamoxifen and anastrozole, was high (Richards 2010).

It is not certain whether or how these international differences in drug use can explain differences in survival rates. Two successive reports from the Karolinska Institute in Sweden have examined cancer survival and mortality across 19 countries in Europe in the light of availability of cancer drugs. The reports concluded that access to new drugs was linked to survival (Wilking and Jönsson 2005; Jönsson and Wilking 2007). However, these studies have been criticised for over-estimating relative survival and using drug data from a more recent period that the cancer outcomes data (Coleman 2007).

The evidence from clinical trials on the impact of cancer drugs on survival in Australia and the USA for 22 adult cancers found that the overall contribution of chemotherapy to five-year survival was just over 2 per cent (Morgan *et al* 2004). This suggests access to drugs is unlikely to be sufficient to explain the observed international survival differences.

Overall co-ordination of treatment

There is some evidence of the importance of co-ordinating the complex clinical pathways involved in treating cancer. For example, Coory and colleagues (2008) have demonstrated a link between the use of multidisciplinary teams and improved survival in lung cancer. It has been a focus of cancer policy for many years to expand the use of multidisciplinary teams (Department of Health 2000). However, research showing the effectiveness of multidisciplinary team work is relatively scarce (Fleissig *et al* 2006) and comparisons between countries of the existence or effectiveness of overall co-ordination are lacking.

Patient factors

Patient factors can be divided into four main groups:

- co-morbidity and fitness
- age
- health-related behaviours
- wider social and economic determinants of health.

These factors are not entirely independent. For example, a patient's health-related behaviours can be influenced by their socio-economic status and co-morbidities.

Co-morbidity and fitness

Co-morbidities and fitness can affect the treatment decision for any given patient. A study by Tetsche *et al* (2008) found one-year and five-year mortality among those with severe co-morbidity was twice as high as those without, even after adjustment for stage of cancer.

Studies of specific co-morbidities have established significant links with cancer outcomes (Extermann 2007; Nakai *et al* 2010). For example, one study found an 11 per cent survival difference between diabetics and non-diabetics treated for colon cancer (Meyerhardt *et al* 2003). Another study found that patients with chronic obstructive pulmonary disease who developed colon, rectal, larynx, prostate or bladder cancer fared significantly worse than patients without it (Van de Schans *et al* 2007). Similarly, Janssen-Heijnen *et al* (2007) found that patients with reduced pulmonary function, cardiovascular disease or neurological co-morbidity who were treated with resection of colorectal cancer, had higher post-operative morbidity and mortality. However, co-morbidity had a negligible effect on outcome once the findings were adjusted for age, stage of cancer and treatment modality.

Studies on the impact of co-morbidity on the decision to treat were inconclusive. Free *et al* (2007) found that 46 per cent of 204 patients with non-small-cell lung carcinoma (stages I–IIIA) were not treated with a view to curing the cancer because of poor lung function, other co-morbidities or advanced age. Similarly, a study of patients with stage III colon cancer showed those with high co-morbidity were less likely to be offered chemotherapy (Sarfati *et al* 2009). However, Loconte *et al* (2009) found that age and co-morbidity were not limiting factors in the application of chemotherapy, but they note that this may reflect patient selection bias. Houterman *et al* (2004) also found that treatment of patients with breast cancer was not affected by co-morbidity; however the chance of a successful outcome was lower for a patient with co-morbidities than for a patient without.

It is unclear how important co-morbidities are when considering international differences in survival. Variations in treatment rates are considerable within and between countries, but existing data do not demonstrate how much of a role co-morbidities or other factors have played in this. No systematic or large-scale study of the extent of variation in co-morbidity or fitness in patients with cancer appears to exist for different countries or areas. The comparative study of lung cancer in Teesside and Varese discussed above (Imperatori *et al* 2006) found that the proportion of potentially operable early-stage cancers was significantly greater in Teesside, but that surgery was significantly more common in Varese. This suggests that, although surgery might be possible, co-morbidity and poor fitness limit surgery more frequently in the UK than in Italy. Co-morbidity and performance status information will be gathered as part of two future ICBP studies.

Age

Cancer survival decreases with age (National Cancer Intelligence Network 2010a). Although incidence of co-morbidities tends to be higher with age, it has been shown that they are independent factors. Therefore, age alone should not be grounds for not undertaking treatment with a view to a cure (Blanco *et al* 2008).

There is substantial evidence that older patients are under-treated (Enger *et al* 2006) and that their outcomes are poorer as a result (Bouchardy *et al* 2007). Several studies suggest that differences in treatment partly explain poorer survival in older people with lung cancer (Peake *et al* 2003) and breast cancer (Wishart *et al* 2010). Even when corrected for tumour characteristics and co-morbidities, studies indicate that older people are less likely to receive intensive investigation and treatment and are more likely to be admitted as emergencies (Turner *et al* 1999; Lavelle *et al* 2007; Raine *et al* 2010). A recent report from the National Cancer Intelligence Network (2011) showed that the proportion of older people receiving radical surgery for cancer was substantially lower than younger people.

Delays in primary care referral may also be a factor; for example, in relation to ovarian cancer (Tate *et al* 2010). Patient delay may also play a part – older women have been found to wait longer before presenting with symptoms of breast cancer (Forbes and Ramirez 2010).

Importantly, major international survival comparisons have found that differences in survival between the UK and other countries were greater for older people (Coleman *et al* 2011; Berrino *et al* 2007; Woods *et al* 2009). Why older people in England should fare comparatively worse than older people in some other countries is not clear. This may be due to late presentation, more extensive co-morbidities or age bias leading to under treatment.

Health-related behaviours

It is well established that the incidence of cancer is related to such factors as smoking, obesity, alcohol intake, diet and physical activity. There is also evidence that successful outcomes can be influenced by the same factors, particularly activity and diet. For example, several studies of colon cancer have compared the survival chances of inactive patients with those undertaking moderate physical activity and identified that those patients engaged in moderate physical activity had a significantly better chance of survival (Meyerhardt *et al* 2006; Holick *et al* 2008; Holmes *et al* 2005). This could be explained by the reduction in body fat and insulin values (Irwin 2009; Barnett *et al* 2008; Goodwin *et al* 2010).

A number of studies have found a link between diet and cancer outcomes. Chlebowski *et al* (2006) found that when patients with breast cancer reduced their dietary fat intake there was a 24 per cent reduction in the risk of recurrence. Thomson and Thompson (2009) concluded that a low-fat high-vegetable diet may be beneficial, but that the results from different studies are not consistent. It may be that the benefits of dietary change are confined to some sub-groups (Pierce 2009).

It is not clear how much emphasis should be placed on these results. Kellen *et al* (2009) concluded that 'lifestyle changes [including physical activity, weight control, and diet] following standard breast cancer are highly recommended', but noted that the scientific evidence remained weak. Vrieling and Kampman (2010) found some indications of a relationship between body mass, activity, diet and outcomes, but concluded that the existing studies did not provide clear evidence of the scale of any impact.

There is no indication of any studies comparing the health-related behaviours of patients with cancer in different countries to explain international survival differences.

Wider social and economic determinants of health

There is substantial evidence from England and many other countries that the incidence of cancer and the chances of successful treatment are related to socio-economic status (Woods *et al* 2006). Studies suggest there are a range of possible factors that underlie these socio-economic inequalities in cancer, including tumour types, tumour aggressiveness, stage at diagnosis, prevalence of co-morbidity, psychosocial factors, screening uptake, access to care and treatment differences (Woods *et al* 2006; Harris *et al* 2009; Raine *et al* 2010).

Among deprived groups, screening uptake is lower (Baker and Middleton 2003; von Wagner *et al* 2009) and there is a tendency for later presentation for some cancers (Macleod *et al* 2009). There is also evidence that people from deprived groups are less likely to receive active or radical treatment and more likely to be admitted as emergencies (Downing *et al* 2007; Crawford *et al* 2009; Raine *et al* 2010). A number of English studies confirm that those in the lower socio-economic or educational groups often experience poorer access to treatment (Sloggett *et al* 2007; Lyratzopolous *et al* 2010; Crawford *et al* 2009; Raine *et al* 2010). Some research suggests that if access to treatment is equal, such as during clinical trials when all patients are given equal standardised treatment, the socio-economic gradient disappears (Nur *et al* 2008; Herndon *et al* 2008; Spilsbury *et al* 2005).

Can differences in the deprivation or the management of people from deprived groups help to explain international differences in survival? A socio-economic gradient in cancer outcomes is evident even in countries with good overall outcomes and a longstanding commitment to equality of access, such as Sweden (Berglund *et al* 2010; Halmin *et al* 2008; Eaker *et al* 2008), Australia (Yu *et al* 2004) and Finland (Pokhrel *et al* 2010). However, the comparison of breast cancer survival rates among different socio-economic groups in England and Australia showed that there was a smaller differentiation between socio-economic groups in Australia than in England (Woods *et al* 2009). This suggests that a wider gap in outcomes between socio-economic groups in England may be contributing to poor cancer survival rates, although research in this area is lacking.

Tumour biology and physiological/biological factors

As understanding of malignancy has grown, it has become apparent that cancers vary considerably beyond their organ of origin and any given broad tumour type may take different forms, require different treatments and offer different chances of success. A number of studies have identified links between outcomes and specific gene variations, suggesting that different genetic sub-types could potentially explain differences in outcome (Baker *et al* 2010; Lawson *et al* 2010). A recent study in breast cancer (Blows *et al* 2010) concluded that six sub-types showed 'distinct behaviours with important differences in short term and long term prognosis'. In a commentary on these findings, Ambs (2010) concluded that the survival patterns observed were independent of any systemic therapy, 'suggesting that tumour biology and molecular heterogeneity within breast cancer sub-types rather than the choice of therapy determined … survival trends'.

However, there is only very limited evidence to suggest that there might be international differences. For example, Christensen *et al* (2004) compared patients with breast cancer in Denmark and Sweden and found differences in the types of tumours in the two countries, but did not estimate the possible impact of this on outcome differences. Bennett *et al* (2008) found changes over time in the proportion of histological sub-types of lung cancer in England, but state that the trend and the distribution is similar to other European populations and argue that tumour differences could account for only a small proportion of differences in outcome.

Conclusion

This brief review of the evidence has shown the complexity of determining what drives international differences in cancer outcomes; it is likely that all steps in the cancer pathway contribute to some extent to these differences. Although various studies suggest some factors explain the differences they find, there are no national or international comparisons of all the potential factors presented in Figure 5 (see p 7).

For some cancers there is good evidence to suggest that English patients are diagnosed at a later stage than in other countries, though the reasons are not yet fully understood. Many of the factors that lead to delay are not unique to this country and, to date, there are no international comparative studies that show why they are more significant in England. A focus on diagnosing more cancers at an earlier stage is therefore extremely important.

Eliminating delay for patients with cancer would help England improve comparative performance, but would not remove all the observed differences between England and higher-performing countries (Department of Health 2010b). Lower treatment rates in the UK and variations within England suggest there is also scope for improving outcomes through improving access to surgery and radiotherapy. Accessibility of drugs is unlikely to have a significant overall effect.

Understanding why international survival differences are greater for older people is an important priority. Co-morbidities, physical fitness, late presentation, delayed diagnosis and access to treatment, especially surgery, all contribute to the relatively poor survival of older people.

A number of other factors, such as co-morbidities, health inequalities, health-related behaviour and tumour characteristics, have also been shown to affect survival. These could contribute to an explanation of the observed differences, but comparative data are not available to estimate the scale of the possible impact of these issues.

Recommendations

The government has recognised that English cancer survival rates lag behind the best-performing countries in the world and is committed to take action to improve them. One-year and five-year cancer survival have been identified as areas for improvement in the NHS Outcomes Framework (Department of Health 2010a) and the cancer strategy commits to saving an additional 5,000 lives by 2015 (Department of Health 2011). This paper has reviewed the evidence and particularly identifies as priorities earlier stage diagnosis, access to surgery and radiotherapy and the management of cancer in older people.

Earlier stage diagnosis

Efforts to diagnose cancer at an earlier stage are particularly important and this has been recognised in the cancer strategy (Department of Health 2011). The National Commissioning Board and Public Health England will need to work closely and effectively together to co-ordinate and oversee initiatives to improve earlier diagnosis, as will GP consortia and health and wellbeing boards at a local level.

There is a continued need for sustained efforts to encourage people to take up their invitation for cancer screening, particularly among groups with typically low uptake (Weller and Campbell 2009).

It is beyond the scope of this paper to comprehensively review the evidence to improve earlier stage diagnosis of cancers producing symptoms. Ongoing research by the National

Awareness and Early Diagnosis Initiative and the ICBP continue to add to this evidence base. However, it is possible to briefly consider the priorities to tackle patient delay, doctor delay and system delay.

A survey tool called the Cancer Awareness Measure was recently developed and validated to monitor public awareness and attitudes about cancer. It will be important for GP consortia and health and wellbeing boards to use this survey tool. A recent systematic review of how to improve awareness and promote earlier presentation found few evidence-based interventions, but noted that many interventions were in development (Austoker *et al* 2009). Therefore, future research to determine effective interventions will be very important. The government is running pilots of social marketing campaigns to encourage people to see their GP if they experience certain symptoms (Department of Health 2011). It is important that these pilots are evaluated as robustly as possible and that further roll out is encouraged where they are proven to be effective.

Looking next at delay by doctors, the challenge of where and how to achieve more timely diagnosis is a considerable one. A GP will see only a handful of new cancers in any one year and may go many years, or indeed a lifetime, without seeing certain rare cancers. The vast majority of cancers are identified because the patient has been experiencing symptoms. However, most patients present with evolutionary and undifferentiated symptoms that are much more likely to be interpreted as something other than cancer. A number of initiatives may be useful, several of which are being taken forward by the government.

- Further refinement of referral guidelines for suspected cancer in primary care, using the best evidence to determine alarming symptoms.
- Significant event audits of cancer diagnoses in general practice, so that practices can reflect and learn from their experiences.
- Providing GPs with information about their performance relative to others, such as their use of the fast-track cancer referral pathway and diagnostic tests.
- Ensuring practices have good systems for getting test results quickly and recalling patients for follow-up appointments.
- Improving GPs' direct access to diagnostic tests for cancer, such as blood tests, x-rays, ultrasound and CT and MRI scans.
- Improving communication between primary and secondary care, so that GPs can access advice from specialist colleagues when needed.

With increasing financial pressures on the NHS, commissioners will need to avoid blanket efforts to reduce referrals from primary care; previous research from The King's Fund (Naylor and Imison 2010) has already identified that this is happening. Such efforts risk damaging attempts to diagnose more cancers at an earlier stage.

Our primary care system is often referred to as a 'gatekeeper' system; patients are triaged, over-treatment is avoided and over-use of hospital services is avoided. Although this primary care model ensures patients requiring chronic disease management are treated in the community whenever possible, it may also result in longer time intervals to diagnosis for some patients with cancer, particularly those with vague or low-risk symptoms.

Access to surgery and radiotherapy

It is more important to improve access to surgery and radiotherapy than access to cancer drugs. In terms of overall allocation of resources, this suggests that the contribution of the Cancer Drugs Fund to improving overall outcomes will be very limited. As discussed, there is significant variation across England in the numbers of patients receiving surgery and radiotherapy, and in the use of the most up-to-date techniques. Royal colleges and professional associations, alongside commissioners and providers, could support surgeons and clinical oncologists to:

- collect, review and publish performance data to understand how their practice differs from others
- support the roll-out of new techniques and technologies.

As acknowledged by the government in 2007, continued investment is needed to increase England's radiotherapy capacity (Department of Health 2007).

Management of cancer in older people

Researchers, policy-makers, commissioners, providers and patient groups will want to understand urgently the worse survival of older people in England, and what can be done about it. Evidence suggesting age bias in access to treatment should be investigated as a priority. The particular experience and needs of older people will need to be considered in any initiatives aiming to improve earlier stage diagnosis or access to treatment.

Health inequalities

While extensive evidence may be lacking that differences in socio-economic inequalities can explain international differences in survival rates, it is clear that people from more deprived groups tend to:

- have a higher incidence of cancer
- be diagnosed later
- have less treatment
- have poorer outcomes.

Tackling health inequalities in the wider social determinants of health, in smoking and obesity rates, and in earlier stage diagnosis and access to treatment are all likely to improve cancer outcomes.

Primary prevention and public health

Although this paper has focused on cancer survival, reducing the incidence of cancer is an important policy priority. Tobacco remains the single biggest lifestyle risk factor, responsible for nearly nine in ten lung cancers and many thousands of other cancer cases. Significant gains in reducing cancer incidence can be made by pursuing a comprehensive tobacco control strategy. Efforts to reduce obesity and tackle excessive alcohol consumption will also help reduce cancer incidence. Continued focus on improving the coverage and uptake of cancer screening will help prevent cancer and diagnose cancers early enough to allow them to be successfully treated.

Research and analysis

There is a clear need to continue research in all these areas, especially research into effective interventions for earlier stage diagnosis.

If we are to fully understand what needs to be done to improve England's cancer survival rates and monitor progress over time, continued investment in cancer registries and data analysis, including the National Cancer Intelligence Network, is essential. Local or regional research and analytical support will be crucial to focus GP consortia on what will maximise improvements in outcomes. Local and national clinical audits will remain important for monitoring performance.

Measurement and the outcomes frameworks

Although cancer survival is an important outcome, survival statistics do not tell us enough about the current performance of the NHS and are not useful to commissioners or the National Commissioning Board for monitoring immediate performance. Relevant proxy and intermediate measures will therefore need to be used on a more regular basis to monitor progress. Using the evidence of the above review, measurement could usefully include:

- incidence
- stage at diagnosis and treatment
- emergency presentations
- screening uptake
- use of the urgent referral pathway
- surgery and radiotherapy rates
- mortality.

While the NHS Outcomes Framework and Public Health Outcomes Framework can hold the health system to account for progress on outcomes, intermediate outcome and process measures will be more immediately useful to commissioners. Stratification wherever possible for age, socio-economic status and co-morbidities will be important. As stressed in the recent Public Accounts Committee report on cancer, improving the collection of stage data should also be a priority (House of Commons Committee of Public Accounts 2011).

Implications for other conditions

Cancer has been a focus area for national policy for over a decade. It benefits from extensive research funding, national investment in statistical analysis and intelligence and a considerable public and political profile, yet great opportunities for further improvement remain and complex questions about priorities to improve survival are still to be answered. Identifying and then implementing change to improve outcomes is complex and takes time. Similar analysis of outcome drivers should inform improvement priorities for other disease areas, both those already highlighted by the Outcomes Framework and those that are not.

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