

Chapter 7. GENERAL DISCUSSION

7.1 Main conclusions

Improvements in survival for breast, colorectal and prostate cancers, but not lung cancers, were seen at national scale between the earlier (1994-1997) and later (1998-2001) parts of the period examined. Improvements in treatment or in early diagnosis are presumably involved, but exaggeration of true survival improvements by lead-time bias cannot be ruled out, especially for prostate cancer.

Regional variation in survival is still apparent, as noted in our previous report (NicAmhlaoibh *et al.* 2004), with survival generally lowest for patients resident outside the Eastern region, except for lung cancer. This variation is partly but not wholly explained by variation in patient or tumour characteristics.

Trends in treatment appeared to be broadly in line with expectations of greater or better-targeted use of radiotherapy and chemotherapy, although no increase in radiotherapy use was seen for breast cancer. An apparent major fall in use of hormonal treatment for breast cancer may also be in line with expectations of improved targeting of appropriate treatment. This may also apply to increased use of hormone therapy and reduced use of surgery for prostate cancer.

At regional scales, there is still substantial variation in the use of particular treatment modalities. These variations are largely unexplained by patient and tumour characteristics, suggesting that geographic and institutional influences on treatment may be critical. Evidence of increased specialization or centralization of services is limited, although further analysis is required.

7.2 Cautions on use and interpretation of multivariate analyses

Analyses presented in this report are, in general terms, aimed at:

1. Identifying and quantifying differences in survival and treatment between years and regions.
2. Assessing if such differences can be 'explained' statistically by other patient and tumour characteristics, e.g. age, stage – i.e. are annual or regional differences still evident after adjustment for possible annual or regional variation in relevant patient and tumour characteristics?

However, the explanatory power of the analyses presented is potentially limited by a number of factors. These include:

1. Incomplete data for some variables.
2. Simplicity of assumptions, e.g. that the relationship between age and treatment, or stage and treatment, is similar in different regions or different years.
3. Related to the latter point, possible variation between patient groups in the 'meaning' of particular variable values. This includes the concept of 'stage migration', whereby patients diagnosed in more recent years (or in some hospitals) may be more likely to be assigned to a correct, higher category of stage because more thorough investigations are made.
4. Lack of information on other potentially relevant variables, e.g. reasons for non-treatment of some cases.

Standard statistical methods, e.g. logistic regression of treatment data, and Cox regression or other modelling of survival data, can only partly allow for such factors, for example:

1. By including missing variable values as 'unknown' (rather than blank). But the meaning of 'unknown' may vary between patient groups. Also, a high proportion of 'unknowns' among one patient group might statistically explain poorer treatment or survival, but might itself be an indicator of poor-quality investigation or care.
2. By introducing interaction terms between, or stratifying for, variables considered likely to have a complex inter-relationship. This can, however, produce over-complex models, and it may not be practicable to include or check for interaction terms for other than age and stage-related variables.
3. By including all potentially relevant available variables, in the hope that some of these may act as proxies for unmeasured factors. But there may be too many variables in the model, and variation in unmeasured factors may still be missed.

For regression-based comparisons of survival, a particular problem is posed by non-proportional hazards. This involves variables for which mortality differences between patient groups are not constant throughout follow-up. This can be allowed for statistically by either stratifying analyses if Cox regression is used or by introducing interaction terms for relevant variables if relative survival modelling is used (as in this report).

For some purposes, analyses adjusted for age and sex only may be the most informative, given the high proportion of 'unknown' data and uncertainty about the consistency of recording for most other variables. For assessment of regional variation and

of time-trends in treatment and survival, we have thus presented age-adjusted (and where relevant sex-adjusted) risk ratios and hazard ratios as the basic summary measures. In some respects, arguably, these are the most important measures.

For more complex models, dropping ‘unknown’ values was not a realistic option, as a high proportion of cases would have been excluded. Trends or regional differences based on only cases with high-quality data would be unlikely to be representative overall. But caution is obviously required in interpreting the results of models incorporating variables that may be substantially incomplete, or for which temporal or regional variation in coding is a possibility.

It is clear from the data analyzed here that lack of microscopic verification, or of information on stage or grade, tends to be associated with poor survival and lack of treatment of cancer patients. Inclusion of these variables in models of regional variation in survival or treatment may reduce (and in a statistical sense explain) some of the regional variation seen. However, such ‘explanation’ could imply under-investigation and resultant under-treatment, not necessarily related to patients’ fitness for treatment. Thus to say that survival among patients from region B is poor in part because microscopic verification levels there are below-average would not necessarily be an adequate ‘explanation’, as equivalent patients from a different region might have been investigated and treated more thoroughly.

In some instances, inclusion of further variables actually increased the apparent magnitude of regional or year effects. In some instances this may reflect unrecognized interactions between those variables and year or region, or interactions which models could not reasonably be expected to allow for. Inclusion of extra variables in a model can also have the effect of increasing the random ‘noise’ in the data, at the expense of clarity.

Further planned analyses will attempt to incorporate measures of patients’ condition or comorbidity (based on case-matching against hospital in-patient data from HIPE) and of patients’ socioeconomic status (area-based deprivation measures). These may provide further clues to observed regional variations in survival or treatment of Irish cancer patients. Interpretation may still be difficult. For example, general patient status, and relevant non-cancer conditions, may not be sufficiently well-documented in hospital records to explain why particular patients fared badly or did not receive particular treatments. When using deprivation measures, there is also the issue of whether variation in socioeconomic status ‘explains’ variation in survival or treatment in any

non-statistical sense. To some extent, socioeconomic status may provide a proxy for the general health or stage at diagnosis of patients. But there is also often an implication that patients of higher socioeconomic status are more likely to receive high-quality treatment. Inclusion of deprivation measures in a model might appear to reduce or ‘explain’ regional variations in survival or treatment, even though the underlying factor might be under-treatment of patients from poorer backgrounds.

7.3 Time-trends in relative survival

In general, results presented here show good evidence of improvements in relative survival for the more treatable cancers (breast, colorectal and prostate cancers) when comparing the 1994-97 and 1998-2001 diagnosis periods. But there was only limited evidence of improved survival for lung cancers, the most fatal of the cancers considered. Regionally, results for the other cancers were generally consistent with improvements. Apparent changes were not always statistically significant, in part reflecting small sample sizes at regional scales.

Possible changes in patient or tumour characteristics over time appeared to provide only a partial explanation of trends in survival. Improvements in treatment are likely to account, in part, for the survival improvements seen. But changes in unmeasured or poorly measured factors could also be involved.

For cancers amenable to earlier detection through screening (organized or unorganized), a further caveat is that increases in average survival time (from date of diagnosis) are not necessarily always associated with true reductions in mortality for those cancers. Earlier detection through screening is generally expected to improve outcomes as a result of cancer being detected, on average, at a less advanced and more treatable stage. There is currently good international evidence of this for breast and colorectal cancers but not for lung or prostate cancers (see *section 7.5*). Even for cancers where there is a proven or well-supported benefit of screening – as measured by actual reductions in cancer mortality rates – *lead-time bias* can exaggerate the benefits if average individual survival (rather than the population-based mortality rate) is measured.

There is good preliminary evidence (not presented here) that the introduction of the BreastCheck screening programme in some regions during 2000-01 is already producing a ‘stage-shift’ towards less advanced, more treatable breast cancers. However, lead-time bias alone will quite likely lead to substantial further improvements in apparent survival (for the age-range 50-64), before real

benefits in terms of mortality reductions become apparent. Within the period covered by this report, it is unlikely that such bias will have had any major influence. The survival improvements seen for breast cancer are thus likely to be largely genuine.

For prostate cancer, very marked improvements in apparent survival are already evident here, even in the absence of organized screening. Available data on tumour grade and other tumour and patient tumour characteristics do not seem to 'explain' the improvements very well. The coincidence of these improvements with very rapid recent increases in case-numbers (by on average 8% per year since 1994), suggests that lead-time bias is likely to be a substantial contributor. This seems to reflect widespread, albeit unorganized use of the Prostate Specific Antigen test for screening purposes. Real benefits of improvements in prostate cancer treatment – notably increased use of hormone therapy – may also be occurring.

7.4 Regional variation in relative survival

Regional variation was most evident from unadjusted data, and from basic multivariate models adjusted for age and sex only (plus cell-type for lung cancer). But the variation seen in the basic model is in one sense a 'true' measure of regional variation in cancer-related survival. This reflects or integrates variation in a range of relevant factors likely to influence survival, directly or indirectly. Such factors may include early detection, thoroughness of diagnostic and prognostic investigations, quality or appropriateness of treatment, and socioeconomic, marital and smoking status. Apart from age and sex (or perhaps even including age), it is arguable that regional disparities in all the important factors influencing survival are themselves part of wider societal disparities relevant to health.

Fuller adjustment for stage and other tumour and patient variables modified and, in general, substantially reduced regional discrepancies. In statistical terms, these variables appeared to 'explain' some of the differences. This applied particularly to prostate cancer, for which little regional variation was apparent in the full model – significantly higher excess mortality (lower relative survival) among patients from the Southern region only. For breast cancer, full adjustment reduced the number of regions with significantly low survival from seven to four (Midland, Southern, South-Eastern and Western regions). For colorectal cancer, survival was significantly low among patients from the Mid-Western, Southern and South-Eastern regions. In contrast, survival of lung cancer patients was significantly high among patients from three regions (Mid-Western, North-Western and Western), although absolute

differences were small for this high-fatality cancer.

In theory, after adjusting for available patient and tumour variables, the remaining variation should reflect variation in treatment or in unmeasured factors. But prognostic and demographic variables were often substantially incomplete, and may have been correlated with the quality of diagnostic or prognostic investigations. Unrecognized or over-complex interactions between variables may also cloud interpretation. Thus the full explanatory power of the models is difficult to assess. Even a 'perfect' model would require cautious interpretation as the factors adjusted for may be crucial influences on survival and may also merit action to reduce disparities.

It is worth noting that no region had significantly poorer survival for all four cancers. Patients from the Southern region did have significantly poorer survival than the reference Eastern region for breast, colorectal and prostate cancers during 1994-2001 as a whole. In the most recent diagnosis period, 1998-2001, only two of those cancers had significantly low survival in the Southern region (and also in the Mid-Western and South-Eastern regions).

7.5 Factors influencing survival

Factors relevant to assessment of regional and temporal survival patterns are discussed further below. These can be considered as potential explanatory factors accounting in part for the patterns seen, or as potential confounders for which adjustment may be needed in order to reveal patterns reflecting quality of treatment. However, the individual factors, and how they influence survival, may also be of interest in themselves.

Findings for the period 1994-2001 as a whole are summarized. Particular weight is given to results of multivariate analyses (also summarized in *Table 7.1*). For age, stage-related variables and tumour grade, multivariate results quoted refer mainly to the first year after diagnosis. This is because it was generally found necessary to allow for interactions between these variables and time after diagnosis, thus age-related and stage-related patterns could not readily be summarized beyond the first year. A number of factors (e.g. comorbidity) not examined in the present study are also discussed.

We have provided brief references to other published studies but have not attempted a detailed review, given the scale of the relevant literature. (see Gospodarowicz *et al.* 2001 for fuller details).

Early detection and screening; method of detection

As noted above, earlier detection, reflecting

organized screening, unorganized screening or other public health initiatives or trends, can be expected to result in improved survival. Some of the improvements are likely to be genuine, but lead-time bias may exaggerate the true benefits. Data on patient and tumour characteristics from this report are consistent with trends towards earlier detection for breast cancer, but there is little or no evidence of this for colorectal and lung cancers. For prostate cancer, the data are more difficult to interpret, but major increases in numbers of cases diagnosed among younger men, in particular, suggest that earlier detection is occurring. During 1994-2001, patients whose breast cancer was screen-detected cases had significantly better relative survival than symptomatically-presenting patients. This applied even after adjustment for other variables (including stage). Survival was also higher for screen-detected than for symptomatic cases of colorectal and prostate cancer. However, for prostate cancer this was not statistically significant after adjustment for other variables. Insufficient data were available for screen-detected lung cancers.

Lung and prostate cancers which presented incidentally, i.e. during examination for other conditions, were also significantly associated with higher survival (compared with symptomatic cases). In contrast, breast cancers which presented incidentally showed the opposite pattern. The reason for this discrepancy is unclear.

An earlier analysis of 1994-98 data (NicAmhlaibh *et al.* 2004) did not examine the influence of method of detection on survival, in part because the vast majority of cases were recorded as having presented symptomatically. In particular, the percentages of cases noted as screen-detected in that period were extremely small – 1.8% for breast, 0.6% for prostate and only 0.2% for colorectal and lung cancer. (Percentages screen-detected during 1994-2001 as a whole were 4.1% for breast, 1.0% for prostate and 0.3% for colorectal and lung cancer.)

Published studies aimed at assessing the benefits of screening broadly agree that properly-organized screening reduces mortality from breast cancer (see review by Vainio & Bianchini 2001). However, even based on results of screening trials, this conclusion is not universally accepted (Olsen & Gøtzsche 2001). For prostate cancer, the benefits of screening are much more controversial, with the general consensus being that there is not yet sufficient evidence that screening reduces mortality from this cancer (see *Box* below). Likewise, for lung cancer there is not yet sufficient evidence that screening saves lives. For colorectal cancer, however, there is good evidence that screening reduces cancer-specific mortality. Note that, for

proper evaluation of screening, the outcome measures assessed are mortality rates among screened compared with non-screened populations, not among patients whose cancers were screen-detected compared with other patients.

Screening for breast, colorectal, lung and prostate cancers

Evidence-based summaries are available as part of the US National Cancer Institute's PDQ Cancer Information Summaries:

(<http://www.cancer.gov/cancertopics/pdq/cancerdatabase>).

Brief extracts are provided below.

Breast cancer: "Based on fair evidence, screening mammography in women aged 40 to 70 years decreases breast cancer mortality. The benefit is higher for older women, in part because their breast cancer risk is higher."

Colorectal cancer: "Based on solid evidence, screening for colorectal cancer reduces colorectal cancer mortality, but there is little evidence that it reduces all cause mortality."

Lung cancer: "Based on fair evidence, screening does not reduce mortality from lung cancer."

Prostate cancer: "Using the PSA test to screen men for prostate cancer is controversial because it is not yet known if this test actually saves lives."

Treatment

Trends or regional variations in survival shown in this report are likely to reflect, in part, the provision of appropriate treatments aimed at a cure or at prolonging life. Explicitly or convincingly demonstrating this link is difficult, however, especially against a background of increased earlier detection for some cancers. One possible approach is to include treatment status within statistical models of survival. This has not been attempted here, in part because patients receiving and not receiving particular treatments are likely to differ in unmeasured characteristics e.g. their general health. Further analyses are planned, to take into account available information on comorbidity (other health conditions in the same patients).

Basic summaries of survival data, stratified by treatment status, are presented earlier in this report. As noted, the survival of treated and untreated patients is likely to reflect other differences between the patient groups involved, rather than their actual treatment. More generally, this caution applies to any attempts to assess the influence of treatment on survival, other than as part of a randomized clinical trial. To an extent, patients' receipt or non-receipt of a particular treatment might provide no more than a proxy variable for unmeasured factors influencing patients' suitability for that treatment. Standard treatment recommendations, stratified by relevant prognostic

or predictive factors, are primarily based on results of randomized trials (cf. *Appendix 1*).

Interactions between treatment and other variables potentially contribute to temporal, regional or wider geographic patterns in the survival of cancer patients. If treatment decisions are not always objectively evidence-based, for example if there are geographic biases in the treatment of older patients unrelated to other clinical factors, under-treatment may contribute to the survival patterns seen.

Age

For all four cancers, analyses unadjusted for other factors indicated significantly poorer relative survival among older patients. This is additional to underlying (non-cancer-related) age effects on survival. The pattern and strength of age-related variation varied between cancers. For lung cancer, there was significantly reduced survival for all patients aged 45 years or more, compared with age-group 15-44. For other cancers, lower survival was mainly evident for patients aged at least 65 or 75 years. Based on the first year after diagnosis, statistical models adjusted for other patient and tumour variables confirmed and provided further detail on these patterns. Significantly low relative survival (high excess mortality) was seen for lung cancer patients aged 45 or more (just over two-fold variation between the youngest and oldest age-groups); for breast and colorectal cancer patients aged 55 or more (three-fold variation between age-groups); and for prostate cancer patients aged 65 or more (three- or four-fold variation between age-groups).

In an earlier analysis of 1994-98 data for the same cancers (NicAmhlaoibh *et al.* 2004), multivariate models of cancer-specific survival were stratified by age, and age effects on survival were not reported for most cancers. However, lung cancer mortality in males was significantly higher in all age-groups over 50 years compared to the under-50 group, with about two-fold variation overall. This was similar to the pattern seen for relative survival during 1994-2001.

For breast cancer, Fitzgibbons (2001) noted a lack of consensus from published studies regarding the prognostic value of age. This reflected differences in study design and the potential confounding effects of factors such as differences in treatment of patients of different ages. Again, no clear prognostic role for age was noted for colorectal cancer by Hobday & Erlichman (2001) after adjustment for other prognostic factors, especially stage. For lung cancer, age was noted as a prognostic factor for non-small-cell carcinoma by Brundage & Mackillop (2001), but particularly in advanced cases. For prostate cancer, Denis &

Murphy (2001) noted that age was a “reliable prognostic factor ... for survival in patients with localized or advanced disease.”

Across a range of cancers, under-treatment and under-investigation of cancers in older patients have been noted as potential contributors to poorer average prognosis among older patients (O’Connell *et al.* 2001, Ng *et al.* 2005). However, it may not be straightforward to establish if this reflects a true bias against older patients, as opposed to reflecting age-related variation in other prognostic factors, especially if those are poorly quantified. For example, in Ireland older patients with lung cancer are less likely to receive treatment but Mahmud *et al.* (2003) considered that adequate adjustment for stage and comorbidity was not possible.

Cancers among younger age-groups are sometimes associated with poorer survival. We found only limited evidence of younger age being associated with poorer survival in this study, for breast and prostate cancers only. Very much the opposite was seen for lung cancer. For breast cancer, some but not all studies have found survival in younger women to be poorer than in older women, reflecting tumours that are more advanced, more aggressive or more likely to recur (Klauber-DeMore 2005-2006). For colorectal cancer, cancers in patients under 40 years of age tend to be more aggressive and to present at a later stage, although early-stage survival may be higher in younger patients (O’Connell *et al.* 2004).

Sex

Unadjusted analyses indicated significantly poorer five-year survival for male compared with female patients with lung cancer. This also appeared to be the case for colorectal cancer. Significant differences were confirmed by multivariate analyses, which estimated mortality risks among female patients as 8% lower for lung cancer and 6% lower for colorectal cancer.

An earlier multivariate analysis of 1994-98 data also noted significantly lower (cancer-specific) mortality among female patients with those cancers – 11% lower for lung cancer and 14% lower for surgically treated colorectal cancer (NicAmhlaoibh *et al.* 2004).

Female lung cancer patients are known from other studies to survive longer, on average, than male patients. Gritz *et al.* (2005) suggested that one factor involved may be smoking, given that, across studies, women consistently have a shorter history of tobacco exposure. Among patients with limited-stage small-cell lung cancer, however, Videtic *et al.* (2005) noted better survival in female than male patients, among both smokers and non-smokers.

For patients diagnosed with incurable cancer, a review by Hauser *et al.* (2006) noted that patients' gender was not associated with survival duration, except for longer survival of female lung cancer patients.

For colorectal cancer, Hobday & Erlichman (2001) did not consider gender a significant prognostic factor, after adjustment for other factors.

Tumour stage and grade

The T, N and M categories of stage were strongly associated with survival, both in univariate analyses and in analyses adjusted for other variables. Based on fully adjusted analyses covering the first year after diagnosis, the T category of stage was associated with a five-fold variation in excess mortality (between categories T1 and T4) for breast cancer, almost four-fold variation for colorectal cancer, and two-fold variation for lung and prostate cancers. Tumour involvement of regional nodes (N category) accounted for an approximate doubling of mortality risk for all four cancers. Most strikingly, distant metastatic involvement (M category) was associated with a ten-fold increased risk for breast cancer, eight-fold for prostate cancer, four-fold for colorectal cancer and two-fold for lung cancer.

Tumour grade is an important component of stage for prostate cancer, and accounted for almost a three-fold variation in mortality. Grade was also an important determinant of survival for breast and colorectal cancers (almost two-fold variation between lowest and highest categories), but had only a small influence on survival for lung cancer.

Overall stage, derived from a combination of T, N and M categories (plus grade for prostate cancer), was not included in statistical models. However, unadjusted analyses indicated substantially poorer survival for stage IV for breast, colorectal and prostate cancers, and stages III, IV and unknown for lung cancer.

Earlier analyses for these cancers during 1994-98 found broadly similar effects of stage and grade on cancer-specific survival (NicAmhlaoibh *et al.* 2004). However, most of the reported stage/grade effects cannot be directly compared between these studies, as the more recent figures mainly refer to the first year following diagnosis. In some instances, notably T category for breast cancer and M category for prostate cancer, this apparently accounts for more marked gradients in survival seen in the present analysis. The other patient and tumour variables included in multivariate analyses also differed somewhat between studies (see also *section 7.6* below).

A caution is also needed on comparisons between hazard ratios based on cause-specific mortality and those based on excess mortality assessed in relative survival terms. Both cause-specific and excess mortality risks aim to measure the 'extra' mortality risk associated with a cancer diagnosis, modified by other variables. However, cause-specific mortality is based on the cause of death attributed for death-certification purposes, thus is potentially open to error. If the severity (e.g. stage) of a cancer influences the likelihood of a patient's death being attributed to their cancer, over and above 'real' effects on mortality risk, hazard ratios assessed by cause-specific analyses could be biased. Further exploration of the data analyzed here, running cause-specific and relative survival analyses on the same data and adjusted for the same variables, might help identify such biases.

Tumour morphology (cell-type)

For breast cancer, carcinomas and cancers of unspecified type were associated with higher mortality risk (2.5-fold higher for non-specific cancer compared with breast-specific adenocarcinoma morphologies). Variation between the other, specific cell-types was comparatively minor, and not statistically significant after adjustment for other variables. An earlier, cause-specific analysis of 1994-98 data (NicAmhlaoibh *et al.* 2004) was stratified by tumour morphology but did not present hazard ratios by cell-type.

Fitzgibbons (2001) noted that "special-type" carcinomas of the breast – including tubular, mucinous, medullary and papillary carcinomas – had a more favourable prognosis, overall or adjusted for stage, than ductal and lobular carcinomas. We did not explicitly examine this but we found no significant survival difference between "other specified carcinoma types" (including papillary and medullary carcinomas) and ductal or lobular adenocarcinomas.

For lung cancer, the fully adjusted mortality risk was 1.4 times higher for cancers of unspecified or rarer cell-types, compared with non-small-cell carcinomas. Unadjusted relative survival was about twice as high for non-small-cell as for non-small-cell carcinomas, but the difference was not significant after adjustment for other variables including stage. The earlier analysis did not report adjusted hazard ratios by cell-type, but unadjusted survival at five years was, again, about twice as high for non-small cell as for small-cell carcinomas (NicAmhlaoibh *et al.* 2004). Brundage & Mackillop (2001) noted the importance of histology for lung cancer, but that "while, strictly speaking, the use of tumor histology to define these two entities is itself an application of a prognostic factor, the distinction between groups is so widely accepted that the

analysis and application of prognostic factors generally now occurs within each group.”

Classification of colorectal and prostate cancers by histological type is less complex, for the majority of patients, and is not considered to be important prognostically (Hobday & Erlichman 2001; Denis & Murphy 2001).

Microscopic verification status

Based on univariate analyses, cancer patients lacking microscopic verification (MV) of their diagnosis had among the lowest survival of any category of patient. For example, five-year relative survival for patients diagnosed during 1994-2001 averaged 20% for breast cancer patients lacking MV (compared to 77% for those with MV); 8% (v. 53%) for colorectal cancer; 5% (v. 10%) for lung cancer; and 25% (v. 76%) for prostate cancer. Multivariate analyses confirmed these patterns for colorectal and prostate cancers, with two-fold or greater variation in excess mortality between patients of different MV status. For breast and lung cancers, the independent effect of MV status was not measured as this variable did not contribute significantly to model-fit.

For the period 1994-98, multivariate analyses by NicAmhlaoibh *et al.* (2004) also found that cancer-specific mortality was twice as high among colorectal and prostate cancer cases lacking MV. This variable did not contribute significantly to model-fit for breast cancer, and analyses for lung cancer required stratification by MV status. Its influence on survival was not directly measured for those cancers.

These findings are not unexpected, as patients with more advanced cancer, or in poorer general health, are less likely to undergo thorough diagnostic investigations.

Smoking status

For all four cancers, patients recorded as current smokers at the time of their diagnosis had a slightly, but significantly, higher excess mortality risk than non-smokers, after adjustment for other characteristics. Excess risks among smokers were 15% higher than among non-smokers for lung cancer, 19% higher for colorectal cancer, 24% higher for breast cancer, but 50% higher for prostate cancer. Significantly elevated risk (lower survival) was also seen among ex-smokers for colorectal cancer (12% higher than among non-smokers) and prostate cancer (54% higher).

Interpreting these findings requires caution, given that the influence of smoking status on survival may also be mediated through other health

conditions. The mortality risks assessed here are ‘excess risks’ among cancer patients compared with the general population, thus in theory should (mainly) reflect the influence of the cancer. However, smoking prevalence in the general population is (by definition) lower than among cancer patients who smoke. Thus some of the excess risk among the latter group may reflect a direct influence of smoking on survival (not just cancer-related survival). In this instance, there seem to be good theoretical grounds for suggesting that relative survival (for cancer patients who smoke) may not necessarily give a good approximation to cancer-specific survival. However, findings here are supported by a previous of 1994-98 data (NicAmhlaoibh *et al.* 2004), which noted significantly elevated cancer-specific mortality risks (18-23% higher) among breast, colorectal, lung and prostate cancer patients who were smokers.

There is evidence from many other studies for a negative influence of smoking on survival of cancer patients. This applies both to overall survival and to survival associated with cancer and its treatment (e.g., Yu *et al.* 1997; review by Gritz *et al.* 2005). Smoking has been found to increase the risk of progression to metastatic disease among patients with localized prostate cancer treated by radiotherapy, both among current smokers (five-fold increased risk) and previous smokers (three-fold increase) (Pantarotto *et al.* 2006). Smoking has also been associated with lower survival among lung cancer patients, independently of the effects of tobacco-related comorbidities (Tammemagi *et al.* 2004). In particular, pulmonary complications following surgery for lung cancer are more likely among smokers (e.g. Vaporciyan *et al.* 2002). Smoking has also been found to reduce wound-healing after surgery in breast cancer and other patients; and to reduce the effectiveness of, or increase complications following, radiotherapy. Less well-studied are possible reduced effectiveness of chemotherapy, and exacerbation of treatment-related weight loss, in patients who smoke during treatment (Gritz *et al.* 2005).

Marital status

For colorectal, lung and prostate cancers, adjusted excess mortality risks among patients who were never married were slightly but significantly higher than among those who were ever married, by 12%, 20% and 29% respectively. Marital status was not included in the multivariate model for breast cancer, thus its independent effect on survival could not be assessed for this cancer. However, unadjusted relative survival was significantly low for breast cancer patients who were never married.

For 1994-98 cases (NicAmhlaoibh *et al.* 2004),

cancer-specific mortality was also significantly higher (by 15-20%) among unmarried colorectal and prostate cancer patients. Again, marital status was not included in the multivariate model for breast cancer (as it did not significantly improve model-fit). For lung cancer the influence of marital status was not directly measured as analyses were stratified by this variable.

Based on US data, Lai *et al.* (1999) noted that, “after controlling for age, race, and treatment, married patients with cancers of all major primary sites had significantly better survival than single, separated, divorced, or widowed patients.” Single patients appeared to have the most consistently poor survival across cancers, and the influence of marital status was more marked for men than for women. Differences in provision or receipt of treatment had been controlled for, and general health status, access to healthcare, and socioeconomic status were suggested as possible factors mediating the influence of marital status.

The influence of marital status on treatment has also been noted as a likely factor influencing survival. For example, Osborne *et al.* (2006) noted that, in the US, unmarried women with stage I or stage II breast cancer were less likely to receive definitive treatment than married women. But, even after adjusting for treatment, tumour stage, comorbidity and socioeconomic status, unmarried women had poorer cancer-related survival. A role for “increased social support and social networks” was proposed. Villingshoj *et al.* (2006) noted significantly higher mortality among colorectal patients who had lost their partner before surgery, compared to patients co-habiting with the same partner as before their surgery. They suggested that the quality or effect of treatment somehow differed between these groups.

Missing or unknown data

Cases flagged as ‘unknown’ or unspecified for a given patient or tumour characteristic generally had higher cancer-associated mortality (poorer relative survival) compared with the baseline/reference groups for this variable. Fully adjusted models confirmed this for:

- T, N and M categories and grade for all four cancers examined;
- tumour morphology (cell-type) for breast and lung cancers;
- smoking status for breast, colorectal and lung cancers;
- microscopic verification status for colorectal and prostate cancers.

However, cases with method of presentation unknown had lower mortality (higher survival) than known symptomatic cases for all four cancers

examined. This perhaps suggests this category included some screen-detected or other asymptotically-presenting cases that were not explicitly identified as such.

Hospital and consultant caseloads or specialization

There are good reasons to expect better outcomes among patients treated by surgeons or other consultants with greater experience of treating those cancers, or in hospitals which treat larger numbers of those cancers. We have not examined the potential influence of these factors in the current report, but further analyses are planned. This may be important, as data summarized in this report indicate that substantial proportions of surgical patients are treated by hospitals or consultants having low annual caseloads.

However, published studies relating cancer outcomes to measures of caseload or specialization do not provide unequivocal results. The outcome measures used also vary somewhat, generally involving either crude (all-cause) or cancer-specific mortality. Some examples are discussed below.

Sainsbury *et al.* (1995) compared survival of breast cancer patients between surgeons in Yorkshire (1979-88). Mortality among patients treated by surgeons treating more than 30 new cases of breast cancer per year was significantly lower (by about 15%) than among patients treated by surgeons treating fewer than 10 cases per year. Higher survival was also found for patients treated by surgeons whose patients had higher rates of chemotherapy and hormone therapy. The authors noted “Had the practice of the surgeons with the better outcomes been used by all treating clinicians, 5-year survival would have increased by about 4-5%.” They recommended “that patients with breast cancer be dealt with only by clinicians who see more than 30 new cases per year and who have a full range of treatment options available within a multidisciplinary setting.” A further study by these authors, covering Yorkshire patients during 1989-94, found a similar influence of workload on survival of breast cancer patients (Mikeljevic *et al.* 2003).

At hospital level, Hebert-Croteau *et al.* (2005) found that overall (all-cause) mortality among lymph node-negative breast cancer patients in Quebec, Canada was significantly higher in hospitals with fewer than 50 new cases per year, compared with those with at least 100 cases per year. This was after adjusting for case mix and physician variables. However, the caseload effect disappeared after adjustment for the type of hospital, i.e. better outcomes in large hospitals reflected factors such as teaching status, research activity and availability of on-site radiotherapy facilities.

For colorectal cancer, a review by Hodgson *et al.* (2001) noted that surgeon expertise and hospital caseload were not associated consistently with long-term survival or with peri-operative mortality.

Likewise, hospital volume and surgeon experience have been found to influence post-operative outcomes for non-small-cell lung cancer, but not consistently across studies (Birim *et al.* 2005).

Comorbidity and general patient health

The influence of comorbidity on cancer-related survival was not examined in this report, but further analysis is planned. Cancer patients having other significant health conditions are less likely to be offered or given appropriate treatment for their cancer, and may have more complications following treatment. Their overall survival prospects, unrelated to their cancer, are also likely to be reduced, although analysis of cause-specific survival should be able to allow for this.

A previous analysis of Irish data from 1994-98 (NicAmhlaoibh *et al.* 2004) did attempt to incorporate comorbidity data obtained through matching of patients to the Hospital In-Patient Enquiry system (HIPE), covering public hospitals mainly. Unadjusted analyses suggested that comorbidity was associated with poorer cause-specific survival of colorectal and prostate cancer at five years. There was no apparent association with lung cancer survival at one year after diagnosis. Inclusion of available data on comorbidity significantly improved the fit of multivariate models of regional variation in survival for breast, prostate and male colorectal cancers. However, the independent influence of comorbidity on survival was not directly measured, as it proved necessary to stratify the analyses by comorbidity status. Comorbidity did not improve model-fit for lung and female colorectal cancers in that analysis.

Many published studies indicate that cancer patients with comorbid conditions have worse outcomes. For example, Hauser *et al.* (2006) reviewed studies of patients diagnosed with advanced-stage cancers, and found that comorbidity was “consistently associated with shorter survival.” Nevertheless, based on comparisons across cancer types differing in their average fatality, Read *et al.* (2004) concluded that “concurrent comorbidities had the greatest prognostic impact among groups with the highest survival rate and the least impact in groups with the lowest survival rate.”

It should be noted, however, that clinically-based studies often use all-cause mortality as the measured outcome, whether short-term (immediate post-operative) or longer-term. It is not always

clear to what extent comorbidity influences or mediates cancer-specific survival (e.g. by influencing treatment choice or post-treatment complications).

Assessment of comorbidity, for the purposes of assessing patients' eligibility for specific treatments, can be somewhat subjective. Singh & Read (2004) reviewed available methods of objectively assessing “comorbid risk” in patients with localized prostate cancer, noting the potential for “personal bias” in treatment decisions unless such objective measures were used.

Socioeconomic factors

The potential influence on survival of material deprivation or other measures of socioeconomic status was not examined in this report. However, a previous analysis (NicAmhlaoibh *et al.* 2004) incorporated deprivation categories assigned to Irish cancer patients diagnosed during 1994-98. Those categories were based on a deprivation index assigned to small areas of residence (district electoral divisions or DEDs), using Population Census data (Small Area Health Research Unit 1997). Survival comparisons were made between patients from ‘affluent’, ‘intermediate’; and ‘deprived’ areas. Deprived areas accounted for 21% of breast cancers, 22% of colorectal cancers, 31% of lung cancers and 19% of prostate cancers during 1994-98.

Having adjusted for other variables, the 1994-98 analysis found that cancer-specific mortality was 25% higher among breast cancer patients from deprived compared to affluent areas, and 15% higher among lung cancer patients from deprived areas. For colorectal and prostate cancers, deprivation did not significantly improve the fit of multivariate models, thus its influence on survival was not examined in detail. Unadjusted analyses of cancer-specific survival did provide some evidence of poorer survival among colorectal and prostate cancer patients from deprived areas.

Kogevinas & Porta (1997) reviewed 42 studies of social class differences in cancer survival, mainly from Europe and North America. They found that “patients in low social classes had consistently poorer survival than those in high social classes”, regardless of the precise socioeconomic measures used. Mortality among patients of low versus high socioeconomic status was generally up to 50% higher. The widest differences were for cancers having a fairly good prognosis, such as cancers of the breast, corpus uteri, bladder and colon.

That review noted that lead-time bias could exaggerate the differences seen. Stage-specific comparisons would not necessarily be a solution, if

staging effort was influenced by socioeconomic factors. Length bias, whereby slower-growing tumours are more likely to be detected early, could also be relevant, if the aggressiveness of cancers differed between socioeconomic groups. Another potential bias considered was that causes of death might be less reliable for disadvantaged cancer patients. The latter group would also tend to be subject to more “competing causes” of death, but cause-specific analyses generally supported findings based on crude survival. Further research to quantify these potential biases was recommended.

Auvinen & Karjalainen (1997) provided a further review of potential explanations (including artifactual ones) for social class differences in cancer patient survival. They noted that, overall, “stage of disease at diagnosis appears to be the most important factor”. Despite this, published studies did not provide clear-cut evidence that diagnostic delay was responsible for stage differences between social classes, nor that such delays necessarily influenced prognosis. The extent to which differences in stage explained survival differences also differed between cancers or studies. The role of treatment was also reviewed. Again, there was conflicting evidence from different studies as to the influence of treatment choice on social class differences in survival. The potential roles of treatment quality, and patients’ compliance with treatment, were even more difficult to assess. Variations between social classes in the biology (e.g. aggressiveness) of tumours, in “host susceptibility” (of the patient) and in psychosocial factors were also considered, but no broad conclusions could be drawn. These authors concluded that social class differences in cancer survival were still only understood at a superficial level.

Potential problems in interpreting analyses of socioeconomic effects on both crude and cause specific mortality have been raised by various authors. Auvinen & Karjalainen (1997) suggested that the use of relative survival measures might improve comparisons between social groups, although it was noted that social-class-specific mortality data were not widely available.

One of the most detailed studies in this area examined relative survival of cancer patients in England and Wales (Coleman *et al.* 1999). Five deprivation categories were defined using the area-based Carstairs index of material deprivation. For correct comparison on relative survival between patients in different deprivation categories, deprivation-specific life tables were first constructed. The observed survival of patients from each category was compared with the

expected survival of the general population in the same category; few previous studies had done this. Relative survival of cancer patients from affluent groups was found to be significantly higher for many cancers, compared with deprived groups. For the period 1981-90, for example, relative survival of patients from the most affluent compared to the most deprived group was 8-9 % points higher for breast cancer, 4-7 % points higher for colon and rectal cancers, 1 % point higher for lung cancer and 3-6 % points higher for prostate cancer. The factors involved were not directly assessed, but suggested possible explanations were: “longer delay in diagnosis or more advanced disease at diagnosis, worse general health or resistance to malignancy, different histological type or more aggressive disease, poorer access to optimal care, and lower compliance with treatment.”

It was noted, however, that a number of other British studies of common cancers, including breast cancer, had found that stage of disease did not account for observed survival differences between deprivation categories (Carnon *et al.* 1994, Schrijvers *et al.* 1995).

Other prognostic factors

A range of other prognostic factors have been identified (Gospodarowicz *et al.* 2001), many reflecting molecular or other aspects of tumour biology. Such factors are increasingly being recorded as a routine part of diagnostic and prognostic investigations. Oestrogen and progesterone receptor status for breast cancer is one of the better-known examples, though was not available for most of the years considered in this report.

Table 7.1 Summary of the influence of patient and tumour characteristics on relative survival of cancer patients diagnosed during 1994-2001: significantly better (↑) or poorer (↓) survival, or no difference (=), compared with baseline group for each characteristic. Findings here are based on multivariate analyses that also included region of residence and year of diagnosis, and indicate the independent effect of each variable after adjustment for other variables.

	Breast cancer	Colorectal cancer	Lung cancer		Prostate cancer
age 15-44 ^a	.	.	.	age 15-54 ^a	.
age 45-54	=	=	↓	age 55-64	=
age 55-64	↓	↓	↓	age 65-74	↓
age 65-74	↓	↓	↓	age 75-84	↓
age 75+	↓	↓	↓	age 85+	↓
male
female	.	↑	↑		.
T1 ^a	.	.	.	T1	.
T2	↓	=	↓	T2	=
T3	↓	↓	↓	T3	=
T4	↓	↓	↓	T4	↓
T X	↓	↓	↓	T X	↓
N negative ^a	.	.	.	N negative	.
N positive	↓	↓	↓	N positive	↓
N X	↓	↓	↓	N X	↓
M negative ^a
M positive	↓	↓	↓		↓
M X	↓	↓	↓		↓
grade 1 ^a
grade 2	=	=	=		=
grade 3+	↓	↓	↓		↓
grade X	↓	↓	↓		↓
ductal/lobular
other adenocarc	=	.	.		.
other carcinoma	=	.	.		.
carcinoma NOS	↓	.	.		.
cancer NOS	↓	.	.		.
other cancer	=	.	.		.
non-small-cell
small-cell	.	.	=		.
other/NOS	.	.	↓		.
MV yes
MV no	.	↓	.		↓
MV X	.	↓	.		↓
symptomatic
incidental	↓	=	↑		↑
screen detected	↑	↑	↑		=
presentation X	↑	↑	↑		↑
non-smoker
ex-smoker	=	↓	.		↓
smoker	↓	↓	↓		↓
smoking status X	↓	↓	↓		↓
ever married
never married	.	↓	↓		↓
marital status X	.	=	=		=

^aFor these variables and cancers, results are based on the first year of follow-up only, as longer-term patterns are too complex to summarize. . Reference (baseline) group, or no comparison available for this variable (or specific category).

7.6 Comparison of final multivariate models for regional variation in survival between this report and NicAmhlaoibh *et al.* (2004)

The geographic patterns of relative survival found for the period 1994-97 in the current report, based on relative survival modelling adjusted for tumour and patient characteristics, were broadly consistent with those found in a previous NCR analysis (NicAmhlaoibh *et al.* 2004), which covered a similar period. Apparent differences in ‘fully adjusted’ regional patterns between the current and earlier report (*Tables 7.2-7.5* below) may reflect a number of factors.

These include (to a lesser or greater extent):

- Differences in precise diagnosis years covered; the closest comparison is between the previous report and diagnosis period 1994-97 in the current report.
- Differences in completeness of follow up; cases diagnosed during 1994-98 had follow-up to 31 December 2001 in the previous report (incorrectly stated there as 1 January 2000), i.e. some cases had less than 4 years of follow-up available; cases diagnosed during 1994-97 had follow-up to 31 December 2003 in the current report (i.e. a full five years of follow-up for all cases).
- Differences in patient characteristics considered for inclusion in the statistical models used; most notably, the potential influences on survival of comorbidity (derived from hospital in-patient data) and area-based deprivation measures examined in the previous analysis for some cancers but not here.
- Differences in the precise mortality parameters included in models; cause-specific mortality was used in the previous report, excess mortality assessed by comparison with background mortality in the current report, although these are in essence alternative approaches to measuring the same basic parameter (i.e. the extra mortality among cancer patients attributable to their cancer).
- Differences in inclusion criteria between reports; although these were largely the same, the previous report excluded all patients who had more than one serious cancer, whereas the current report, for consistency with EURO CARE criteria, includes those patients (but only for their first serious cancer).
- Differences in age-groups used for adjustment of models; the previous report used age-groups ≤ 40 , 41-50, 51-60, 61-70, 71-80 and 80+

years); the current report uses age-groups 15-44, 45-54, 55-64, 65-74 and 75+ years for breast, colorectal and lung cancers, and 15-54, 55-64, 65-74, 75-84 and 85+ years for prostate cancer (EURO CARE age-groups).

- Differences in coding for other variables; for example, the previous report distinguished N categories 0, 1, 2, 3 and unknown for breast cancer, but the current report simplified this to N negative, N positive or unknown, to minimize the complexity of models.
- Random or unpredictable differences, resulting less directly from the above factors or other minor differences in datasets.
- Differences in presentation of results for colorectal cancer; specifically, the previous report did not report results of a combined model for both sexes, thus direct comparison between reports is not possible.

However, for most cancer/region combinations the cause-specific and excess mortality hazard ratios, compared to patients from the Eastern region, differ mainly in magnitude or statistical significance, rather than qualitatively. In no instance for the most directly comparable years (1994-98 / 1994-97) were cause-specific and excess hazard ratios both contradictory and significant. Overall (except for colorectal cancer as far as can be judged), there was a tendency for the previous reports’ analyses to ‘explain’ more of the regional variation during comparable diagnosis periods. Possibly this reflects adjustment for comorbidity or deprivation measures in the previous analysis, although other factors such as those listed cannot be ruled out. Nor does it follow that one or other analysis necessarily allows the ‘correct’ explanation or interpretation of geographic patterns seen. As noted earlier, there potential additional problems posed by, for example, incomplete availability of data for some variables, or inconsistency of data-definitions between patient groups.

A fuller analysis of the data is planned, incorporating more complete information on comorbidity and deprivation than was possible previously. However, we would reiterate a caution made earlier regarding deprivation. A patient’s socioeconomic background may ‘predict’ or explain their survival to some extent, but it is arguable that this is an inadequate explanation that does not capture the underlying factors influencing survival.

Table 7.2 Comparison of regional patterns of mortality risk among breast cancer patients between this report (relative survival) and a previous analysis of 1994-98 data (cause-specific survival). Hazard ratios shown are from 'full' models adjusted for patient and tumour characteristics; statistically significant hazard ratios are shown in bold.

Region	^a CSHR (95% CI)	^b EHR (95% CI)	EHR (95% CI)	EHR (95% CI)
	1994-98 NicAmhlaoihb <i>et al.</i> 2004	1994-97 this report	1998-2001 this report	1994-2001 this report
E	1.000	1.000	1.000	1.000
M	1.076 (0.836-1.384)	1.171 (0.908-1.510)	1.379 (1.068-1.780)	1.277 (1.068-1.527)
MW	1.122 (0.885-1.421)	0.986 (0.800-1.216)	1.240 (0.979-1.570)	1.069 (0.914-1.250)
NE	1.144 (0.915-1.431)	1.240 (1.000-1.537)	1.015 (0.796-1.293)	1.139 (0.971-1.336)
NW	0.960 (0.751-1.226)	1.134 (0.897-1.434)	0.973 (0.742-1.277)	1.066 (0.894-1.271)
S	1.332 (1.123-1.581)	1.242 (1.052-1.466)	1.067 (0.878-1.297)	1.162 (1.025-1.317)
SE	0.955 (0.774-1.179)	1.146 (0.944-1.392)	1.407 (1.142-1.735)	1.222 (1.061-1.407)
W	1.127 (0.915-1.387)	1.239 (1.022-1.503)	1.332 (1.067-1.662)	1.262 (1.093-1.457)

^aCSHR = cause-specific hazard ratio. ^bEHR = excess hazard ratio (based on relative survival).

Table 7.3 Comparison of regional patterns of mortality risk among colorectal cancer patients between this report (relative survival) and a previous analysis of 1994-98 data (cause-specific survival). Hazard ratios shown are from 'full' models adjusted for patient and tumour characteristics.

Region	CSHR (95% CI)		EHR (95% CI)	EHR (95% CI)	EHR (95% CI)
	1994-98 NicAmhlaoihb <i>et al.</i> 2004		1994-97 this report	1998-2001 this report	1994-2001 this report
	female	male	sexes combined	sexes combined	sexes combined
E	1.000	1.000	1.000	1.000	1.000
M	0.884 (0.678-1.153)	1.357 (1.086-1.693)	1.036 (0.870-1.233)	1.111 (0.922-1.338)	1.066 (0.939-1.210)
MW	1.306 (1.023-1.667)	1.238 (1.024-1.497)	1.069 (0.906-1.261)	1.269 (1.092-1.474)	1.152 (1.032-1.286)
NE	0.918 (0.732-1.149)	0.952 (0.786-1.153)	0.873 (0.747-1.020)	0.995 (0.860-1.151)	0.917 (0.825-1.020)
NW	1.065 (0.850-1.333)	1.144 (0.945-1.386)	1.015 (0.873-1.179)	1.093 (0.926-1.291)	1.038 (0.929-1.160)
S	1.028 (0.872-1.213)	1.305 (1.133-1.504)	1.327 (1.188-1.483)	1.145 (1.019-1.286)	1.240 (1.145-1.343)
SE	1.004 (0.825-1.221)	1.214 (1.035-1.425)	1.125 (0.991-1.276)	1.071 (0.935-1.227)	1.100 (1.003-1.206)
W	1.133 (0.931-1.379)	1.073 (0.916-1.257)	1.114 (0.978-1.269)	0.955 (0.832-1.096)	1.027 (0.935-1.129)

Table 7.4 Comparison of regional patterns of mortality risk among lung cancer patients between this report (relative survival) and a previous analysis of 1994-98 data (cause-specific survival). Hazard ratios shown are from 'full' models adjusted for patient and tumour characteristics.

Region	CSHR*	EHR (95% CI)	EHR (95% CI)	EHR (95% CI)
	1994-98 NicAmhlaoihb <i>et al.</i> 2004	1994-97 this report	1998-2001 this report	1994-2001 this report
E	1.000	1.000	1.000	1.000
M	0.935	0.903 (0.786-1.037)	0.931 (0.818-1.059)	0.924 (0.841-1.015)
MW	0.963	0.856 (0.762-0.961)	0.868 (0.777-0.969)	0.871 (0.804-0.943)
NE	0.947	0.857 (0.764-0.960)	1.104 (0.991-1.229)	0.976 (0.903-1.055)
NW	0.914	0.835 (0.739-0.944)	0.872 (0.773-0.983)	0.855 (0.785-0.931)
S	0.954	0.969 (0.888-1.058)	0.973 (0.892-1.061)	0.978 (0.919-1.039)
SE	1.082	0.968 (0.877-1.069)	1.119 (1.014-1.235)	1.035 (0.966-1.109)
W	0.874	0.785 (0.705-0.875)	0.894 (0.804-0.994)	0.839 (0.779-0.905)

* 95% CIs for 1994-98 analysis were incorrectly shown in the previous report and are not repeated here.

Table 7.5 Comparison of regional patterns of mortality risk among prostate cancer patients between this report (relative survival) and a previous analysis of 1994-98 data (cause-specific survival). Hazard ratios shown are from 'full' models adjusted for patient and tumour characteristics.

Region	CSHR (95% CI)	EHR (95% CI)	EHR (95% CI)	EHR (95% CI)
	1994-98 NicAmhlaoibh <i>et al.</i> 2004	1994-97 this report	1998-2001 this report	1994-2001 this report
E	1.000	1.000	1.000	1.000
M	1.063 (0.859-1.316)	1.098 (0.843-1.429)	1.139 (0.827-1.569)	1.128 (0.923-1.377)
MW	1.108 (0.903-1.360)	0.934 (0.728-1.198)	1.544 (1.152-2.069)	1.104 (0.913-1.335)
NE	0.915 (0.744-1.125)	0.845 (0.655-1.090)	1.472 (1.111-1.949)	1.072 (0.889-1.292)
NW	1.064 (0.868-1.305)	0.869 (0.670-1.126)	1.038 (0.777-1.386)	0.934 (0.772-1.129)
S	1.128 (0.955-1.332)	1.231 (1.003-1.511)	1.350 (1.075-1.696)	1.248 (1.073-1.450)
SE	0.950 (0.794-1.137)	0.921 (0.738-1.151)	1.387 (1.072-1.794)	1.086 (0.919-1.284)
W	0.916 (0.768-1.093)	0.725 (0.580-0.908)	1.239 (0.958-1.604)	0.894 (0.755-1.057)

7.7 Time-trends in treatment

The proportion of patients receiving any tumour-directed treatment showed no significant trend for breast cancer during 1996-2001, increased for lung and to a lesser extent colorectal cancer, and fell slightly for prostate cancer. Use of surgical treatment increased slightly for breast cancer, fell slightly for lung and to a lesser extent colorectal cancers, and fell more markedly for prostate cancer. Radiotherapy use increased markedly for prostate and colorectal (especially rectal) cancers, and to a lesser extent for lung cancer, but showed no trend for breast cancer. For breast cancer, the recorded use of hormonal treatment fell substantially, nationally and in all regions of residence, at the same time as a significant increase in the use of chemotherapy. Chemotherapy use also increased substantially for colorectal and lung cancers, and use of hormonal treatment increased moderately for prostate cancer.

Trends in treatment appeared to be broadly in line with expectations of greater or better-targeted use of radiotherapy and chemotherapy. A notable exception was the lack of an increase in radiotherapy use for breast cancer. Reduced use of hormonal treatment for breast cancer may also be in line with expectations of improved targeting of appropriate treatment. This may also apply to increased use of hormone therapy and reduced use of surgery for prostate cancer.

In many instances, the trends during 1994-2001 as a whole are consistent with those during the shorter period 1996-2001. However, we have focused on trends during the latter period, to minimize biases resulting from possible under-recording of treatments in earlier years. Such bias might have arisen as, in the first year or two of National Cancer Registry operation, collection of treatment data largely targeted the first four months after diagnosis, although in practice many later

treatments were also recorded.

7.8 Regional variation in treatment

As noted in an earlier report (NicAmhlaoibh *et al.* 2004), there was clear regional variation within Ireland in the proportions of patients receiving particular treatment modalities. This applied both overall (1994-2001) and during earlier (1994-97) and more recent (1998-2001) diagnosis periods. For a given cancer type, regional variations were not necessarily the same for different treatment modalities. In general, there patients from a given region were relatively more likely to receive particular treatment modalities compared with others. To some extent, such regional variations may have been 'compensatory', if different treatment modalities or combinations of modalities of broadly equivalent effectiveness were used. Thus overall treatment varied less between regions than did individual treatment modalities. Nevertheless, given the range of variation seen for some cancers and modalities, it is likely that patients from some regions received, on average, more appropriate or less appropriate treatment compared with other regions.

Objectively comparing the 'quality' of treatment, in relation to best international practices and national or international recommendations, however, will require further work – not least to agree the standards for comparisons. Ireland's involvement in the European Cancer Health Indicators Project (EUROCHIP) should provide a good basis for such comparisons (cf. <http://www.tumori.net/eurochip/>).

The data available for this analysis did not allow direct assessment of the reasons why particular patients did or did not receive particular treatment modalities. However, it was possible to model and adjust for the effects of a number of relevant patient and tumour variables, but note the cautions expressed earlier. For most of the regional

comparisons presented, adjustment for the available ‘explanatory’ and prognostic data did not fully remove the regional variation seen. In part, this may be because a high proportion of cases were missing data for given variables. Another possible explanation is that unmeasured factors relating to patient’s condition or comorbidity, or their willingness to accept treatment, may have varied regionally. Regional variation in the ‘choice’ of treatments preferred or offered by clinicians – whether related to local availability of services or otherwise – could also be involved.

It may be relevant that cases with “unknown” values for a given tumour or patient variable tended to be less likely to receive treatment than cases with known values. Among other possibilities, this could indicate that many such patients were considered too ill or too old for treatment or detailed investigations. The interplay between treatment and the completeness or quality of diagnostic or prognostic information also complicates interpretation of ‘adjusted’ analyses.

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Appendix 1 Standard treatments for breast, colorectal, lung and prostate cancer, adapted from the US National Cancer Institute's PDQ Cancer Information Summaries.* Non-standard treatments that are subject to further evaluation in clinical trials are not shown.

Cancer site	Prognostic group ^a	Surgery	Radiotherapy	Chemotherapy	Hormone	combinations ^b
Breast	<i>stages I-III A, operable IIIC:</i>					
	local-regional, node negative, low risk	cur, cur'	adj		adj	s, sr, sh, srh
	local-regional, node negative, intermediate risk	cur, cur'	adj	adj	adj	s, sr, sh, sch, srh, srch
	local-regional, node negative, high risk	cur, cur'	adj	adj	adj	s, sr, sc, sh, sch, src, srh, srch
	local-regional, node positive	cur, cur'	adj	adj	adj	s, sr, sc, sh, sch, src, srh, srch
	<i>IIIB, inoperable IIIC, IV:</i>					
	IIIB, IIIC or inflammatory	cur'	adj	adj	adj	scr, schr
	IV	pal	pal	pal	pal	c, h, ch, cr, cs, hs, chr, chs
Colon	stage I	cur				s
	stage II	cur				s
	stage III	cur'		adj		sc
	stage IV	(pal), (cur)	(pal)	pal		s, r, c
Rectum	stage I	cur, cur'	(cur), adj	adj		s, r, src
	stage II	cur'	adj	adj		src
	stage III	cur'	adj, pal	adj, pal		rc, src
	stage IV	pal, (cur)	pal	pal, adj		s, c, sc, cr
Lung	<i>non-small-cell:</i>					
	stage I	cur, cur'	cur	adj		s, r, sc
	stage II	cur, cur'	cur	adj		s, r, sc
	stage IIIA	cur, cur'	cur, adj	adj		s, r, cr, sr, scr
	stage IIIB	cur'	cur, adj, (pal)	cur, adj		c, r, cr, scr
	stage IV		pal	cur		c, r
	<i>small-cell:</i>					
	limited stage	cur'	adj	cur, adj		c, cr, sc, scr
	extensive stage		adj, pal	cur, adj		c, r, cr
Prostate ^c	stage I	cur, cur'	cur, adj			s, r, sr
	stage II	cur, cur'	(adj)		adj	s, r, sh, rh
	stage III	cur, pal	cur, adj, pal		cur, adj, pal	s, r, h, rh
	stage IV	pal	cur, adj, pal		cur, adj	s, r, h, sr, rh, srh

cur = curative (as single modality); cur' = curative surgery in combination with other treatment modalities;
adj = adjuvant (curative or prophylactic, in combination with surgery or other treatment modalities);
pal = palliative (primarily for symptom relief, as single modality or in combination); () = in selected patients.

^aStage groupings are based on the 6th edition of the TNM staging scheme.

^bMain combinations (or single-modality treatments): surgery etc (s), radiotherapy (r), chemotherapy etc (c), hormone therapy (h); combinations shown are not necessarily complete lists.

^cFor prostate cancer, "careful observation without further immediate treatment" is also standard for stage I.

*<http://www.cancer.gov/cancertopics/pdq/cancerdatabase>