Chapter 4

Interpretation of population-based cancer survival data

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Introduction

In order to describe completely the experience of cancer in a population, it is necessary to know not only its incidence and mortality, but also the survival of cancer patients. There are three main sources of information about survival: the randomized controlled clinical trial, which represents the 'gold standard' for the evaluation of forms of treatment; the hospital-based study, which aims to provide information about the outcome of treatment in particular settings; and population-based survival from cancer registries, which reflects a broader range of cancer control activities, including screening and the organization of treatment services. Each of these has its limitations: survival information from trials and published hospital series is often biased by patient selection, whereas population-based survival data may lack the details of stage and treatment which are of particular interest to the clinician.

The rationale of a randomized clinical trial is to eliminate the confounding effects of factors such as age and comorbidity in order to isolate the effects of treatment. This is achieved in two ways: by adopting selection criteria which exclude some subjects (such as those with comorbid conditions) and random allocation of the remainder into groups in which the only systematic differences are the treatments to be received. This approach is essential in order to determine the *efficacy* of particular treatments. However, the *effectiveness* of cancer services in general depends not only on the efficacy of particular treatments but also on the context in which they are applied.

Evaluating effectiveness requires estimation of survival in unselected groups of cancer patients, which is a key aim of most cancer registries. Estimates of survival in such groups may be influenced by a range of prognostic and other factors (see Table 1). In accounting for these, the methodology of clinical trials cannot be deployed, since selection would invalidate the generality of results and it is impossible, of course, to randomize cancer patients to different health care systems. Therefore another approach is required when evaluating survival at the population level and making comparisons between population groups which are heterogeneous in respect of prognostic factors. Some factors such as age and sex can be accounted for in the statistical methodology used to estimate survival. Information on other factors such as comorbidity may not even be present in cancer registry data. For these, the best we can do is to be aware of their possible influences or, as has been attempted in the EUROCARE study (Berrino *et al.*, 1995), augment the basic cancer registry information with 'high resolution' data. The remainder of this chapter provides a review of comparability issues: that is, data quality factors (e.g. methods of ascertainment and follow-up), host factors (e.g. age, sex, risk of death from other diseases), tumour-related factors (e.g. extent of disease) and health care factors (e.g. availability and quality of diagnosis and treatment services) which influence population-based estimates of survival.

Data quality factors

Inevitably, the quality of cancer registration data will vary according to the availability of source data, the experience of registry staff and other factors. This variation complicates the interpretation of survival data based on routine cancer registry data (Hanai & Fujimoto, 1985). Of particular concern is the completeness of ascertainment. If cases of cancer which are not registered represent a random sample from the total, then there should be no systematic bias in survival results. However, this is unlikely to be the case, since the probability of being registered tends to be correlated with prognosis: for example, elderly patients not seen in hospital are less likely to be registered than younger patients, for whom curative treatment may have been attempted. Estimates of survival may therefore be artificially

Table 1. Factors influencing population-based survival data

Data quality factors
- Completeness of ascertainment
- Accuracy of registration
- Completeness of follow-up
- 'Death certificate only' (DCO) registrations

Host factors
- Age
- Sex
- Race/Ethnicity
- Comorbidity
- Socioeconomic status
- Behaviour (including awareness of cancer symptoms and compliance with treatment)

Tumour-related factors
- Extent of disease
- Site (including subsite) of tumour
- Morphology of tumour
- Tumour biology

Health care-related factors
- Screening
- Diagnostic facilities
- Treatment facilities
- Quality of treatment
- Follow-up care

raised for a particular registry area if ascertainment is not complete. Similarly, the accuracy of diagnostic information for cancer patients tends to be correlated with prognosis. For example, a registry relying exclusively on a particular pathology laboratory for diagnostic information might tend to classify cases from other sources in nonspecific categories for primary site. Such cases would be excluded from tumour-site-specific survival analyses, whereas data for another registry might include cases with clinical diagnoses. Again, the effect of this aspect of data quality would be to increase the survival estimate for a registry which allocated a large proportion of cases to nonspecific diagnostic categories.

In cancer registry data, there are usually some subjects for whom the registration of cancer was based on information from the death certificate only (DCO). By convention, such cases are excluded from survival analyses since — by definition — their survival time is zero. This convention was adopted in the present study. If the proportion of DCO cases is relatively low, say less than 10%, then excluding them from the analysis does not greatly influence survival estimates. However, larger proportions of DCO cases are problematic, since they may mean that cases of poor prognosis (which would have been registered by other means if the registry had had better ascertainment procedures) are excluded, thus artificially increasing estimates of survival. Some of the registries in the present study have quite large proportions of DCO cases.

Under either active or passive follow-up systems, individuals can be lost due to migration, breaking off contacts with local authorities or other changes in living conditions. Normally, registries assume that a subject is alive until a notification of death is received, or active follow-up results in a confirmation of death. Many of the individuals who are lost to follow-up will, in fact, have died, so that a registry with a large proportion of individuals with whom they have lost contact will report artificially high survival. However, the direction of the bias is unpredictable, and will depend on local circumstances. For example, loss to follow-up may occur when subjects with a relatively good prognosis are obliged to move away from their original cancer registry area to receive treatment.

A common feature of most of the aspects of data quality discussed above is that poor data quality tends to increase estimates of survival. A key aim of the international network of cancer registries is to standardize data collection methods and indicators of data quality. We believe that the differences in survival between the registries reported in the present study are mainly due to factors other than data quality (see the discussion in Chapter 16). However, it is important to be aware that apparently high survival rates for some registries may have been influenced by data quality factors. Detailed information on data quality, including data quality indicators such as the proportion of DCO registrations and the proportion of cases with histological verification, can be seen in the individual registry chapters.

Host factors

Age at diagnosis is an independent prognostic factor for many types of cancer. This operates in two ways: age may be correlated both with the risk of dying from a particular type of cancer and with the risk of dying from some other cause. In the present study, we adjusted for age using age-standardized relative survival (to take account of variations in age-specific

background mortality and differences in the age distributions of the populations being compared).

Sex is less commonly associated with variations in survival and, for this reason, many registries combined data for males and females in the interests of increasing the precision of survival estimates. However, survival from some cancers, such as malignant melanoma, has been seen to be greater for women in some developed countries, which is probably due to a greater recognition of early symptoms and a willingness to seek medical attention.

Comorbid conditions experienced by cancer patients may vary substantially between registry populations. Comorbidity affects survival by presenting an additional source of risk of death, making it less likely that a patient will be offered curative treatment and, if it is offered, less likely that the patient will be able to withstand the effects of the treatment itself.

Socioeconomic differences in survival have been reported for many sites of cancer within populations in Europe (Kogevinas, 1991) and the USA (Berg *et al.*, 1977). Socioeconomic status tends to be correlated with strong prognostic factors such as extent of disease at diagnosis, but it has been shown to have a residual effect which may be due to inequalities in access to medical care facilities, compliance with treatment regimens, coping strategies or social support. Within developed countries, race is also associated with survival, although the extent to which this operates independently of socioeconomic status is unclear (Howard *et al.*, 1991). Berg *et al.* (1977) propose a host vulnerability hypothesis in which the poor nutritional status, general health and immunological status (related to alcoholism) of some social and racial groups leads to lower survival from cancer. Clearly, socioeconomic conditions in developed and developing countries are grossly different, to the extent that inequalities in access to medical care are likely to be of particular significance in the present study.

Tumour-related factors

By convention, cancer registry data are aggregated within categories defined by the anatomical site of the tumour. When comparing international survival data, caution must be exercised when the distributions of tumour subsites vary. The same point applies to variations in the frequency of morphological types of tumour within categories of site, and variations in tumour biology, as expressed by differences in natural history and aggressiveness of clinical course (e.g. breast cancers with variations in the frequencies of tumour markers such as hormonal receptor status; variations in the grade of non-Hodgkin lymphomas).

The stage of disease at diagnosis is generally the most important factor determining the survival of cancer patients. This is because certain treatments may be available only for early-stage tumours, and any treatment is more likely to be successful if initiated before metastasis has occurred. Therefore variations in the stage distributions of tumours in populations being compared are of particular concern. Some of the registries involved in the present study were able to supply data on extent of disease, which we have used in interpreting results for these regions. However, even when such data are available, variations in diagnostic technology such as those between developed and developing countries are likely to lead to measurement error. Stage of disease at diagnosis is influenced both by the general level of health awareness in the population, and by the presence or absence of programmes of early detection for cancer. The effect of the former is seen clearly with respect to cervical cancer statistics recorded in patients admitted to the Radiumhemmet Hospital, Stockholm, Sweden since 1920. Even before the introduction of screening programmes, there was a dramatic change in the proportion of cases diagnosed at early stages (I and II), from less than 20% in 1920 to some 80% in 1965. (Pontén *et al.*, 1995).

Health care-related factors

Factors relating to the health care of cancer patients in developed and developing countries are of particular concern in the present study. There are a number of ways in which the availability of, and access to, screening services and diagnostic and treatment facilities can influence survival. Screening programmes aim to detect early-stage cancers or premalignant tumours so that the disease can be treated at an early stage, which is generally more effective. However, interpreting survival statistics in terms of the benefit to patients resulting from screening is problematic, since one consequence of early detection is to bring forward the date of diagnosis of a condition, whether or not this has the desired effect of reducing risk of death from the disease. This is called 'lead-time bias'. In addition, screening programmes may result in the detection of disease that would not otherwise have been diagnosed at all during the life of the patient — so-

called 'overdiagnosis bias' (Morrison, 1985). This latter will necessarily result in a marked improvement in survival, and one that is independent of any 'downstaging' effect of screening which, theoretically at least, could be monitored in cancer registry data. Overdiagnosis almost certainly accounts for the huge increases recently observed in the reported incidence of prostate carcinoma in the USA, and the corresponding changes in survival (Kosary *et al.*, 1995). As far as the results in this volume are concerned, however, they are likely to be little influenced by screening programmes. With certain exceptions (described in the relevant chapters), screening programmes are not extensive or systematically implemented in developing countries and, where information on extent of disease is available, it will be observed that, for many cancers, more patients are presenting late in the course of their disease than would be expected from experience in Europe or North America.

Diagnostic facilities may also influence survival by ensuring that a specific and correct diagnosis can be made. Improvements in the sensitivity of diagnosis may have the effect of inducing 'stage migration' in which, for example, tumours of limited metastatic activity which at one time would have been inaccurately described as simply invasive, may be reallocated to the metastatic category, thus increasing estimates of survival of individuals in both metastatic and the nonmetastatic groups (Feinstein *et al.*, 1985). This phenomenon can operate on a geographical as well as a temporal basis (Farrow *et al.*, 1995). Therefore, comparisons of stage-specific survival data from settings with very different diagnostic facilities cannot be made with confidence. It should be noted that comparisons of survival of groups comprising patients with tumours of all stages combined are not subject to this problem, as long as there is no selection bias due to greater diagnostic specificity in one population compared with another.

The availability of treatment facilities for cancer patients affects the survival of those for whom curative treatment would have the potential to succeed. Therefore the issue of availability of treatment facilities is bound up with the availability of other facilities, such as screening programmes and diagnostic facilities. Survival data from cancer registries cannot be used to make direct comparisons of populations in terms of the quality of care available, although some studies have shown that the survival of some cancer patients is prolonged after treatment at specialized cancer centres (Stiller, 1994). However, results of this kind are difficult to interpret because of selection criteria for specialized care, which may determine the apparently better results rather than the quality of care received *per se*.

Conclusions

The previous discussion indicates the difficulty of making meaningful comparisons of survival among groups of cancer patients with varying demographic and socioeconomic characteristics, and served by very different health care infrastructures, using retrospectively collected data from cancer registries. It is certainly important to realize that variations are not simply due to the availability and quality of medical services. However, as will be seen from the discussion in Chapter 16 'An overview of cancer survival in developing countries', a comparison of the magnitude of differences between countries provides at least an indirect indication of the relative importance of early detection and treatment for certain major cancers.

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