‘Cure’ from breast cancer among two populations of women followed for 23 years after diagnosis

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Background: Although survival from breast cancer has greatly improved over the past three decades, there is little consensus as to whether a population of women diagnosed with breast cancer can ever be considered ‘cured’ of the disease.

Patients and methods: We examined population ‘cure’ among women aged 15–99 years diagnosed with breast cancer from 1980 to 1995 in the West Midlands (England) and New South Wales (Australia). We calculated interval-specific excess mortality rates and fitted a number of statistical models to evaluate ‘cure’.

Results: There was little evidence that these women could ever be considered cured of the disease because excess mortality due to breast cancer was evident among young and middle-aged women up to 23 years after their diagnosis. Older women diagnosed in New South Wales displayed some evidence of ‘cure’. However, this was estimated to occur only after the women’s 75th birthday.

Conclusions: There is no strong evidence of the existence of a ‘cured’ subpopulation among young or middle-aged women diagnosed with breast cancer in either West Midlands or New South Wales during the period 1980–1995. Additional follow-up data would permit ‘cure’ to be assessed for women diagnosed more recently than 1995.

Key words: Australia, breast cancer, cure, England, long term, survival

introduction

Although clinical cure from cancer is currently impossible to establish with complete certainty in an individual patient, ‘cure’ is a concept which can be defined at a population level. The ‘cured’ subpopulation is the proportion of patients among whom no additional, or ‘excess’, mortality is observed compared with the population from which they are drawn [1]. Thus, population cure is obtained when the excess mortality rate reaches zero or, equivalently, the relative survival function reaches a plateau, indicating that the mortality experienced by the surviving cured proportion of the patient population is the same as that of their counterparts (Figure 1).

The literature examining either long-term relative survival or cure among breast cancer patients is relatively small, but it has covered a number of different population groups over a 50-year time period [2–18]. Without exception, these analyses show a significant improvement in the long-term survival of women diagnosed with breast cancer during the 1940s and up to the 1970s. However, the evidence they present as to whether population cure has been attained for a subset of the patient population is inconsistent. Where long-term survival has been examined, excess mortality has generally been observed after long-term follow-up [2–5, 7, 13, 14, 17], although not in all population groups [2, 10, 13]. Where a statistical model has been used to examine cure, a cured proportion has not been consistently found [6, 9, 11, 12, 18]. These cohorts of breast cancer patients were diagnosed at least 10 years before important advances in the diagnosis and management of breast cancer occurred during the 1980s, as well as the introduction of population-based mammographic screening programmes implemented from the late 1980s to the early 1990s.

Here, we investigate the existence of a cured proportion among women diagnosed with breast cancer much more recently, from 1980 to 1995, in two separate populations followed for 23 years after diagnosis. We examine long-term excess mortality rates and estimate cure using a number of different statistical models.

patients and methods

tumour data

Data on all invasive breast cancers diagnosed among women aged 15–99 years at diagnosis in West Midlands (England) and New South Wales (Australia) during the period 1 January 1980 to 31 December 1995 were obtained directly from the West Midlands Cancer Intelligence Unit and the New South Wales Central Cancer Registry. Tumour records included information on date of diagnosis, date of death, age at diagnosis, and extent
of disease. Follow-up was complete for all women up to 31 December 2002. Women were excluded if their first breast cancer occurred after a previous invasive malignancy at a different anatomic site (multiple primary) or if the sequence of dates was illogical. Women reported to have a survival time of <1 day were also excluded. A total of 80 313 women were analysed, 42 811 in West Midlands and 37 502 in New South Wales (95% of the total number eligible). Missing dates of diagnosis were imputed at the midpoint of the diagnosis month where month but not day of diagnosis was known and at the midpoint of the year where only the year of diagnosis was known. The information on extent of disease provided by the West Midlands Cancer Intelligence Unit was recoded according to the rules used by the New South Wales Central Cancer Registry in consultation with the coding staff of both registries. This resulted in a comparable variable consisting of four categories: localised (confined to the organ of origin), regional (spread to adjacent muscle, organ, fat, connective tissue, or regional lymph nodes), distant (distant metastasis), and disease of unknown stage.

relative survival analyses

In analysing the survival of a group of cancer patients, it is preferable to describe the survival which is related directly to the disease rather than the observed (crude) survival of the patient group. This concept is known as ‘net survival’: the survival that would occur if mortality from other causes of death was removed. Relative survival is the most defensible method of estimating net survival in population-based studies, since it does not rely upon accurate reporting of cause of death [19]. Relative survival is the ratio of the observed (crude) survival of the cancer patients and the survival that would have been expected if the patients had the same age- and sex-specific mortality in each period (background mortality) as the general population [20].

We required life tables for each region in order to estimate expected survival. Observed annual age group-specific death rates were calculated for each region in 1991 and 2001 using counts of deaths and populations obtained from Office for National Statistics for England and Wales and the Australian Bureau of Statistics. The resulting abridged life tables were translated into smooth, complete (single year of age) sets of regional mortality rates up to 100 years of age using a reducible four-parameter model life table system [21], constrained to three independent parameters. The Government Actuary’s Department life tables 1991 and 2001 for each country were used as the reliable standards.

Estimates of relative survival (survival from the disease of interest), and of the associated breast cancer-specific excess mortality rate (or hazard), were then derived for time intervals up to 23 years after diagnosis by age group at diagnosis, calendar period of diagnosis, and extent of disease. We used the maximum likelihood approach for individual records [22] as implemented by the StataTM [23] algorithm strel [24]. Expected mortality for women dying during the period 1980–1995 was derived from the 1990–1992 life tables while the 2000–2002 life tables were used for women dying during the period 1996–2002.

result models

Examination of interval-specific relative survival and excess hazard rates provides one means of assessing whether the mortality of a patient cohort can be attributed to the disease in question [25]. However, it is preferable to estimate formally the proportion of the patient population cured using a statistical model [26]. Estimates of population cure from such models are less dependent upon time intervals at the end of follow-up in which both the number of deaths and the number of subjects under observation are at their smallest and may be too small to obtain statistically robust estimate, even in the case of reasonably large samples [17].

Two types of statistical models have so far been derived to estimate population cure: mixture and non-mixture models. We applied both types to our data. A mixture model for cancer survival data was first described by Boag in 1949 [27]. These models assume that, initially, a population of cancer patients consists of two distinct groups: those ‘bound to die’ from their disease and those who can be considered as cured. A number of alternative parametric mixture models for cure have since been derived using the same basic formulation:

\[
R(t) = \exp\left(\ln(C) + \exp\left(\ln(1 - C) \times S_0(t)\right)\right),
\]

where, \(R\) denotes the relative survival, \(C\) the cured fraction, and \(S_0\) the survivor function for the time to failure, \(t\), conditional on ultimate failure [15].

More recently, a non-mixture model has been extended to relative survival [26]. This approach, rather than assuming that the cancer population consists of two distinct groups, models the probability of zero recurrence for each individual. Here, the survival function is expressed in terms of a function of the proportion cured:

\[
R(t) = \exp\left(\ln(C) F_z(t)\right).
\]

The survival function of a non-mixture model has an asymptote at the cure fraction (\(C\)), and the cumulative hazard has an asymptote at \(\ln(C)\). The non-mixture model has not previously been applied to relative survival.

Mixture and non-mixture models both assume a prespecified parametric distribution, such as a Weibull or exponential distribution, for the distribution of individual patient survival times or for the underlying hazard (6, 9). Three different probability distributions were examined: the Weibull, log-normal, and generalised gamma distributions. We thus fitted six separate statistical models, defined by two separate features (model type and probability distribution), in order to examine whether a cured population was present. Fitting this range of models minimised the chance of not finding cure simply due to the assumptions of the model being inappropriate for the patterns of breast cancer survival.

The models were fitted using the StataTM [23] algorithms strmix and strnmix [28].

results

For women diagnosed from 1980 to 1987, the excess mortality rate between the 15th and 23rd anniversaries of diagnosis was greater than zero for all extent of disease groups and for all women diagnosed before their 65th birthday (Table 1). This
suggests that these groups of women continued to die as a consequence of their malignancy during the 16th to 23rd years of follow-up and thus that they could not be considered cured of cancer within 23 years of their diagnosis. Similarly, the excess mortality rate for women diagnosed from 1988 to 1995 between the 10th and 15th anniversaries of diagnosis was greater than zero for all extent of disease groups and for women <80 years at diagnosis. The breast cancer-related mortality rate was negative for some groups of 65–69, 70–79, and 80- to 99-year-old women (Table 1). This implies that some groups of women who were diagnosed at older ages could be considered cured after their 80th birthday.

Fitting cure models to these data also suggested continuous breast cancer-related mortality up to the end of follow-up for the majority of women. Around one in six of the models failed to converge. One reason for this is that the principal assumption of the statistical models, that a plateau in the relative survival curve would eventually be reached, was inappropriate for the data examined. Non-convergence was most common for groups of women >60 years of age and for localised and unstaged disease.

Even when a statistical model was estimated successfully, more often than not the relative survival predicted by the model was very different from that actually observed. This further suggested that the assumption of cure was not appropriate for breast cancer patients because the rates predicted from the cure model and those observed were not similar. Where predicted survival did closely correspond to that observed, it was common that the estimated ‘time to cure’ occurred after 95% of the deaths had elapsed. This suggests that there was evidence of reduced excess mortality, but that this occurred in the portion of the follow-up time with substantially reduced statistical power. In many instances, cure was estimated to have occurred beyond the end of follow-up, again indicating that the underlying assumptions of the model were not appropriate for the data.

Older women diagnosed in New South Wales displayed some evidence of cure, but this was not the case in the West Midlands. In New South Wales, for three age groups of older women, one or more cure models displayed an acceptable fit to the observed data (Figure 2A–D) as well as a negative mean excess mortality rate (Table 1), similarly implying population cure. The modelling analyses suggested that around half of the women diagnosed in New South Wales in the period 1980–1987 aged either 65–69 or 70–79 years could be considered as cured. However, the estimate of the time taken for cure to be reached exceeded 10 years for the youngest group and 8 years for the oldest, implying that cure was not achieved before 75 years of age. In the West Midlands, although negative excess mortality was observed for women >70 years (Table 1), the cure models did not display a good fit to these data. The relative survival rates predicted by the models were very different from the rates observed. This suggests that although excess mortality was substantially reduced 10 or 15 years after diagnosis, the overall pattern of survival was not consistent with the presence of a cured subpopulation.

### discussion

Our analyses show that young and middle-aged women diagnosed up to 1995 with breast cancer experienced continuous excess mortality attributable to their disease up to 23 years after diagnosis. This was the case in both populations examined. Some evidence of cure was found among older women diagnosed in New South Wales, but not in West Midlands.

The plateaux in our relative survival curves for breast cancer were not nearly as evident as has been shown for other...
Figure 2. Observed (grey) and modelled (black) relative survival and excess mortality rates with the number of deaths and the modelled proportion cured for women diagnosed with breast cancer in New South Wales. (A) 1980–1987 aged 65–69 years. (B) 1980–1987 aged 70–79 years. (C) 1988–1995 aged 70–79 years. (D) 1988–1995 aged 80–99 years. 95% confidence intervals are given for the observed relative survival rates and observed interval-specific excess hazard rates and around the estimated proportion cured. The modelled estimates are derived from mixture models using the generalised gamma distribution (A)–(C) and a non-mixture model using the generalised gamma distribution (D).

Figure 3. Observed (grey) and modelled (black) relative survival and excess mortality rates with the number of deaths and the modelled proportion cured amongst cancer patients aged 60–69 years diagnosed during 1988–1995 and followed up to 2002. (A) Women in the West Midlands with breast cancer. (B) A 10% sample of women in England and Wales with colon cancer. 95% confidence intervals are given for the observed relative survival rates and observed interval-specific excess hazard rates and around the estimated proportion cured. The modelled estimates are derived from a mixture model using the Weibull distribution.
malignancies such as colon cancer [1, 29]. This is illustrated by Figure 3 which compares women aged 60–69 years diagnosed with breast cancer during the period 1980–1987 in the West Midlands with a 10% sample of women diagnosed with colon cancer in England of the same age and during the same time period. In contrast to breast cancer, a clear plateau in the relative survival curve for colon cancer is reached within 10 years of diagnosis.

One reason why cure models might display a poor fit to breast cancer in comparison to other malignancies is that the models might not be flexible enough to reflect the probability distribution of survival times of women bound to die as a consequence of breast cancer [28]. However, lack of flexibility is unlikely to explain the lack of cure that we observe here among young and middle-aged women with breast cancer since these groups displayed persistent excess mortality throughout the 23 years of follow-up.

Absence of cure among women with breast cancer is consistent with the majority of previous work, in which long-term excess mortality has been detected well into the second and third decades of follow-up [2–5, 7, 13, 14, 17]. Others have declared cure for some subgroups of breast cancer patients [6, 9, 11, 12, 18]. These authors used similar assumptions to this study. However, they did not apply formal restrictions of model fit, whereas in our analyses, we frequently found that the cure model was not suitable for breast cancer data. This was shown by the large number of models which failed to converge, by the fact that many of the survival curves we observed were very different from those predicted by the cure model and by the tendency for the model to predict cure to have occurred after 95% of the deaths had elapsed. As such, it is possible that our results may represent a more conservative approach to cure estimation. Our analyses also indicate that although cure models are very useful for improving the understanding of the natural history of disease when cure is a reasonable assumption, the models should be used with caution when there is some doubt as to whether this assumption is reasonable.

The absence of cure for young and middle-aged women with breast cancer is clinically plausible since it has been established more recently that a substantial proportion of women have disseminated micro-metastatic disease at diagnosis despite a primary tumour which is apparently localised [30]. The women in this study would have benefited from more recent advances in treatment, particularly during the 1980s. Additionally, a large proportion of women aged 50–69 years diagnosed in the more recent period (1988–1995) would have been screen-detected since screening programmes commenced in both West Midlands and New South Wales between 1988 and 1991. Consequently, lack of cure among women diagnosed during the late 1980s and early 1990s raises the possibility that the introduction of early detection programmes combined with improved management of breast cancer did not result in cure within 15 years of diagnosis. Examination of cure by screen-detection status, and according to treatment received, is required in order to formally evaluate this and to better understand whether cure is attained by some groups of breast cancer patients.

Extent of disease at diagnosis was missing for 15% of women in New South Wales and 13% in West Midlands. Because of their poorer survival, the inclusion of these cases in their true (unknown) extent of disease group is unlikely to have influenced the long-term excess mortality from breast cancer and the existence of cure. However, it would have reduced the short-term survival in all groups.

We have examined excess mortality and cure among women diagnosed with breast cancer in two populations during the period 1980–1995 and shown that cure is not reached in either population in 23 years. Examination of cure according to detection method and treatment received would help us understand if this is the case for all breast cancer patients. Follow-up data beyond 2002 will also enable cure to be examined for women diagnosed after 1995 who received more recently implemented therapeutic regimens.

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references