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Subsequent mortality experience in five-year survivors of childhood, adolescent and young adult cancer in Scotland: A population based, retrospective cohort study

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Available online 8 June 2013

KEYWORDS

Adolescent Child Cohort studies Mortality Neoplasms Prognosis Risk Survivors Young adult **Abstract** Aim: To assess the risk of death in patients who survive at least 5 years after diagnosis of childhood, adolescent or young adult cancer.

Patients and Methods: This was a population-based retrospective cohort study using linked national cancer registry and mortality records in Scotland. The study population consisted of 5229 individuals who were diagnosed with cancer before the age of 25 years between 1981 and 2003, and who survived at least 5 years after the date of diagnosis of their primary cancer. Indirect standardisation was used to calculate mortality ratios standardised for age and sex and absolute excess risks (AERs) compared to the general Scottish population.

Results: During 58,358 person-years of follow-up, there were 359 deaths among the cohort of cancer survivors. The overall SMR was 6.1 (95% confidence interval (CI) 5.5–6.7) and AER 51 (45–58) per 10,000 person-years. Largely because of age- and sex-related differences in background mortality, SMRs were higher in patients diagnosed at 0–14 years (SMR 11.0, 95% CI 9.3–12.9) than 15–24 years (4.7, 4.1–5.3), and in females (9.2, 7.8–10.8) than males (4.8, 4.2–5.5). SMRs and AERs varied substantially by primary cancer and by underlying cause of death. In general, SMRs were little altered by standardisation for an area-based indicator of socio-economic deprivation. Adjusted for age and sex, the risk of death was significantly lower in five-year survivors diagnosed during 1998–2003 compared to those diagnosed during 1981–1985 (Relative hazard ratio, 0.54, 95% CI 0.36–0.81).

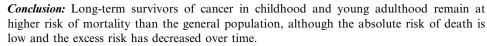
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1. Introduction

Continuing advances in therapy mean that approximately 80% of children and young people with cancer can now expect to be alive 5 years after diagnosis. However, approximately two thirds of survivors experience at least one late effect, and approximately one third experience a late effect that is severe or life threatening. At least twelve publications, in some cases involving the same cohorts described at different time points, have reported that five-year survivors of childhood cancer have a 7-17-fold increased risk of mortality from all causes, compared to the general population.²⁻¹³ The excess mortality is not limited to cancer but also applies to non-cancer causes of death. Many studies have demonstrated an increased risk of second primary cancers arising in survivors of childhood cancer. 14-21 Other long-term complications include effects on the endocrine, cardiac and pulmonary systems, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, neurocognitive dysfunction, and psychosocial manifestations. 1,22-24

Long term morbidity and mortality risks in child-hood cancer survivors relate largely to treatment modality, although they may also be determined by individual host characteristics. The fundamental challenge among this group of patients is to further improve survival prospects while minimising the incidence and severity of treatment-induced late effects. 25

Although the risk of second primary malignancies following childhood cancer has been extensively studied in the United Kingdom (UK) and elsewhere, 14-21 less attention has been devoted to other late effects of therapy, such as cardiac disease. A major active follow-up study, the British Childhood Cancer Survivor Study, ²⁶ is currently underway, and although this is gathering very detailed data, it may not be entirely representative since it relies on patients consenting to participate. A single centre study from Sheffield, UK suggested that survivors of childhood cancer may have a tendency to over-report serious late effects, such as second primary cancers, compared to what is documented in hospital medical records.²⁷ A recent report on cardiac outcomes from five-year survivors of selected childhood cancers in the United States (US) reported increased risks of selfreported congestive heart failure, myocardial infarction, pericardial disease and valvular abnormalities compared to siblings.²³ The authors noted that the proportion of deaths among eligible participants who refused to participate or who were lost to follow-up was higher than among study participants suggesting that the reported risks may be underestimates. On the other hand, studies from specialist centres tend to overestimate the prevalence of chronic disease, ²⁸ emphasising the need for studies to be population-based, if possible.

Compared to follow-up of younger children, considerably less research has been carried out into late effects of therapy for cancer diagnosed during adolescence or young adulthood, 4,29,30 although there is evidence that around half of survivors of adolescent cancer experience late effects of therapy.³¹

The aim of the present study was to describe patterns of mortality among a cohort of patients who have survived at least 5 years after the diagnosis of cancer in childhood, adolescence or young adulthood in Scotland.

2. Patients and methods

The study population comprised patients registered with the Scottish Cancer Registry who survived at least 5 years after the diagnosis of cancer in childhood, adolescence, or young adulthood (age between 0 and 24 years). We decided to study this combined age group in the interests of greater statistical power, and because this age group is now managed in the context of a single national network of clinicians in Scotland (the 'Managed Service Network for Children and Young People with Cancer'). In Scotland, cancer registration records are linked to mortality records by computerised probability matching, which is believed to be highly accurate.³² Emigrations of patients registered with cancer from Scotland to other UK countries are notified to the cancer registry by the National Health Service Central Register (NHSCR). We included data for individuals whose year of diagnosis was in 1981 (the first year of the linked database in Scotland)³² or subsequent years up to 2003 (to allow 5 years' survival, and at least one further year's follow-up). Follow-up was from 5 years after diagnosis to date of emigration from Scotland, date of death, or end of 2009, whichever occurred first.

In terms of diagnosis of first cancer, the study population was re-classified according to the third edition of the International Classification of Childhood Cancer (ICCC-3) (0–14-year-olds)³³ and the most up-to-date version of the diagnostic classification of cancer in adolescents and young adults (15–24-year-olds) developed by Birch et al.³⁴ The data were then mapped to a common 'study classification'. Briefly, this was based primarily on ICCC-3 but with separation of group XI (Other malignant epithelial neoplasms and malignant

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