UNIVERSITY OF BIRMINGHAM

The second Long term follow-up study Newsletter

Welcome

Several years ago now you very kindly helped us with a study of people treated for cancer, leukaemia, tumour or similar illness in childhood and indicated that you would like to receive Study Newsletters to inform you of the main study findings. Welcome to the second Long Term Follow-Up Study (LTFU Study) Newsletter.

For more information on the study please go to the article on page 2 'The why, who, what, how and when?'

We would like to start by saying a big 'Thank you' to all individuals who returned a completed LTFU Study questionnaire and to any family members or friends who may have assisted them. We would also like to thank the general practitioners who took the time to forward the LTFU Study questionnaires to their patients.

Without the very helpful cooperation of both the general practitioners and the study participants it would not have been possible to successfully complete this study.

We would also like to take this opportunity to apologise for the unavoidable delay to this second LTFU Study Newsletter. Due to the nature of the study, and in particular the fact that nearly 15,000 individuals were eligible to take part in the questionnaire survey, the data collection process has been extended over several years. This has meant that data has only been available for analysis relatively recently and therefore initial study findings have only recently become available. However, despite the delay, we hope that you find the articles included in this Newsletter on the initial study findings to be of interest.

Contents

Should you have any questions or concerns regarding anything in the Newsletter please call the free telephone helpline at the Study Co-ordinating Centre on 0800 328 9419 and a member of the Study Team will be pleased to help you.

THE KAY KENDALL LEUKAEMIA FUND

CANCER RESEARCH UK

The why, who, what, how and when?

Why is the study important?

This is the first large-scale population-based study to be undertaken of individuals who have survived childhood cancer, leukaemia, tumour or similar illness (from this point referred to as just 'childhood cancer'). The study looks at a wide variety of possible adverse health and social outcomes of childhood cancer and its treatment. The main reason for doing the study was to collect information which could be used to estimate the risk of adverse health and social problems that may occur in both those surviving childhood cancer and their children and to look at how such risks may vary in relation to factors such as type of childhood cancer and treatment received.

Who was eligible for inclusion?

To be eligible individuals needed to be diagnosed with cancer or a similar illness in Britain before the age of 15 years, between 1st January 1940 and 31st December 1991 and to have survived at least 5 years from the date of diagnosis. The study population was identified through the National Registry of Childhood Tumours. Data has been collected from those aged at least 16 years using a questionnaire that was sent to them via their general practitioner (GP).

The Study Co-ordinating Centre stopped dispatching packages in September 2006. At this point the entire cohort (including people of all ages and also those who have died) consisted of 17,981 individuals. Only those who were alive and aged at least 16 years were eligible to receive a questionnaire. The final number of individuals available for the postal questionnaire survey was 14,836.

Who responded to the questionnaire survey?

A major source of information for the LTFU Study is the questionnaire completed by adults who have survived childhood cancer. A total of 10,483 people had returned a completed questionnaire to the Study Co-ordinating Centre by 20th December 2006 corresponding to 70.7% of those available for the survey. For a variety of overwhelmingly justifiable reasons, 1625 individuals who were eligible to receive a questionnaire were not sent a study package by their GP and therefore did not have the opportunity to complete a study questionnaire. The 10,483 completed questionnaires correspond to 79% of the individuals who were sent a questionnaire by their GP.

Completed questionnaires were returned by a higher proportion of females (75%) than males (67%). There was little variation in response rates between the ages of 20 and 54 years with them remaining between 69% and 74%. However lower response rates (60%) were observed for people aged less than 20 years and higher rates of between 75% and 79% in those aged at least 55 years.

The majority of questionnaires (87%) were completed independently with the remainder being completed by someone helping the study participant but with as much input from the participant as possible. Most commonly the helper was a parent (68%) but for 16% of individuals needing help the questionnaire was completed as an interview undertaken over the telephone with a member of staff at the Study Co-ordinating Centre.

Pregnancies and offspring

The questionnaire collected information on pregnancies and the children of study participants. In those who had returned a completed questionnaire (10,483 individuals) there were around 7000 pregnancies and 5500 liveborn offspring.

Implications for clinical care

The results from the LTFU Study are likely to have several broad implications for people surviving childhood cancer and the clinical care offered to them:

- It will provide unbiased and reliable information about whether there is any increased risk of medical or social problems in the long term for survivors of childhood cancer or similar illness. This would be valuable information for individuals who have survived childhood cancer, their families and those who provide medical and other support to them
- Understanding these risks may be helpful in the planning of clinical follow-up guidelines so that follow-up can be more focused towards those at greater risk
- Understanding the risk of late effects may be useful in planning future treatment practices and protocols by suggesting treatments less likely to cause problems in the longer term

Major strengths of this British LTFU Study

The LTFU Study undertaken in Britain has a number of clear strengths: large size; ability to address a wide variety of adverse outcomes; population-based study population; linkage with the National Health Service Central Registers and the National Registry of Childhood Tumours ensuring reliable identification of second primary neoplasms and efficient and virtually complete tracing of the current whereabouts of individuals eligible for the questionnaire survey; the inclusion of people diagnosed between 1940 and 1991 means that 48% have been followed for at least 20 years after initially surviving five years and 49% have been treated since 1980 (and therefore with relatively modern therapies).

The future

There are many reasons to regularly monitor people surviving childhood cancer at about 5 to 10 year intervals especially as significant numbers of these individuals reach mature adulthood. It is therefore anticipated that individuals who were eligible for this study will be approached again in the next few years. It is also hoped that the study population might be extended to include people diagnosed after 1991 to ensure that information is available relating to the entire range of treatment experiences including more modern therapies. It is becoming increasingly important to investigate how an individual's genetic makeup may influence how likely they are to be affected by particular health problems. Such investigations require a source of DNA and it is therefore hoped to obtain this (probably through a saliva sample) as part of any future fieldwork.

The information for this section was taken from: Hawkins MM, Lancashire ER, Winter DL, Frobisher C, Reulen RC, Taylor AJ, Stevens MCG and Jenney M. (2008) The British Childhood Cancer Survivor Study: Objectives, Methods, Population Structure, Response Rates and Initial Descriptive Information. Pediatric Blood and Cancer 50; 1018–1025.

Long-term follow-up of individuals surviving childhood cancer

Why is follow-up important?

Although childhood cancer is rare high levels of survival mean that most of those diagnosed survive into adulthood with approximately 1 in 1000 young adults having survived childhood cancer. Uncertainties concerning the long-term health of individuals surviving childhood cancer provide strong justification for their continued follow-up.

Current follow-up practices

The Study Co-ordinating Centre has been involved in a study that aimed to explore current clinical follow-up practices among people surviving childhood cancer in Britain. This was investigated using a postal survey of Children's Cancer and Leukaemia Group (CCLG), formerly United Kingdom Children's Cancer Study Group, clinicians, who treat most children with cancer in Britain. A completed questionnaire was returned by 71 clinicians.

Although the majority of clinicians reported follow-up of all those surviving childhood cancer in a hospital clinic until at least 5 years after the end of treatment there was a small proportion (3%) who reported discharging patients to their general practitioner (GP) earlier than this. For time periods longer than five years after the end of treatment, wide variation was found in the extent to which they are discharged from hospital follow up. Just over half of the clinicians (52%) indicated following up all of their patients for life whilst just under half (45%) reported discharging at least some of their patients. The majority of patients who were discharged had either been diagnosed with a benign or a stage 1 tumour or had been treated with surgery alone. However, a few clinicians reported discharging all or most such patients. Those discharged from hospital follow-up were overwhelmingly discharged to their GP. Once individuals had been discharged from hospital follow-up at least 5 years after the end of their treatment, only 44% of the clinicians continued to monitor the health of these patients through regular health updates. Such health updates were generally via a letter or a postal questionnaire to either the individual surviving childhood cancer or their GP.

A need for national guidelines

The level of variation observed in clinical long-term follow-up practices of people surviving childhood cancer highlights the need for national guidelines concerning standardised levels of clinical follow-up required for specific groups of these individuals. The Late Effects Group of the CCLG has recently updated its guidelines for the clinical follow-up of people surviving childhood cancer and has also produced a related package for them.

You can find this at www.aftercure.org, or for more information on the package see 'After Cure' on page 8.

The information for this section was taken from: Taylor A, Hawkins M, Griffiths A, Davies H, Douglas C, Jenney M, Wallace WHB, Levitt G. (2004) Long-term follow-up of survivors of childhood cancer in UK. Pediatric Blood and Cancer 42: 161–168

Getting married or living with a partner

Marriage rates in individuals surviving childhood cancer

From questionnaires returned for the LTFU Study, marital status was assessed in 9954 adults who had survived childhood cancer – 34% had married, and an additional 10% had at some point in time co-habited with a partner.

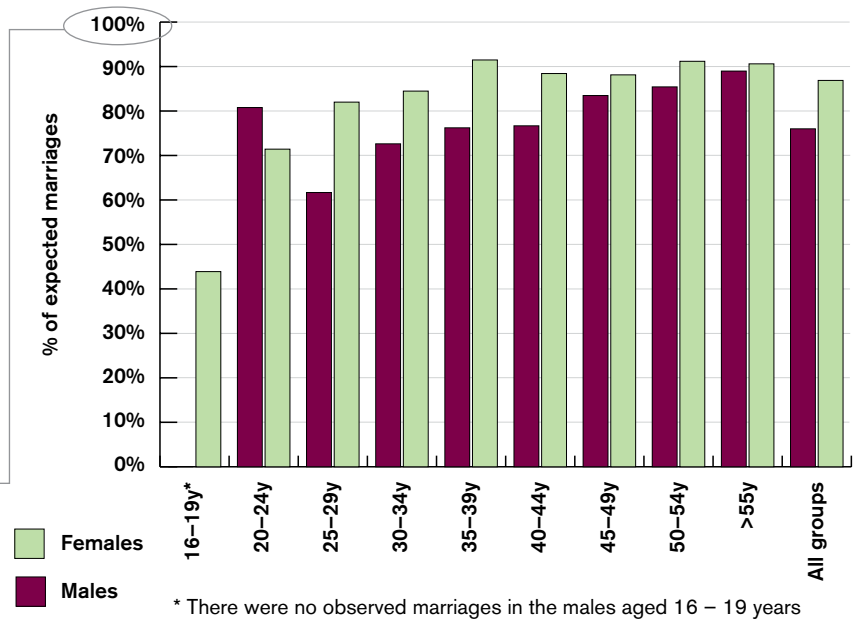
Do individuals who have survived childhood cancer marry more, less or the same as the general population?

Consistently across five year age groups, the number of study participants ever married was lower than would be expected from the general population (Figure 1). This difference was greater for males than females, and for individuals surviving tumours of the central nervous system (mostly brain tumours), compared to the other study participants.

The information for this section was taken from: Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. (2007) Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. International Journal of Cancer 121: 846–855.

If the study participants were marrying at a level similar to the general population you would expect values of 100%. A value below 100% suggests that the number of marriages in individuals surviving childhood cancer was below the number of marriages occurring in the general population.

Figure 1: Comparison of the observed number of marriages in adults who have survived childhood cancer with the number of marriages expected from the general population, in age and sex specific groups.



* There were no observed marriages in the males aged 16 – 19 years

Health status among individuals surviving childhood cancer

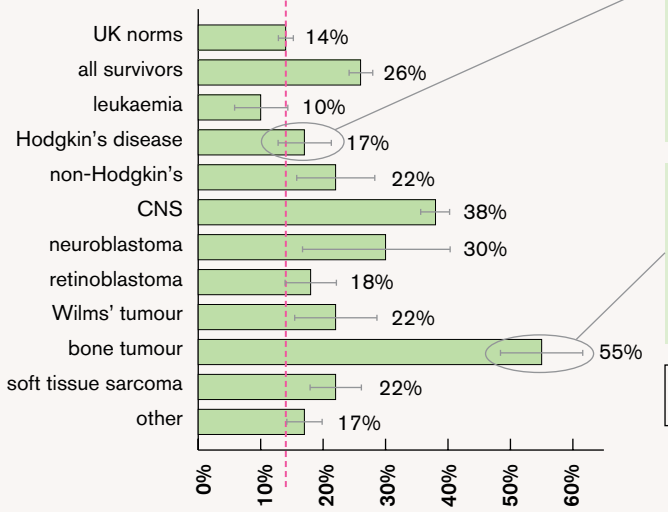
and how it compares to the general population

This study looked at different aspects of physical and mental health among people surviving childhood cancer. For example, we looked at how these individuals are affected in carrying out daily activities such as walking or carrying groceries. The physical and mental health of the study participants was then compared with people from the general population to see whether there were any differences. The study revealed that most study participants were doing very well and that most did not differ from the general population with regard to physical or mental health. We found that only a minority of all respondents rated their own health status as substantially below that of the general population. In particular, a large proportion of people surviving a bone tumour or a tumour of the central nervous system (mostly brain tumours) reported difficulties with their physical health. Figure 2 shows the percentage of study participants being limited in specific daily activities compared to the general population ('UK norms'). For example, over 60% of individuals who had survived a bone tumour said that they had problems with walking a mile compared with 16% in the general population and 21% of study participants originally diagnosed with a central nervous system tumour had difficulties with bathing and dressing themselves compared with 5% in the general population.

The information for this section was taken from: Reulen RC, Winter DL, Lancashire ER, Zeegers MP, Jenney ME, Walters SJ, Jenkinson C, Hawkins MM. (2007) Health-status of adult survivors of childhood cancer: A large-scale population-based study from the British Childhood Cancer Survivor Study. International Journal of Cancer 121: 633–640

Figure 2: Percentage of individuals who have survived childhood cancer reporting being limited in specific daily activity or other problem.

1) % limited in moderate activities

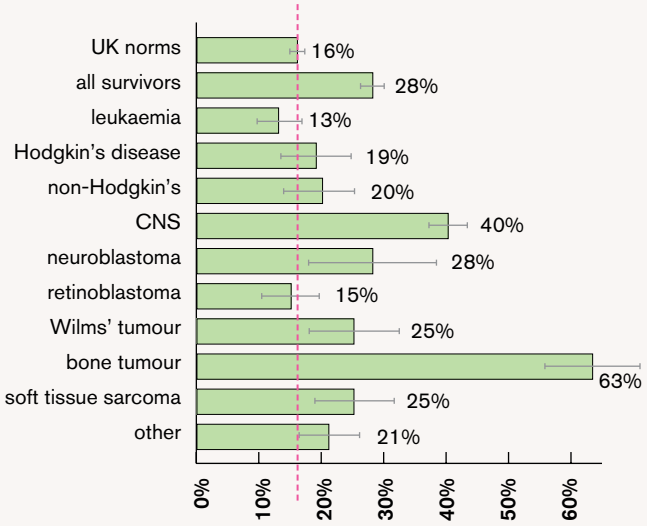


As the line at the end of the grey bar crosses the red line (that represents the percentage limited in moderate activities in the general population) this indicates there is no evidence that survivors of Hodgkin's disease differ from the general population with regard to these activities.

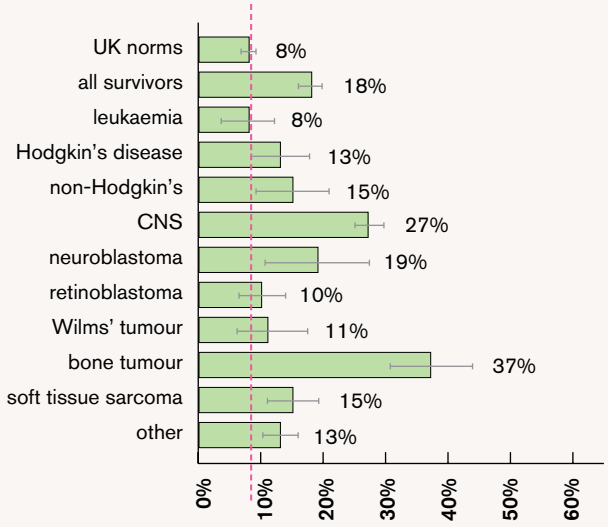
As the line at the end of the grey bar does not cross the red line (that represents the percentage limited in moderate activities in the general population), and it also lies to the right of the red line, this shows that survivors of CNS tumours are more limited than the general population with regard to these activities.

represents the limitation for the specified activity in the general population

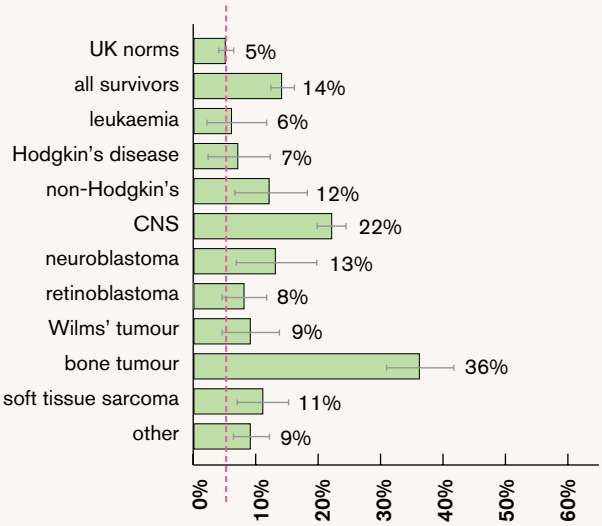
2) % limited in walking a mile



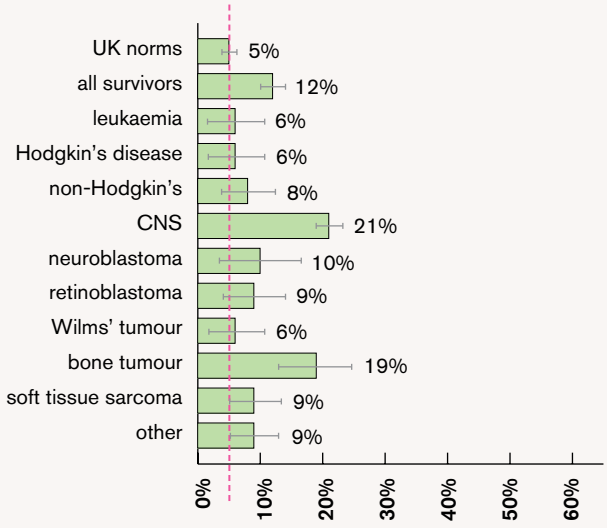
3) % limited in climbing stairs



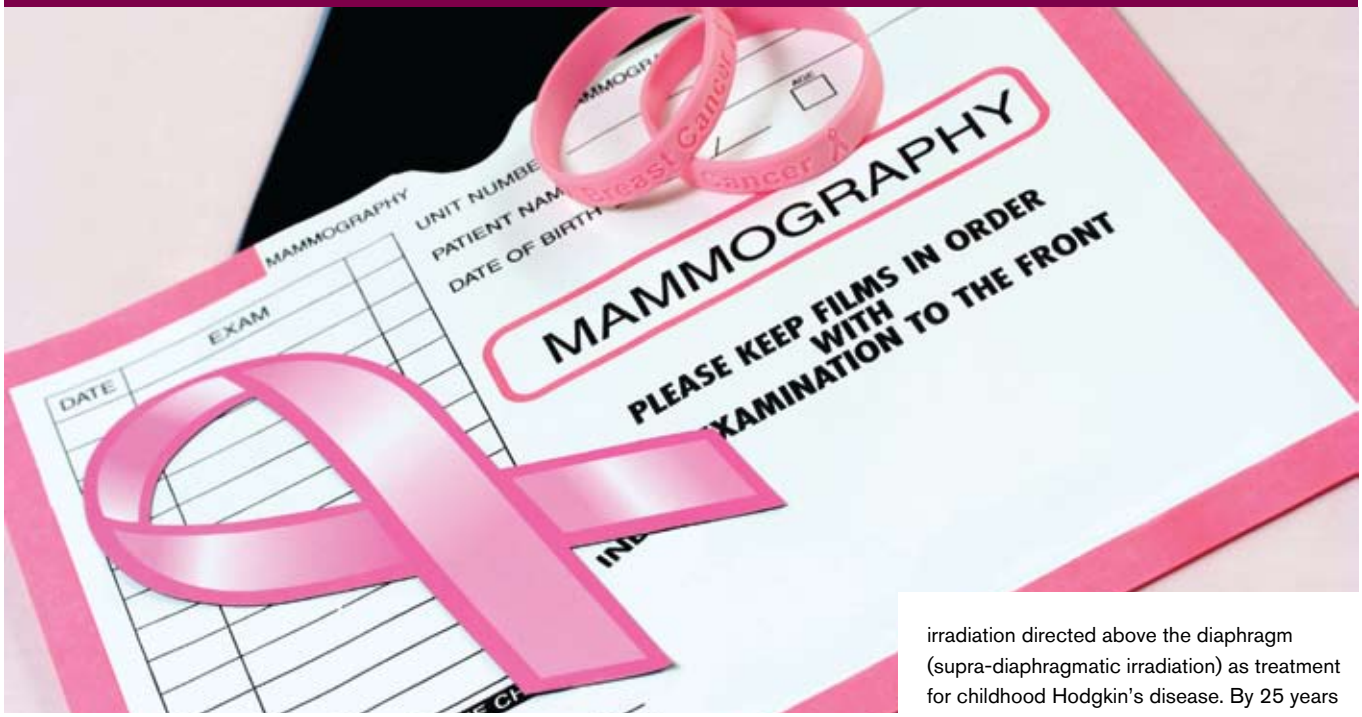
4) % limited in walking 100 yards



5) % limited in bathing and dressing



Breast cancer risk after childhood Hodgkin's disease



Current knowledge

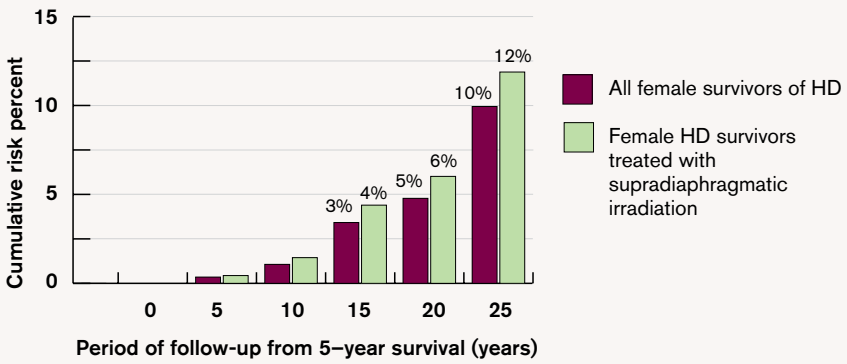
Treatment of Hodgkin's disease has led to greatly improved survival in recent years. The proportion of individuals surviving for at least five years after diagnosis of childhood Hodgkin's disease in Britain between 1992 and 1996 was 95%, this compares to a proportion of less than 40% for children diagnosed between 1962 and 1966. This increase in survival, largely due to the use of chemotherapy and radiotherapy, has been accompanied by an inevitable increase in the focus on the late effects of treatment. The most serious late effects of treatment include an increased risk of second primary solid cancers and leukaemias, cardiovascular disease and infertility. It is known that there is an increased risk of breast cancer in women who have survived Hodgkin's disease and were treated with radiotherapy, in particular, mantle irradiation, (which often includes irradiation of breast tissue). Relatively high doses of mantle irradiation treatment were used in the past, particularly during the 1970s and 1980s. Previously published studies have reported a wide variation in risk of breast cancer among females surviving childhood Hodgkin's disease. In November 2003 the Department of Health began a recall of all women treated for Hodgkin's disease under the age of 35 years with supradiaphragmatic irradiation (ie. irradiation directed above the diaphragm). The women are invited for an interview and to monitor their risks of breast cancer.

British population-based information from the long term follow-up study

To provide British estimates of risk to inform surveillance programmes, we carried out the first British population-based cohort study of breast cancer in females surviving childhood Hodgkin's disease. From the underlying cohort of the LTFU Study, there were 383 women who had survived at least five years following a diagnosis of childhood Hodgkin's disease. Sixteen of these went on to develop invasive breast cancer after initially surviving five years, which was approximately 11.5 times as many cases of invasive breast cancer as expected when compared to the general British female population in the same age groups. All of these 16 individuals had been treated with irradiation directed above the diaphragm (supra-diaphragmatic irradiation) as treatment for childhood Hodgkin's disease. By 25 years of follow-up after initially surviving five years, 10% of all female survivors of childhood Hodgkin's disease developed invasive breast cancer rising to 12% among those treated with supradiaphragmatic irradiation (see Figure 3). These figures, although greater than expected, are at the lower end of previous international estimates. We hope that our data will provide a basis for future surveillance and for counselling individuals surviving childhood Hodgkin's disease as to their likely risk of breast cancer.

The information for this section was taken from: Taylor AJ, Winter DL, Stiller CA, Murphy M, Hawkins MM. (2007) Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. International Journal of Cancer 120: 384–391

Figure 3: Percentage of female 5-year survivors of childhood Hodgkin's disease (HD) developing breast cancer by increasing periods of follow-up.



Second primary tumours after Wilms' tumour

Wilms' tumour occurrence and survival rates

Wilms' tumour (or nephroblastoma) is the most frequent kidney cancer of childhood but it is still relatively rare, with about 75 new cases occurring each year in the UK. It mostly affects children below the age of five. Survival from Wilms' tumour has increased steadily since the introduction of chemotherapy and radiotherapy in the 1960s. Among children diagnosed in Britain between 1996 and 2000, 91% survived at least 5 years which compares to 77% when all forms of childhood cancer are considered for the same time period. The increase in survival has been accompanied by an increase in the monitoring of late effects of treatment. For individuals surviving Wilms' tumour, many of these late effects are due to abdominal and pulmonary irradiation (used to treat the original Wilms' tumour in the kidney(s) and occasionally spread into the lungs) and treatment with chemotherapy. The development of second primary tumours in individuals surviving Wilms' tumour is one of the more serious late effects and these may occur many years after the diagnosis of the original cancer.

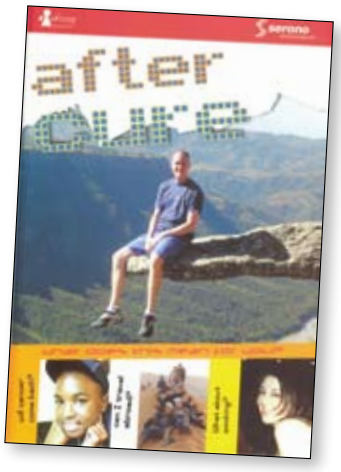
Risks of second primary tumours among the Wilms' tumour survivors in the long term follow-up study

A population-based cohort study within the LTFU Study was carried out to determine the risk of second primary tumours in survivors of Wilms' tumour in Britain. A cohort study is one in which a group of individuals (in this case individuals surviving Wilms' tumour) is followed up over time to look at what disease they develop. In the current study the outcome of interest was diagnosis with a second primary tumour. There were 1441 Wilms' tumour survivors: 732 males (50.8%) and 709 females (49.2%), followed up on average for 19.3 years after initially surviving 5 years. We observed 81 second primary tumours, including 52 solid tumours, three acute leukaemias and 26 basal cell carcinomas (a non-life threatening type of skin cancer). The 52 second solid tumours we observed compared to 7.8 such tumours we would have expected to occur had the cohort been at the same risk as the general British population for the same age and sex groups. To express this in another way we can say that there were approximately 6.7 times as many second solid tumours observed in the population of individuals surviving Wilms' tumour compared to that expected from general population information. The percentage of Wilms' tumour survivors diagnosed with solid second primary tumours by ages 30, 40 and 50 years was 2.3%, 6.8%, and 12.2% respectively. In conclusion, the overall risk of second primary neoplasms in the survivors of Wilms' tumour included in the LTFU Study has been quantified and solid second tumours tended to develop in the irradiated tissue (abdominal/pelvic and thoracic (chest area)). Continued follow-up up of these individuals is important in order to monitor such late effects of treatment and evaluate whether the risk decreases following more recent treatment practices involving lower doses of irradiation.

The information for this section was taken from: Taylor AJ, Winter DL, Pritchard-Jones K, Stiller CA, Frobisher C, Lancashire ER, Reulen RC, Hawkins MM. (2008) Second Primary Neoplasms in Survivors of Wilms' Tumour – a Population-based Cohort Study from the British Childhood Cancer Survivor Study. International Journal of Cancer 122; 2085–2093.

After cure

The Late Effects Group of the Children's Cancer and Leukaemia Group (CCLG) has produced a package aimed at young people aged 16 or over who have survived cancer.



The package covers a variety of topics such as:

- follow-up and future care
- education and jobs
- disability issues
- life insurance and mortgages
- fertility
- travel
- lifestyle – how to keep healthy
- information about survivor groups

The addresses of some useful websites are also included. In addition there are 18 fact-sheets about the effects of different treatments on different parts of the body.

To access this information please go to: www.aftercure.org

Survivors' conference

A photograph of some survivors taken at the most recent Survivors' conference, an annual event organised by CLIC Sargent.

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