Mortality among children and young people who survive cancer in Northern Ireland

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INTRODUCTION

Children who have had cancer now have an excellent chance of surviving their disease with 80% of patients alive 5 years from diagnosis. However previous studies have shown these patients are at a higher risk of death from other causes in later life, primarily as a result of recurrence or continuation of their cancer, but also due to the side effects of treatment leading to second cancers and cardiac disease.

We investigate long term mortality among childhood cancer survivors, and also include young people (aged 15-24) diagnosed with cancer or benign/uncertain brain tumours in N. Ireland between 1993 and 2013.

METHODS

Data on all patients diagnosed with either a malignant cancer or a non-invasive brain tumour when aged 0-24 during 1993-2013 were extracted from the Northern Ireland Cancer Registry (NICR). Information on each patient’s sex, age, date of diagnosis and cancer type was included with the latter classified into ten main groups based upon their ICD10 code.

Follow up of these patients in order to determine their status up to 31/12/2013 was conducted by electronically matching the extracted data on children and young people to the NICR to identify second malignancies, the medical card register from the HSC Business Services Organisation (BSO) to identify those who emigrated (5%) and deaths information from the General Register Office (GRO).

Cause of death was classified into the same groups as the cancer diagnosis plus a further five categories relating to non-cancer causes of death (Circulatory, Respiratory, External, Congenital Malformation and other). For deaths prior to 2001 cause of death was coded using the ICD9 classification.

In a small number of cases where death was recorded and a cause of death could not be identified (30 patients) a manual exercise was conducted in an attempt to obtain this information through physical examination of BSO and GRO records (as opposed to electronic matching). However the cause of death for 14 patients could not be identified. These
patients were thus assigned a cause of death to be same as 
their first cancer (total Deaths 215).

TREND ANALYSIS

The trends in age-standardised cancer incidence rates were 
investigated over the twenty-one year period using the 
JoinPoint program\textsuperscript{7,8} to provide a summary measure for the 
trend in the form of the annual percentage change (APC) in 
the age-standardised rate. If a significant change in direction is 
identified then the trend is broken up into different segments 
based upon the points where the trend changes and APCs are 
then presented for each segment.

SURVIVAL

Observed survival was calculated using the Kaplan-Meier 
method for patients diagnosed in 1993-2008 with estimates 
for survival up to 20 years. The proportion of patients who 
 survive a specified amount of time after the point that they 
are diagnosed with cancer was calculated regardless of the 
cause of death. This calculation results in a lower estimate 
of survival than net or relative survival, both of which take 
account of general background mortality.

Excess mortality from all causes was calculated for children 
diagnosed during 1993-2012 who survived at least one-year 
from diagnosis of their first cancer and for those diagnosed 
during 1993-2008 who survived at least five-years from 
diagnosis of their first cancer.

Using standardized mortality ratios (SMRs- defined as the 
ratio of the observed number of deaths within the cancer 
survivor population to the expected number of deaths that 
would occur within the general population), the expected 
number of deaths was calculated by first determining the 
total number of person-years (the cumulative survival time 
in years) by sex, five-year age group and year of diagnosis 
and then multiplying this by the mortality rate in the general 
population for that sex, age and year combination.

Cancer mortality rates for cancer patients were separated into 
those who died from their first cancer including a recurrence) 
and those who died of a second different cancer, with the 
later forming the basis of a comparison with the general 
population.

RESULTS

Between 1993-2013 there were 2,633 persons (aged 0 to 
24) diagnosed with cancer (including non-invasive brain 
tumours) in Northern Ireland, an average of 125 people per 
year. Of these 1,386 (52.6%) were male while 1,247 were 

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Cancer type ( ICD10 ) & \multicolumn{3}{c|}{Ages 0-24} & \multicolumn{3}{c|}{Ages 0-14} & \multicolumn{3}{c|}{Ages 15-24} \\
& Both sexes & Male & Female & Both sexes & Male & Female & Both sexes & Male & Female \\
\hline
All cancers & 2,633 & 1,386 & 1,247 & 1,139 & 644 & 495 & 1,494 & 742 & 752 \\
Bone C40-C41 & 105 & 67 & 38 & 44 & 26 & 18 & 61 & 41 & 20 \\
Brain, eye & CNS * & 611 & 326 & 285 & 364 & 197 & 167 & 247 & 129 & 118 \\
Breast C50 & 11 & 0 & 11 & 0 & 0 & 0 & 11 & 0 & 11 \\
Digestive organs C15-C26 & 63 & 31 & 32 & 27 & 14 & 13 & 36 & 17 & 19 \\
Female genital C51-C58 & 107 & - & 107 & 6 & - & 6 & 101 & - & 101 \\
Leukaemia C91-C95 & 454 & 262 & 192 & 334 & 196 & 138 & 120 & 66 & 54 \\
Lip, oral cavity & pharynx C00-C14 & 36 & 20 & 16 & 10 & 4 & 6 & 26 & 16 & 10 \\
Lymphoma C81-C86 & 350 & 199 & 151 & 107 & 77 & 30 & 243 & 122 & 121 \\
Male genital C60-C63 & 186 & 186 & - & 9 & 9 & - & 177 & 177 & - \\
Mesothelial & soft tissue C45-C49 & 99 & 63 & 36 & 55 & 33 & 22 & 44 & 30 & 14 \\
Respiratory organs C30-C39 & 32 & 19 & 13 & 11 & 6 & 5 & 21 & 13 & 8 \\
Skin C43-C44 & 319 & 100 & 219 & 26 & 8 & 18 & 293 & 92 & 201 \\
Thyroid & other endocrine C73-C75 & 116 & 38 & 78 & 49 & 24 & 25 & 67 & 14 & 53 \\
Urinary C64-C68 & 86 & 48 & 38 & 71 & 42 & 29 & 15 & 6 & 9 \\
Other - all others in range C00-C97 & 58 & 27 & 31 & 26 & 8 & 18 & 32 & 19 & 13 \\
\hline
\end{tabular}
\end{table}

*C69-C72, D32, D33.0-33.4, D35.2-35.4, D42, D43.0-43.4, D44.3-44.5

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female. Of these patients 1,139 (43.3%) were aged 0-14 with the remainder (1,494 patients) aged 15-24.

Among the children and young people diagnosed with cancer, 59 patients (2.2%) had two or more cancers recorded during 1993-2013, with 18 of these cancers occurring after the age of 24. In total, 2,676 tumours were diagnosed among children and young people during 1993-2013.

There were differences between the two age groups studied. Among children aged 0-14, brain (including eye and CNS) cancer, and leukaemia were the two most common cancers. They collectively made up almost two thirds of all cancers diagnosed representing 32% and 29% of cancers respectively. The distribution of cancer type was similar for boys and girls, with very few gender specific cancers diagnosed in this age group.

Among young people (aged 15-24) skin cancer was the most common cancer making up one fifth (19.6%) of cases. This was followed by brain, eye and other CNS tumours (16.5%) and lymphoma (16.3%). Leukaemia was less frequent in this age group than among children making up 8.0% of all cancers. The distribution of cancers by type differed between males and females. Among females skin cancer was the most common (26.7%) while male genital cancer (specifically testicular cancer which made up 99% of this group) was the most common among males (23.9%). Brain, eye and CNS tumours and lymphoma were also common for both sexes; however 13.4% of female cases were gynaecological cancers, while skin cancer was the fourth most common male cancer (12.4% of cancers). (Table 1)

**TRENDS**

During 2009-2013 there were 134 children and young people diagnosed with cancer each year for the first time, a slight increase of 9% on the 123 per year diagnosed during 1994-1998. During this period, the number of cases increased by an average of 0.6% per year. The increase was slightly greater

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**Table 2:**

Observed survival from cancer among children and young people (aged 0-24) by sex and age: Patients diagnosed 1993-2008, followed up to end of 2013

| Sex     | Survival time | Ages 0-24 | Ages 0-14 | Ages 15-24 |
|---------|---------------|-----------|-----------|------------|
|         | Observed survival (95% CI) | Observed survival (95% CI) | Observed survival (95% CI) |
| Male    | 3 months      | 96.4% (95.1%, 97.4%) | 96.3% (94.1%, 97.6%) | 96.6% (94.7%, 97.8%) |
|         | 6 months      | 94.2% (92.6%, 95.5%) | 93.3% (90.7%, 95.2%) | 95.0% (92.9%, 96.5%) |
|         | 1 year        | 89.3% (87.3%, 91.1%) | 88.7% (85.6%, 91.3%) | 89.8% (87.0%, 92.1%) |
|         | 5 years       | 75.8% (73.1%, 78.3%) | 74.3% (70.1%, 78.0%) | 77.1% (73.4%, 80.4%) |
|         | 10 years      | 72.8% (69.9%, 75.4%) | 71.8% (67.4%, 75.6%) | 73.6% (69.6%, 77.1%) |
|         | 15 years      | 72.2% (69.2%, 74.9%) | 70.9% (66.5%, 74.9%) | 73.3% (69.3%, 76.9%) |
|         | 20 years      | 70.6% (67.2%, 73.6%) | 70.3% (65.6%, 74.4%) | 70.8% (65.8%, 75.1%) |
| Female  | 3 months      | 98.1% (97.0%, 98.8%) | 97.5% (95.3%, 98.7%) | 98.4% (97.0%, 99.2%) |
|         | 6 months      | 96.2% (94.8%, 97.3%) | 95.1% (92.3%, 96.9%) | 97.0% (95.2%, 98.1%) |
|         | 1 year        | 92.2% (90.3%, 93.7%) | 90.2% (86.7%, 92.8%) | 93.5% (91.1%, 95.2%) |
|         | 5 years       | 83.2% (80.6%, 85.4%) | 80.9% (76.5%, 84.6%) | 84.6% (81.4%, 87.4%) |
|         | 10 years      | 80.7% (78.0%, 83.1%) | 78.7% (74.1%, 82.6%) | 82.0% (78.5%, 85.0%) |
|         | 15 years      | 79.5% (76.6%, 82.1%) | 77.8% (73.1%, 81.8%) | 80.6% (76.9%, 83.8%) |
|         | 20 years      | 79.2% (76.2%, 81.8%) | 77.0% (72.0%, 81.2%) | 80.6% (76.9%, 83.8%) |
| Both sexes | 3 months      | 97.2% (96.4%, 97.9%) | 96.8% (95.4%, 97.8%) | 97.5% (96.4%, 98.3%) |
|         | 6 months      | 95.2% (94.1%, 96.0%) | 94.1% (92.3%, 95.5%) | 96.0% (94.7%, 97.0%) |
|         | 1 year        | 90.7% (89.3%, 91.9%) | 89.4% (87.1%, 91.3%) | 91.6% (89.9%, 93.1%) |
|         | 5 years       | 79.3% (77.4%, 81.0%) | 77.2% (74.2%, 79.8%) | 80.9% (78.5%, 83.1%) |
|         | 10 years      | 76.5% (74.5%, 78.3%) | 74.8% (71.7%, 77.6%) | 77.8% (75.2%, 80.2%) |
|         | 15 years      | 75.6% (73.6%, 77.5%) | 73.9% (70.7%, 76.8%) | 76.9% (74.2%, 79.4%) |
|         | 20 years      | 74.7% (72.5%, 76.7%) | 73.2% (69.9%, 76.2%) | 75.8% (72.8%, 78.5%) |

Note: Data for more than 5 years are estimates as full 20 year follow up is only available for earlier diagnosis years

CI: Confidence interval
among males than females (10% vs. 7%) with an increase from 64 to 71 male patients per year and an increase from 59 to 64 female patients per year; however the changes by sex were not statistically significant.

Among children aged 0-14 there was little change in the average number of patients diagnosed each year with 58 patients diagnosed each year from 1994-1998 (33 male, 25 female) and 60 patients from 2009-2013 (34 male, 26 female). While there was little change overall, the number of cases declined between 1994 and 2004, and increased annually by 2.9% per year between 2004 and 2013.

Among young people (aged 15-24) there were 75 patients diagnosed with cancer each year for the first time during 2009-2013, an increase of 15% on the 65 per year diagnosed during 1994-1998. The increase was slightly greater among males than females (23% vs. 8%) with an increase from 30 to 37 male patients per year and an increase from 35 to 38 female patients per year. While the annual percentage change in the number of cases was not significant for each sex, for both sexes combined the number of cases increased by 0.9% per year.

ONE YEAR SURVIVORS
There were 2,284 patients aged 0-24 at diagnosis who survived at least one year from a cancer diagnosis in 1993-2012. Of these 972 (42.6%) were aged 0-14 at diagnosis, while 1,312 were diagnosed aged 15-24. There were slightly more male than female survivors (1,190 vs. 1,094) among those diagnosed at age 0-24, however this difference was mostly a result of a greater number of male survivors diagnosed at age 0-14 than in older ages (545 vs. 427).

The most common primary cancers among these survivors were brain, eye and CNS tumours (22.5%), followed by leukaemia (16.4%), lymphoma (13.9%) and skin cancer (13.2%). Among those diagnosed at age 0-14 brain, eye and CNS cancer (31.0%) and leukaemia (29.4%) made up two thirds of survivors. Among those diagnosed at age 0-14-24 however, skin cancer was the most common (21.4%) followed by lymphoma (16.5%), brain, eye and CNS tumours (16.2%) and male genital cancer (16.5%).

FIVE YEAR SURVIVORS
There were 1,527 patients aged 0-24 at diagnosis who survived at least five years from a cancer diagnosis in 1993-2008. Of these 647 (42.4%) were aged 0-14 at diagnosis, while 880 were diagnosed as young adults aged 15-24. The most common cancers among these survivors were similar to those who survived one year from diagnosis

SURVIVAL
Survival from cancer among children and young people was generally good with 90.7% of patients diagnosed in 1993-2008 alive one year from diagnosis, while after five years, 79.3% of patients were still alive (Table 2). Ten-year survival is estimated to be 76.5% and twenty-year survival to be 74.7%.

Survival among females was higher than among males. Five years survival among females was 83.2% compared to 75.8% among males – the difference in one year survival was similar. By twenty years from diagnosis the difference had increased to 79.2% for females compared to 70.6% for males. Part of the reason for this difference may be a result of the different cancer types experienced by each sex with more bone (five-year survival 67.9%) and less skin (five-year survival 96.7%) or thyroid and endocrine (five-year survival 84.8%) in males than females.

There was very little difference in survival between the 0-14 and 15-24 age groups with one-year survival at 89.4% and 91.6%, five-year survival at 77.2% and 80.9% and twenty-year survival estimates at 73.2% and 75.8% respectively.

Five-year observed survival for study patients diagnosed in 1993-2008 was 74.7% for brain, eye and other CNS cancer (including non-invasive tumours), 70.4% for leukaemia and 86.8% for lymphoma. For leukaemia survival was much better among those aged 0-14 than those aged 15-24 due to a much higher proportion of acute lymphocytic leukaemia (ALL) in this age group (78.7% of leukaemia’s in the 0-14 age group vs. 50.0% in the 15-24 age group) which has better survival than other leukaemia types. (Table 3)

EXCESS MORTALITY
Among children and young people who survived at least one year, deaths from all causes were 25 times (SMR=24.7 (95% CI 22-27.5,) P<0.001) higher than the number found in a similar cohort of children and young people in the general population. However this includes the cancer the survivor was originally diagnosed with. Excluding this cause, the one-year survivors were over twice as likely to die from additional causes (SMR = 2.2,(95%CI 1.3-3.0) p=0.005) than in the general population. This risk was slightly greater for females, SMR 3.3(1.5-5.0) P=0.012 than males SMR=1.6 (0.8-2.5)p=0.142 with the increased risk not reaching statistical significant for males.

Among children and young people who survived at least five years, deaths from all causes were seven times higher than the number found in a similar cohort of children and young people in the general population (SMR = 7.3,(5.5-9.2) p<0.001). This includes the cancer the survivor was diagnosed with, thus even after five years some patients died from a continuation of their original cancer or from recurrences of this cancer. This risk was higher among females than males (10 times greater vs. 6 times greater). Excluding the primary cancer as a cause, the excess deaths in five-year survivors, although three times greater than the mortality rate in the general population (SMR= 3.2 (95% CI 0.4, 6.1)p= 0.122,) did not reach statistical significance.

DISCUSSION
In Northern Ireland, approximately 125 children and young people aged 0-24 are diagnosed with cancer for the first time
### Table 3:
**Observed survival from cancer among children and young people (aged 0-24) by type and age: Patients diagnosed 1993-2008, followed up to end of 2013**

(A) AGES 0-24

| Survival time | Bone | Skin | Mesotheial & soft tissue | Female genital |
|---------------|------|------|--------------------------|----------------|
| 3 months      | 98.7% (90.9%, 99.8%) | 99.6% (97.1%, 99.9%) | 93.6% (85.3%, 97.3%) | 98.8% (91.8%, 99.8%) |
| 6 months      | 98.7% (90.9%, 99.8%) | 99.2% (96.8%, 99.8%) | 89.7% (80.5%, 94.7%) | 96.4% (89.2%, 98.8%) |
| 1 year        | 97.3% (89.8%, 99.3%) | 97.9% (95.1%, 99.1%) | 80.8% (70.1%, 87.9%) | 92.7% (84.6%, 97.6%) |
| 5 years       | 67.9% (56.0%, 77.2%) | 96.7% (93.5%, 98.3%) | 55.1% (43.4%, 65.3%) | 86.5% (77.0%, 92.3%) |
| 10 years      | 56.8% (44.3%, 67.5%) | 94.8% (90.9%, 97.0%) | 53.4% (41.7%, 63.8%) | 83.8% (73.7%, 90.3%) |
| 15 years      | 56.8% (44.3%, 67.5%) | 94.8% (90.9%, 97.0%) | 53.4% (41.7%, 63.8%) | 83.8% (73.7%, 90.3%) |
| 20 years      | 56.8% (44.3%, 67.5%) | 94.8% (90.9%, 97.0%) | 49.6% (36.5%, 61.4%) | 83.8% (73.7%, 90.3%) |

(B) AGES 15-24

| Survival time | Male genital | Urinary | Brain, eye & CNS |
|---------------|--------------|---------|------------------|
| 3 months      | 99.3% (95.1%, 99.9%) | 99.3% (95.1%, 99.9%) | 95.8% (93.5%, 97.3%) |
| 6 months      | 97.9% (93.6%, 99.3%) | 97.9% (93.6%, 99.3%) | 92.8% (90.1%, 94.8%) |
| 1 year        | 96.5% (91.8%, 98.5%) | 96.5% (91.8%, 98.5%) | 86.9% (83.5%, 89.6%) |
| 5 years       | 92.3% (86.5%, 95.7%) | 92.3% (86.5%, 95.7%) | 74.7% (70.5%, 78.4%) |
| 10 years      | 92.3% (86.5%, 95.7%) | 92.3% (86.5%, 95.7%) | 70.3% (65.9%, 74.3%) |
| 15 years      | 91.1% (84.7%, 94.9%) | 91.1% (84.7%, 94.9%) | 70.3% (65.9%, 74.3%) |
| 20 years      | 88.2% (78.3%, 93.7%) | 88.2% (78.3%, 93.7%) | 69.6% (64.9%, 73.8%) |

Note: Data for more than 5 years are estimates as full 20 year follow up is only available for earlier diagnosis years.

CI: Confidence interval, CNS: Central Nervous System
Brain, eye and CNS includes non-invasive brain tumours
each year. Long term survival for these people is generally good, with four out of five patients still alive 5 years from their diagnosis. In concordance with other studies\textsuperscript{2,3} we found that deaths as a result of a continuation of the patient’s cancer continue to occur after the five-year point and that patients who are free from their first cancers are at an elevated risk of death from second cancers and from other causes. While 59 young people had a record of a second cancer, we were unable to verify whether the second cancer was a consequence of the first. We do know however from registry records that they were two separate cancers.

Compared to other studies\textsuperscript{2,3}, this study has the disadvantage of being based upon a relatively small number of patients, thereby reducing our ability to investigate some causes of death in particular, respiratory disease and infections. In addition, follow up time was limited to 20 years after diagnosis, with only several hundred patients having that length of follow up time. As a result, the full risk of some conditions, such as circulatory disease, cannot be assessed as the maximum age attained by patients is late thirties and early forties which is before the risk of death from heart disease, stroke and respiratory ailments becomes fully apparent.

The 5% of patients who have emigrated were considered lost to follow up in all survival and excess mortality analysis. These patients were censored at the date they left Northern Ireland and it is thus assumed that if these patients had stayed in Northern Ireland they would not have altered the conclusions drawn from the current analysis. It is difficult to assess the validity of this assumption. In addition, there will undoubtedly be patients in the data who have left Northern Ireland but whose status is unknown to NICR. These patients would appear to survive indefinitely and may artificially increase the long term survival estimates by a small margin.

The number of patients without a cause of death assigned (14 patients) is small. While the assumption that these patients all die from their first cancer is reasonable, it is possible that the absence of information on these patients may influence the conclusions about some of the less frequent causes if in fact, any of these patients did die from the less common causes of death.

Skin cancer accounted for 20% of the cancers diagnosed in those aged 15-24. Exposure to UV radiation is a known carcinogen and skin cancer risks can be modified by taking care in the sun especially in childhood. Skin cancer is recognised as a growing problem in N. Ireland where malignant melanoma and squamous cell skin cancer numbers have doubled in the past 20 years\textsuperscript{1}. Further efforts in prevention are recommended.

This study identifies that excess mortality continues five years after diagnosis. This finding highlights the need for ongoing monitoring of young cancer survivors in later life, in particular with regards to potential side effects and long term health implications of treatments such as radiotherapy and chemotherapy. This need is widely recognised throughout Europe with strategic plans\textsuperscript{4} introduced which recommend particular consideration to monitoring of follow up conditions.

Despite the difficulties and limitations of this study we have highlighted some of the more serious longer term consequences of cancer among children and young people so that appropriate action can be taken to address this ongoing concern. We plan to repeat this work in later years when we have more data accumulated and recommend the gathering of general health data on childhood cancer survivors in a routine manner. Also, efforts to reduce skin cancer in the Northern Ireland population should continue.

The full analysis will be available on the N. Ireland Cancer Registry website www.qub.ac.uk/nicr

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