Childhood cancer survivors and their offspring studied through a postal survey of general practitioners: preliminary results

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SUMMARY. A postal survey is being carried out among the general practitioners of survivors of childhood cancer born before 1963 and treated in Britain. The response rate is currently about 88%. Based on a preliminary analysis of 2001 questionnaires it emerged that fewer childhood cancer survivors married than was expected from the general population. The number of live births to female survivors was 57% of that expected from general population rates. The frequency of congenital malformations among the offspring was not in excess of that expected on the basis of large population based surveillance rates and the number of malignant tumours observed was broadly similar to that expected from general population rates, although the results were based on very small numbers. The present data, taken together with other studies of the offspring of cancer survivors, provides grounds for optimism with regard to the inherited component of childhood cancer and the effects of radiotherapy and cytotoxic drugs on germ cell mutation.

Introduction

CHILDHOOD cancer comprises a rare group of diseases where modern therapy has contributed to substantial improvements in survival. Currently about half of those diagnosed with cancer before the age of 15 years survive beyond five years; thus each year in Britain there are 600 more survivors. As increasing numbers of them survive into their reproductive years they will provide further insight into the familial component of childhood cancer; additionally they constitute a group of individuals treated with mutagenic therapy (radiotherapy or cytotoxic drugs) before entering their reproductive years and will therefore provide information on the possible mutagenic effects of treatment on germ cells. These effects may manifest as an increased frequency of fetal deaths or diseases in the offspring. The information will also provide reliable data for those counselling survivors and their families about future risks and the prospects of a 'normal' life experience.

Some individuals are not aware of the nature of their childhood disease and a direct approach to them for information could cause considerable anxiety. Even survivors who are aware of their diagnosis could experience worries that might otherwise not be aroused. After detailed consultation with the Medical Research Council and British Medical Association it was agreed that an approach to the survivors' general practitioners was more appropriate. This is considered an acceptable method for avoiding anxiety in patients and leaves general practitioners the option to refuse if they consider information should not be released.

A pilot study to test the study methods showed that the response rate was high, almost 90%, and was unaffected by the length of questionnaire sent and that general practitioners were able to provide adequate information to answer several important research questions. A small separate study among obstetricians verified the accuracy of almost all information provided by general practitioners.

Another large study sharing some of the objectives of our own has already published results: it is based on survivors of childhood and adolescent cancer and a group of sibling controls from five cancer centres in the USA.[1,2]

Method

The study population was defined as survivors of childhood cancer resident in Britain at initial treatment and born before 1963. The current general practitioner for most survivors was obtained by 'flagging' the records of cases at the National Health Service central registers in Southport and Edinburgh. This flagging identified the most recent family practitioner committee or health board, from which the name and address of the current general practitioner could be obtained.

A questionnaire was designed to obtain information available to general practitioners in the following areas: diagnosis and treatment of the original tumour; subsequent health and its relationship to the tumour and its treatment; impairments, disabilities or problems experienced by survivors; marital status; a full fertility and reproductive history, including details of all pregnancies of female survivors and all children fathered by male survivors; and, finally, the health of all offspring born to both male and female survivors. The questionnaire occupied nine A4 sides plus a double sided A4 sheet to complete for each pregnancy or child.

Returned questionnaires were inspected and any important information that the general practitioners had not provided was requested by follow-up letter or telephone.

If questionnaires were not returned within about two months a reminder letter was sent together with another questionnaire. A second reminder was sent, if required, after a further two months.

Results

For this paper, only a preliminary analysis has been attempted, therefore all interpretations are provisional. Most analyses need to be carried out for specific diagnostic and treatment subgroups of interest. Not all areas contained in the questionnaire are reported here; we deliberately restrict attention to areas considered important, unlikely to change substantially with further analysis or the incorporation of more cases, and amenable to a relatively simple analysis. Except for the overall response rate, the results presented are based on the initial 2001 questionnaires returned completed.

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Response rate

Originally the study population consisted of just over 3100 individuals. However, the diagnostic information for some of these was poor. If there was doubt as to whether an individual had experienced a childhood cancer and all other ways of checking this had been tried then they were included in the study. General practitioners have provided diagnostic information on many of these and some have been excluded from the study because their condition was not a tumour or was benign. The study is still in progress and at present we have identified 2566 current general practitioners and have received 2265 questionnaires returned completed to some extent, a response rate of 88%. Already there are about 200 cases with insufficient identification details to trace them in the National Health Service central registers; also there are about 50 cases for whom we are awaiting a response from a family practitioner committee or health board.

Characteristics of group analysed

The composition of the 2001 cases was very similar to the whole study population in terms of sex, age, type of malignant disease and treatment. The distribution of these cases in relation to diagnosis and treatment was influenced by the fact that almost 80% were treated before 1970. In particular leukaemia accounted for less than 4% of survivors and cytotoxic drugs were received by only 14% of survivors. Table 1 gives a breakdown by diagnosis and treatment for the 2001 cases.

Table 1. Childhood cancer survivors — tumour types and treatment.

	Number (%) of cases	
Diagnosis		
Leukaemia	76	*(3.8)*
Hodgkin's disease	185	*(9.2)*
Non-Hodgkin lymphoma	130	*(6.5)*
Neuroblastoma and ganglioneuroblastoma	67	*(3.3)*
Wilms' tumour	117	*(5.8)*
Retinoblastoma	224	*(11.2)*
Central nervous system tumour	591	*(29.5)*
Malignant bone tumour	105	*(5.2)*
Other	506	*(25.3)*
Total	2001	*(100.0)*
Treatment		
No record	47	*(2.3)*
None	22	*(1.1)*
Surgery alone	593	*(29.6)*
Radiotherapy alone	278	*(13.9)*
Cytotoxic drugs alone	53	*(2.6)*
Surgery and radiotherapy	779	*(38.9)*
Surgery and cytotoxic drugs	16	*(0.8)*
Radiotherapy and cytotoxic drugs	132	*(6.6)*
Surgery, radiotherapy and cytotoxic drugs	81	*(4.0)*
Total	2001	*(100.0)*

Marriage

The percentage of survivors to have ever married, prior to the time of survey, was compared with the percentage of the population of England and Wales in 1984 who had ever been married[3] (Table 2). There appeared to be a consistent deficit of marriage among survivors which was found across all age and sex strata. However, the deficit was less among older women and the implications of this are discussed later.

Table 2. Comparison of proportion of cancer survivors who have ever married with expected proportion.

Sex and age (years)	Number of survivors	Percentage ever married	
		Survivors	England and Wales population
Males			
22–24	266	*14*	*27*
25–29	359	*33*	*60*
30–34	237	*51*	*80*
35–39	138	*63*	*88*
40–44	47	*70*	*90*
Females			
22–24	225	*27*	*48*
25–29	302	*49*	*76*
30–34	213	*69*	*89*
35–39	104	*82*	*94*
40–44	39	*82*	*95*

Live births to females

The number of live births to female survivors was compared with the number expected from general population data, using the age specific fertility tables for different calendar years[4] (Table 3). Overall, we observed only 57% of the number of live births expected. A substantial deficit of live births was apparent at all ages, but particularly among younger women.

Table 3. Numbers of livebirths to female survivors.

Age (years)	Number of livebirths		
	Observed	Expected	Observed/expected
Up to 19	86	169.1	0.51
20–24	273	472.8	0.58
25–29	179	316.1	0.57
30–34	59	92.5	0.64
35–44	6	12.1	0.50
All	603	1062.6	0.57

Congenital malformations in offspring

The types of congenital malformations and the proportions of different types observed in the offspring of cancer survivors are not substantially different from those observed in the general population. No highly penetrant single dominant gene defects have appeared in a child that is not present in one of the parents; such an occurrence would raise the possibility of germ cell mutation resulting from anti-cancer therapy. For the purposes of comparison with numbers of congenital malformations expected, on the basis of large population based surveillance data,[5] we restrict attention to potentially lethal or handicapping malformations among the offspring. A potentially lethal or handicapping congenital malformation is broadly any major macroscopic abnormality of structure which is attributable to faulty development and which is present at birth. For female survivors 27 congenital malformations were observed in 601 live and stillbirths and for male survivors there were 19 malformations in 432 live births. The frequency of congenital malformations is not substantially in excess of that expected; a more precise conclusion requires confirmation of the malformations observed through a survey of the obstetric hospitals where the survivors' children were born.

Cancer in offspring

The freqency and type of cancer observed among the offspring is given in Table 4. Two malignant neoplasms, other than retinoblastoma, were observed among the offspring and approximately one was expected from general population rates of malignant disease.[6,7] It is notable that seven survivors of heritable retinoblastoma that produced offspring with retinoblastoma were reported to have received genetic counselling prior to conception.

Table 4. Cancer among the offspring of survivors.

	Number of offspring	Malignant neoplasms observed		Approx. number expected
		Parent	Child	
Offspring of female survivors	587	Bilateral retinoblastoma (1)	Malignant teratoma testis (1)	0.5
		Sarcoma (1)	Acute monocytic leukaemia (1)	
		Retinoblastoma (11)	Retinoblastoma (12)	
Offspring of male survivors	431	Retinoblastoma (5)	Retinoblastoma (6)	0.4

Discussion

The response of general practitioners to postal surveys has been previously reported to vary from just over 50% to slightly under 90%.[8,9] The 88% response rate to our survey was very satisfactory, particularly when the length of the questionnaire is considered. However, our pilot study indicated that questionnaire length did not affect response appreciably and it is likely the subject matter of the study was considered important by most general practitioners receiving a questionnaire.

We have found that obtaining information on childhood cancer survivors and their offspring through general practitioners has proved successful. Critical evaluation of the information has shown that, despite certain limitations, it is very useful. There has been no other large population based or widely representative study of childhood cancer survivors within Britain. As an alternative to approaching the survivors themselves, with the risk of causing them unnecessary anxiety, we consider general practitioners are probably the best source available to meet the aims of our study.

When interpreting the results it is important to remember that the experience of the study population reflects the types of therapy and the survival rates prevailing, for the most part, before 1970. It is possible that the findings will not apply to more recently treated cases, since both the proportion of patients surviving different tumours and the nature of therapy have changed substantially since then.

The tendency for the marriage rate for older female survivors to be closer to that of the general population than for men and younger women raises a problem of interpretation. It appears that general practitioners' records can be inaccurate in relation to marital status, particularly for men and those who rarely attend the surgery.[10] Therefore the percentage of the study population ever married, particularly among the male and younger female survivors, is likely to be an underestimate and the deficit of marriage when compared to the general population is likely to be exaggerated. We interpret the data as indicating a lower level of marriage among the survivors, but the magnitude of the deficit is uncertain. In the five-centre study in the USA[1] survivors were slightly less likely to marry than sibling controls, 75% of cases were ever married compared with 82% of controls.

The lower numbers of live births to female survivors than among the general population is greatest among the youngest women; since general practitioners' records of reproductive events are likely to be more accurate for younger women and their more recent pregnancies this strengthens our confidence in interpreting this greater deficit as real. In subsequent analyses we shall investigate various hypotheses to account for the deficit, since it appears that undermarrying can explain only part of the deficit observed. Various possibilities need to be considered including: infertility related to disease or its treatment, medical advice concerning possible risks, and a personal decision not prompted by medical advice. We have some measure of all these factors except the last. In the five-centre study[1] married survivors not known to be infertile reported 87% of the number of pregnancies reported by sibling controls.

It is possible that the numbers of observed congenital malformations are an underestimate because our means of ascertainment was retrospective information available to the general practitioners. However, we have restricted consideration to congenital malformations that are potentially lethal or handicapping and these are less likely to have been missed. The types and proportions of different congenital malformations observed do not seem particularly unusual. There have been previous studies of congenital malformations among the offspring of survivors of malignant disease;[2,11,12] the evidence indicates that the risks are broadly similar to those experienced by the general population. Study of the progeny of the survivors of the atomic bombs[13] does not reveal evidence of an excess of congenital malformations among offspring conceived after the explosion.

Among the offspring of survivors, ignoring the occurrence of inherited retinoblastoma, the risk of malignant disease was similar to that expected from general population rates. Although our comparison is based on very small numbers it is in agreement with previous large studies of the offspring of survivors of cancer.[1,2]

The present data, therefore, taken together with other studies of offspring of cancer survivors, provide grounds for optimism with regard to the inherited component of childhood cancer and the effects of anti-cancer treatment on germ cell mutation. Eventually it should be possible to combine the present data with that from other large series to provide more precise answers to these important questions.

In the future we plan to extend the study of offspring of survivors of childhood cancer to include those born and treated more recently, but now well into their reproductive years. The offspring will be followed up indefinitely to monitor the frequency of malignant disease and mortality rates.

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