Life after childhood cancer: marriage and offspring in adult long-term survivors - a population-based study in the Piedmont region,Italy

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Abstract

The majority of childhood cancer cases survive to adulthood. We describe the experience of marriage and reproduction as indicators of quality of life, in a population-based cohort of adult long-term survivors after early cancer reported to the Childhood Cancer Registry of Piedmont. The study included 1237 survivors with a malignant neoplasm diagnosed during 1967–2000 when aged 0–14 years, who attained age 18 years. Vital and marital status and number of offspring were assessed through the Vital Statistics Offices. Marriage and fertility deficits were estimated by comparison with the Piedmont population. Among the individuals included in this study, 919 (74.3%) never married and never lived as married. The marriage deficit was 32% [observed/expected 0.68; 95% confidence interval (CI): 0.55–0.83] in men and 18% (observed/expected 0.82; 95% CI: 0.68–0.98) in women. A total of 179 children were born to 120 women, with a fertility deficit of 41% (observed/expected 0.59; 95% CI: 0.51–0.69). In conclusion, the observed decrements in marriage in men and women and fertility in women suggest that efforts should be made to improve the recovery from physical and psychological traumas related to diagnosis and treatment of cancer.

Introduction

In western countries, remarkable advances in therapies have increased the number of childhood cancer survivors in the last four decades (Ries et al., 2004; Šteliarová-Foucher et al., 2004; Gatta et al., 2005; Dama et al., 2006). Therefore, attention to the long-term effects of treatment have become crucial, including those that may impair the physical and psychological well-being affecting the quality of life of childhood cancer survivors, for instance, undermining their educational achievements, employment and social ability (Apajasalo et al., 1996; Feeny et al., 1999; Langeveld et al., 2002). Developing an autonomous family life and having children are important indicators of the recovery from the physical and psychological traumas related to the diagnosis and treatment of cancer. Survivors have been reported to have lower rates of marriage and parenthood in that they distrust their reproductive capacity and/or worry about future health problems their children might

suffer because of their cancer history. This occurs also in the presence of a high perceived quality of life as a consequence of denial mechanisms that compensate or even overcompensate the objectively measurable late effects of childhood cancer (Apajasalo et al., 1996; Feeny et al., 1999; Langeveld et al., 2002). Indeed, from a sociological perspective, marriage is seen as a positive factor of the adult life, representing a kind of modern 'passage rite' towards grown-up age (Saraceno, 1996). Poor marriage experiences of childhood cancer survivors, especially among central nervous system (CNS) cancer survivors, and lower rates of marriage among men compared with women have been reported (Byrne et al., 1989; Green et al., 1991; Mostow et al., 1991; Rauck et al., 1999; Pastore et al., 2002; Frobisher et al., 2007; Madanat et al., 2008). Subfertility and premature ovarian failure are frequent side effects of cancer therapy in young girls and adolescents. Pregnancy deficits have been observed in cohort studies of childhood cancer survivors (Chiarelli et al., 1994; Byrne et al., 1987; 2004a, 2004b; Fosså et al., 2005; Curry et al., 2006; Sklar et al., 2006; Magelssen et al., 2008).

Most of the previous investigations are hospital-based (Byrne et al., 1989; Green et al., 1991; Mostow et al., 1991; Rauck et al., 1999; Byrne et al., 1987, 2004a, 2004b; Sklar et al., 2006). Population-based studies have the advantage of representing the entire population of survivors of all types of childhood cancer (Chiarelli et al., 1994; Pastore et al., 2002; Frobisher et al., 2007; Madanat et al., 2008). In this study, we evaluated the marriage and reproduction experience in a large population-based cohort of adult long-term childhood cancer survivors recorded in the Childhood Cancer Registry of Piedmont (CCRP), located in the north-west of Italy.

Methods

The CCRP is a population-based registry recording only cases of malignant tumours diagnosed in children (0–14 years) resident in Piedmont. Procedures for data collection and classification have been described elsewhere (Dama et al., 2006). The CCRP registered 3297 individuals between 1967 and 2001; the 1237 of them who survived to age 18 years were included in this study.

The CCRP updates every 2–3 years the vital status of registered cases as well as marital status and number of children using information from the regional Vital Statistics Offices of the whole country. Follow-up information was last updated on 30 June 2004. The child population in Piedmont decreased in size over the study period, from approximately 900 000 in 1967–1978 to approximately 500 000 in 1990–2000. Date of entry was the date of the 18th birthday. When marriage was the outcome variable, person-years of observation were calculated from date of entry to 30 June 2004, death, migration or marriage, whichever occurred first; date of last follow-up, death or migration defined follow-up time when number of children was the outcome variable.

Marriage analyses

Marital status was categorized as 'never married and never lived as married', 'currently married or living as married', 'divorced or separated' and 'widowed'; its frequency distribution was analysed by sex, age at diagnosis (0–4, 5–9, 10–14 years), period of diagnosis (1967–1978, 1979–1989, 1990–2000), tumour type and vital status at the end of follow-up. Dates of marriage, dates of

divorce and lists of all people comprising the household, and their relationship, were obtained from Italian Registrar Offices, allowing us to identify unmarried couples living as married.

We compared observed and expected number of marriages, separately for men and women, using the Piedmont population age-specific and calendar period-specific marriage rates. Marriage rates were calculated as the age-specific and calendar period-specific number of marriages celebrated in Piedmont (National Institute of Statistics, 2002; http://demo.istat.it/) divided by the corresponding population of Piedmont (National Institute of Statistics, 1988–2001, 2002). The National Institute of Statistics (ISTAT) only provided the number of marriages for the period 1988–2002, during which 76 and 75% of the total number of marriages in the survivors' cohort occurred for men and women, respectively.

Fertility analyses

We compared the observed with the expected number of children born to childhood cancer survivors applying the Piedmont female population age-specific and calendar period-specific fertility rates to the cohort of women survivors (National Institute of Statistics, 1998, 2000). The observed/expected ratio was only estimated for women, as ISTAT does not provide male population fertility rates.

The completeness of offspring information collected through Italian Registrar Offices was assessed comparing this information with that obtained through questionnaires mailed to 1005 5-year survivors aged over 15 years in 2000 extracted from the CCRP database for a previous study on quality of life (Alessi et al., 2007). Only three children (out of 160) were missed by collecting information through Vital Statistics Offices. Statistical analyses were performed using SAS (Release 8.2; SAS Institute Inc., Cary, North Carolina, USA).

This work is part of a series of studies on the health-related quality of life of long-term childhood cancer survivors that was approved by the ethical committee of the University of Turin.

Results

Among the 1237 survivors included in this study, 1147 (92.7%) were alive at the end of follow-up in 2004, 77 (6.2%) had died and 13 (1.1%) were lost to follow-up. Leukaemias (25.8%), lymphomas and reticuloendothelial neoplasms (16.0%), CNS and miscellaneous intracranial and intraspinal neoplasms (23.1%) were the largest groups. Mean age at the end of follow-up was 28.5 (range 18.1–51.7) and 28.6 (range 18.0–51.3) years in men and women, respectively.

Table 1 shows the distribution of survivors' marital status by sex, age at diagnosis, period of diagnosis, tumour type and vital status at the end of the follow-up as well as person-years of observation by age and marital status. Nine hundred and nineteen (74.3%) long-term survivors never married; of the 318 ever married, 14 were divorced or separated and two widowed. The proportion of married survivors increased rapidly with attained age (age at follow-up) after the 30th birthday and reached 75% among those aged above 40 years.

	Ever married or ever lived as married, *N* (%)	Total, *N* (%)
Sex		
Men	139 (20.3)	686 (55.5)
Women	179 (32.5)	551 (44.5)
Age at diagnosis (years)		
0–4	76 (20.9)	364 (29.4)
5–9	88 (24.0)	366 (29.6)
10–14	154 (30.4)	507 (41.0)
Age at follow-up (years)		
18–29	74 (9.7)	763 (61.7)
30–39	179 (46.3)	387 (31.3)
40+	65 (74.7)	87 (7.0)
Period of diagnosis		
1967–1978	185 (49.1)	377 (30.5)
1979–1989	122 (20.1)	606 (49.0)
1990–2000	11 (4.3)	254 (20.5)
Diagnostic groups		
ALL	80 (28.0)	286 (23.1)
ANLL	4 (12.1)	33 (2.7)
Hodgkin's disease	35 (32.7)	107 (8.6)
NonHodgkin's Lymphoma	20 (22.0)	91 (7.4)
CNS tumours	47 (16.4)	286 (23.1)
Ependymoma	3 (12.5)	24 (1.9)
Astrocytoma	22 (18.0)	122 (9.9)
Medulloblastoma	1 (2.5)	40 (3.2)
Other CNS tumours[a]	21 (21.0)	100 (8.1)
SNS tumours	10 (19.6)	51 (4.1)
Retinoblastoma	10 (27.8)	36 (2.9)
Wilms' tumour	15 (20.6)	73 (5.9)
Osteosarcoma	15 (35.7)	42 (3.4)
Ewing's Sarcoma	5 (21.7)	23 (1.9)
Rhabdomyosarcoma	9 (23.7)	38 (3.1)
Fibrosarcoma and other sarcomas	19 (40.4)	47 (3.8)
Other tumour types	49 (39.5)	124 (10.0)
Vital status		
Alive	305 (26.6)	1147 (92.7)
Dead	10 (13.0)	77 (6.2)
Vital status unknown	3 (23.1)	13 (1.1)
Total	318 (25.7)	1237 (100.0)
Person-years contributed by the survivors in different age-groups (years)		
18–29	444 (17.3)	4224 (41.6)
30–39	1590 (62.0)	4837 (47.7)
40+	531 (20.7)	1088 (10.7)

ALL, acute lymphocytic leukemia; ANLL, acute nonlymphoid leukemia; CNS, central nervous system; SNS, sympathetic nervous system.
[a]Other gliomas, miscellaneous intracranial and intraspinal neoplasms, unspecified intracranial and intraspinal neoplasms.

Table 2 shows the observed/expected marriage ratios with respect to the general Piedmont population, by tumour type, age at diagnosis and period of diagnosis. Men had a lower observed/expected ratio [0.68; 95% confidence interval (CI): 0.55–0.83] than women (0.82; 95% CI: 0.68–0.98). The highest marriage deficit was observed among survivors of CNS tumours: observed/expected ratio 0.43 (95% CI: 0.23–0.74) for men and 0.50 (95% CI: 0.29–0.80) for women.

	Observed	All tumour types (*N*=1237)	ALL (*N*=286)	ANLL (*N*=33)	Hodgkin's disease (*N*=107)	NonHodgkin's lymphoma (*N*=91)	CNS tumours (*N*=286)	Other tumour types (*N*=434)
Age at diagnosis (years)								
Men								
0–4	27	0.72 (0.48–1.05)	1.03 (0.47–1.95)	0.00 (0.0–38.78)	0.00 (0.0–2.97)	0.46 (0.01–2.57)	0.33 (0.00–1.83)	0.73 (0.42–1.18)
5–9	25	0.55 (0.36–0.82)	0.80 (0.26–1.86)	1.07 (0.01–5.96)	0.62 (0.17–1.58)	0.46 (0.09–1.35)	0.36 (0.12–0.85)	0.61 (0.25–1.27)
10–14	45	0.75 (0.54–1.00)	0.91 (0.45–1.62)	0.75 (0.01–4.15)	0.60 (0.26–1.19)	0.46 (0.05–1.65)	0.52 (0.21–1.07)	1.02 (0.58–1.66)
Women								
0–4	34	0.80 (0.55–1.12)	0.87 (0.45–1.52)	0.00 (0.0–87.01)	1.11 (0.01–6.19)	1.61 (0.32–4.70)	0.44 (0.05–1.57)	0.75 (0.43–1.22)
5–9	34	0.73 (0.51–1.03)	0.77 (0.38–1.38)	0.38 (0.00–2.13)	0.64 (0.01–3.56)	0.00 (0.0–2.04)	0.46 (0.15–1.08)	1.05 (0.60–1.70)
10–14	58	0.90 (0.68–1.16)	1.15 (0.61–1.97)	1.27 (0.02–7.08)	0.99 (0.47–1.81)	0.76 (0.15–2.23)	0.54 (0.26–0.99)	1.06 (0.66–1.62)
Period of diagnosis								
Men								
1967–1978	58	0.72 (0.55–0.94)	0.92 (0.49–1.57)	0.53 (0.01–2.95)	0.40 (0.11–1.03)	0.48 (0.10–1.41)	0.51 (0.21–1.06)	0.88 (0.59–1.25)
1979–1989	38	0.63 (0.45–0.87)	0.88 (0.44–1.57)	2.12 (0.03–11.81)	0.75 (0.32–1.48)	0.47 (0.09–1.38)	0.37 (0.14–0.82)	0.64 (0.29–1.22)
1990–2000	1	0.37 (0.00–2.05)	2.23 (0.03–12.41)	0.00 (0.0–249.01)	0.00 (0.0–10.10)	0.00 (0.0–8.35)	0.00 (0.0–5.89)	0.00 (0.0–4.46)
Women								
1967–1978	57	0.83 (0.63–1.07)	0.85 (0.48–1.38)	0.00 (0.0–6.29)	1.11 (0.40–2.41)	0.78 (0.09–2.81)	0.56 (0.21–1.23)	0.88 (0.58–1.28)
1979–1989	62	0.82 (0.63–1.06)	1.03 (0.63–1.59)	0.81 (0.09–2.91)	0.77 (0.25–1.81)	0.79 (0.16–2.32)	0.47 (0.23–0.87)	1.00 (0.63–1.52)
1990–2000	7	0.74 (0.30–1.53)	0.00 (0.0–3.54)	0.00 (0.0–9.68)	1.39 (0.02–7.71)	0.81 (0.01–4.49)	0.45 (0.01–2.50)	1.05 (0.28–2.70)
Total								
Men	97	0.68 (0.55–0.83)	0.92 (0.60–1.36)	0.84 (0.09–3.05)	0.57 (0.30–1.00)	0.46 (0.17–1.00)	0.43 (0.23–0.74)	0.80 (0.57–1.09)
Women	126	0.82 (0.68–0.98)	0.91 (0.64–1.27)	0.58 (0.07–2.10)	0.95 (0.49–1.66)	0.79 (0.29–1.72)	0.50 (0.29–0.80)	0.94 (0.70–1.23)

Among the survivors included in this study, 184 (14.9%) had children. Sixty-four men (9.3%) had 102 children and 120 (21.8%) women had 179 children. Table 3 reports the ratio of the observed to the expected number of children born to female survivors by tumour type, age at diagnosis and period of diagnosis. Compared with the general population, female survivors had 41% lower probability of being parous; the observed/expected ratio was 0.59 (95% CI: 0.51–0.69) for all tumour types. Fertility deficits were similar in all subgroups except acute lymphocytic leukemia survivors – the largest one – where there was no significant deficit (observed/expected ratio 0.80, 95% CI: 0.60–1.04).

Table 3 Childhood Cancer Registry of Piedmont 1967–2000; ratio of observed to expected number of children and corresponding 95% confidence interval among women.Expected number of children is based on the Piedmont female population age-specific and calendar period-specific fertility rates.ALL, acute lymphocytic leukemia; ANLL, acute nonlymphoid leukemia; CNS, central nervous system.

	Observed	All tumour types (*N*=551)	ALL (*N*=141)	ANLL (*N*=16)	Hodgkin's disease (*N*=38)	NonHodgkin's lymphoma (*N*=27)	CNS tumours (*N*=127)	Other tumour types (*N*=202)
Age at diagnosis (years)								
0–4	41	0.58 (0.42–0.79)	0.92 (0.56–1.42)	0.00 (0.00–34.43)	0.40 (0.01–2.23)	1.04 (0.21–3.05)	0.38 (0.08–1.12)	0.39 (0.21–0.66)
5–9	58	0.68 (0.51–0.88)	0.86 (0.53–1.33)	0.49 (0.06–1.78)	0.83 (0.09–2.99)	0.00 (0.00–1.27)	0.46 (0.22–0.85)	0.76 (0.49–1.13)
10–14	80	0.55 (0.44–0.68)	0.60 (0.32–1.03)	0.00 (0.00–2.93)	0.48 (0.26–0.83)	0.52 (0.14–1.32)	0.56 (0.35–0.85)	0.57 (0.38–0.83)
Period of diagnosis								
1967–1978	115	0.70 (0.58–0.84)	0.95 (0.65–1.35)	0.00 (0.00–4.13)	0.62 (0.32–1.08)	0.74 (0.20–1.89)	0.73 (0.45–1.10)	0.60 (0.44–0.80)
1979–1989	59	0.49 (0.37–0.63)	0.68 (0.42–1.04)	0.52 (0.06–1.88)	0.36 (0.10–0.92)	0.34 (0.04–1.21)	0.38 (0.20–0.65)	0.50 (0.29–0.80)
1990–2000	5	0.31 (0.10–0.71)	0.00 (0.00–1.79)	0.00 (0.00–5.25)	0.00 (0.00–2.99)	0.47 (0.01–2.61)	0.00 (0.00–1.00)	0.61 (0.16–1.57)
Total	179	0.59 (0.51–0.69)	0.80 (0.60–1.04)	0.37 (0.04–1.33)	0.50 (0.29–0.82)	0.52 (0.21–1.07)	0.51 (0.36–0.71)	0.57 (0.44–0.72)

Expected number of children is based on the Piedmont female population age-specific and calendar period-specific fertility rates.
ALL, acute lymphocytic leukemia; ANLL, acute nonlymphoid leukemia; CNS, central nervous system.

Discussion

In this population-based study, we evaluated the experience of marriage and reproduction in long-term survivors of childhood cancer. As compared with similar investigations conducted in other countries, major strengths of our study are a longer registration period including cases diagnosed until year 2000 and absence of recall bias. We confirm the overall negative impact of childhood cancer diagnosis and treatment on both marital status (Byrne et al., 1989; Green et al., 1991; Mostow et al., 1991; Rauck et al., 1999; Pastore et al., 2002; Frobisher et al., 2007) and reproductive rates (Chiarelli et al., 1994; Byrne et al., 1987, 2004a, 2004b; Fosså et al., 2005; Curry et al., 2006; Sklar et al., 2006; Madanat et al., 2008; Magelssen et al., 2008).

We found a greater deficit of marriages in both sexes – 32% in men and 18% in women –, compared with the United Kingdom (Frobisher et al., 2007) and an even wider gap compared with the United States (Byrne et al., 1989). We acknowledge differences in the definition of marriages: the American cohort included 'living as married' which is not feasible in our data, and in the analysis of the British cohort (Frobisher et al., 2007), only survivors who were alive at the time of the survey had been included probably leading to a slight overestimation of marriage rates. As the deficits were obtained comparing cohorts of survivors with the general population they belong to, differences are more likely to reflect local socio-cultural phenomena rather than inability to procreate. One could speculate that the same determinants of the continuing fall of marriages and fertility rates in Italy are exacerbated in this cohort of cancer survivors. Conversely, lower rates of marriages in Italian survivors may reflect lack of professional counselling in this country.

Lower marriage rates were particularly evident among men and among CNS tumour survivors. The difference between sexes may be because of a higher probability of infertility among men after

cancer treatment (which we cannot assess in our study) or to emotional disabilities which could be overcome with appropriate counselling (Byrne et al., 1989; Gray et al., 1992; Rauck et al., 1999). High marriage deficit among CNS tumour survivors is likely to be related to the distinctively high rate of late effects in this group, including growth deficit, limitations in psychomotor development and low achievement of social goals such as education and employment (Gray et al., 1992; Rauck et al., 1999; Alessi et al., 2007). Among lymphoma survivors, very low marriage rates were observed in our study amongst men only. The expected reduction of fertility among men treated with alkylant drugs and/or with subdiaphragmatic radiotherapy (Chiarelli et al., 1994) may indeed act as a deterrent not only to procreation but even to marriage. However, the proportion of cohort members who married increased significantly after age 30 years and was greater than 70% after age 40 years indicating a substantial delay of marriage rather than a permanent status. Given the young mean age of the cohort, many are expected to marry in the future.

The experience of infertility is a serious life crisis, triggering strong emotional reactions in childhood cancer survivors. Infertility, coupled with the stress of having a cancer diagnosed early in life, is a severe physical and psychological burden for survivors (Gray et al., 1992). Both males and females treated with chemotherapy, surgery and/or radiation may suffer reproductive function deficits (Curry et al., 2006; Signorello et al., 2006; Edgar and Wallace, 2007; Green et al., 2009a, 2009b). Different sensitivity of sexual organs to therapies between sexes is well known: the ovary may be more resistant to the effects of alkylating agents than the testes (Chiarelli et al., 1994). Nonetheless, typical rates of infertility in childhood cancer survivors – wih the inability to procreate – are lower than 8% in either sex (Chiarelli et al., 1994; Green et al., 2009a, 2009b). The 41% deficit that we observed in our cohort is therefore more likely because of psychological barriers linked to fears of various nature, including concerns that the parents' disease and/or treatment might affect the health of their children. Female childhood cancer survivors experience increased impaired fertility and women who choose to procreate and succeed face more pregnancy complications than their healthy counterparts (Signorello et al., 2006; Edgar and Wallace, 2007; Magelssen et al., 2008; Green et al., 2009b). However, there is evidence that children born to survivors have no excess of malformations, cytogenetic syndromes, or single-gene defects (Boice et al., 2003; Fosså et al., 2005; Magelssen et al., 2008; Winther et al., 2009). Appropriate counselling can help these patients to overcome their fears.

It is noteworthy that the comparison with the general population, which accounts for secular trends in marriage and fertility rates, identified a significantly negative trend over periods of diagnosis only in the likelihood of having offspring and not of marriage. This may indicate that the effect of period of diagnosis (as proxy of therapy strategies) acts more on the physical rather than the psychological side.

Limitations of this study include the number of cases and the lack of detailed information about therapies, which prevented analyses on the association between therapies and fertility. The estimate of male fertility deficit was not feasible, as the male fertility rates for the Piedmont general population were not available. The estimate of female fertility deficit is likely to be confounded by the higher prevalence of married women in the general population than in the childhood cancer survivors cohort. Married women are expected to be more inclined to have children than unmarried women (Pinnelli et al., 2004; National Institute of Statistics, 2006, 2007); by applying the reference fertility rates to the cohort of women survivors, where the marriage deficit was estimated to be 18% with respect to the general population, we expect that the fertility deficit observed in our cohort may be partly attributed to the lower prevalence of marriage and not only to an impaired reproductive

capacity. Unfortunately, we could not control for this factor as routine statistics did not provide fertility rates separately for married and unmarried women.

In conclusion, this population-based study shows the persistence of psychological, social and clinical sequelae of childhood cancer survivors among the adults of the CCRP cohort. Some groups need constant monitoring to evaluate the impact of childhood cancer on the achievement of life goals like long-term personal relationship and having children. Young prepuberal patients may be facing loss of fertility with no, or limited, caregivers' support in adulthood. Therefore, it is crucial that at the time of diagnostic workup, paediatric oncologists approach their young patients as potential long-term survivors and develop a plan that takes into account the impact of treatment on fertility without jeopardizing survival. Results of this study encourage counselling of current survivors and their families about fertility after successful treatment (Zebrack et al., 2007; De Bruin et al., 2009; Mitchell et al., 2009).

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