Marriage and parenthood among childhood cancer survivors: a report from the Italian AIEOP Off-Therapy Registry

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ABSTRACT

Background
The aim of this study was to describe the patterns of marriage and parenthood in a cohort of childhood cancer survivors included in the Off-Therapy Registry maintained by the Italian Association of Pediatric Hematology and Oncology.

Design and Methods
We analyzed a cohort of 6,044 patients diagnosed with cancer between 1960 and 1998, while aged 0 to 14 years and who were 18 years old or older by December 2003. They were followed up through the regional vital statistics registers until death or the end of follow up (October 30, 2006), whichever occurred first, and their marital status and date of birth of their children were recorded. The cumulative probabilities of being married and having a first child were computed by gender and compared by tumor type within the cohort. Marriage and fertility rates (the latter defined as the number of live births per woman-year) were compared with those of the Italian population of the same age, gender, area of residence and calendar period by means of the observed to expected (O/E) ratios.

Results
During the follow-up period, 4,633 (77%) subjects had not married. The marriage O/E ratios were 0.56 (95% CI: 0.51-0.61) and 0.70 (95% CI: 0.65-0.76) among men and women, respectively. Overall, 263 men had 367 liveborn children, and 473 women had 697 liveborn children. The female fertility O/E ratio was 0.57 (95% CI: 0.53-0.62) overall, and 1.08 (95% CI: 0.99-1.17) when analyses were restricted to married/cohabiting women

Conclusions
Childhood cancer survivors are less likely to marry and to have children than the general population, confirming the life-long impact of their previous disease on their social behavior and choices. The inclusion of counseling in the strategies of management and long-term surveillance of childhood cancer patients could be beneficial to survivors as they approach adulthood.

Key words: childhood cancer, marriage, fertility, long-term survivors, quality of life.

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Introduction

Improved cancer therapies have increased life expectancy. This means that approximately 70% of children diagnosed with cancer between 0 and 14 years of age are now expected to survive for at least five years from diagnosis, with a large majority of them reaching adulthood.[1-5] One of the main objectives of pediatric oncologists is to offer the cured child a chance to lead a normal life. In the current social frame, marriage and reproduction are considered as some of the standards of normal social behavior.[6] Health care providers should, therefore, inform all former patients on the potential increased risk of having children with birth defects, and the increased risk of cancer,[7] by clarifying if and when these risks exist.[6]

Previous studies have considered marriage and parenthood as important indicators of psychological adjustment and achievement of social life goals by cancer survivors.[8, 9] Most retrospective cohort and case-control studies conducted in the US, Canada and UK found marriage rates to be lower than expected, especially among survivors of childhood central nervous system (CNS) cancer,[9-14] and reported treatment-related fertility deficits.[15-19] In Italy, the only attempts to assess the experience of marriage and parenthood of childhood cancer survivors have been carried out in a single region situated in the North-West of the country (representing approximately 7% of the whole Italian population) using data of the Childhood Cancer Registry of Piedmont.[13,20]

In the present study, we used data from administrative sources and from the Italian Off-Therapy Registry (OTR),[21-23] maintained by the Italian Association of Pediatric Hematology and Oncology (AIEOP), to evaluate the experience of marriage and parenthood in a large cohort of long-term childhood cancer survivors.

Design and Methods

The Italian Off-Therapy Registry

The OTR was established in 1980, when 34 Pediatric Oncology Units affiliated to AIEOP agreed to pool their databases, which have information on children diagnosed with cancer between 0 and 14 years of age who have reached completion of treatment in complete continuous remission (the off-therapy stage), regardless of subsequent disease evolution. OTR registration procedures have been described elsewhere.[21-23] The OTR is a hospital-based cohort collecting both demographic (gender, place and date of birth, and place of residence at diagnosis) and clinical data. Information on individual patients is periodically updated by the registry coordinating centre in Monza, Northern Italy, with a special focus on events such as relapses, new primary malignancies and vital status. OTR's coverage of childhood cancer cases has been estimated to range between 45% for CNS tumors to 85% for lymphohematopoietic malignancies.[24]

This study investigated a cohort of 6,044 patients, diagnosed with cancer before 15 years of age between 1960 and 1998, who had attained a minimum age of 18 years by the end of December 2003. The minimum survival time for subjects of the cohort was, therefore, four years.

Follow-up procedures

The Cancer Epidemiology Unit of the University of Turin retrieved information on the vital and marital status of the study population from the Vital Register Offices of their towns of residence. Survivors were classified as 'never married and never lived as married', 'married' or 'lived as married'. For married individuals, the Register Offices provided dates of marriage. Unmarried couples living as married were inferred based on the composition of the household. In case of changes between two contacts with the Register Offices, cohabitation start and end dates were estimated as the mid-date between the two. Information on the number of children and their date of birth was also obtained from the Vital Register Offices.

Follow-up information for the 6,044 subjects of the study was last updated on October 30, 2006. The follow-up and classification procedures have been described in detail elsewhere.[25]

Statistical analyses

Within-cohort comparisons

Time-to-first marriage or cohabitation and to birth of the first child were calculated from the date of the 18th birthday to the start of the relationship and birth of the first liveborn child, respectively. Cumulative incidence of first marriage and birth of the first child were estimated taking into account death as a competing risk event.[26] Statistical significance of differences in the cumulative incidence of marriage and birth of the first child for different tumor types was tested using the Gray's test.[27,28]

Comparisons between the cohort and the general population

The marriage and fertility rates in the cohort of survivors were compared to those of the general population, provided by the Italian Institute of Statistics (ISTAT).[29-33] Since no information on cohabitation in the general population was available, the marriage comparison was restricted to legal marriages. The reference marriage rates used to compute expected numbers were defined as the ratio between the number of marriages by persons aged x to x+1 in a specific year t divided by the number of person-years contributed by persons at risk of marrying (unmarried, divorced or widowed) aged x to x+1 in year t in the study area. Separate calculations were made for the two genders. The indicator of fertility used was the maternal age-specific fertility rate, defined as the ratio between the number of live births to mothers aged x to x+1 in calendar year t divided by the number of person-years contributed by women aged x to x+1 in year t in the study area. We computed the ratio between the observed (O) and the expected (E) number of marriages and live births, calculated by applying the age-, calendar period- and area-specific marriage and fertility rates of the general population to stratum-specific person-years contributed by the cohort. We stratified data into three macro-areas (Northern Italy, Central Italy, Southern Italy and Islands), characterized by different rates of marriage and fertility, and assumed the rates of the most populous region in the area as a reference (Lombardy in the North, Lazio in the Center, and Campania in the South and Islands). Because of the incomplete information provided by ISTAT, marriage analyses had to be restricted to the period 1980-2004 (excluding approximately 3% of the total number of marriages in the survivors' cohort). For fertility analyses, we used the fertility rates specific for each macro-area. Fertility analyses had to be restricted to the period 1979-2004 and to women, because no male fertility reference rates were available. The Breslow-Day test was used to assess the O/E ratio trends by calendar years of diagnosis.[34]

The gender ratio (M/F) in liveborn offspring was calculated and compared with the offspring gender ratio of the general population.

Statistical analyses were carried out using SAS (Release 8.2, by SAS Institute Inc., Cary, NC, USA) and Stata 9.1 (Release 9.1, by Stata Corporation, College Station, Texas, USA).

Results

The cohort of 6,044 eligible subjects contributed 44,161 person-years of observation. Marital status information was obtained for 5,975 subjects. At the last follow up, 5,686 (94.1%) were reported to be alive, 255 (4.2%) dead, and 103 (1.7%) lost to follow up. Table 1 shows the distribution of marital status of long-term childhood cancer survivors by gender, age at diagnosis, year of diagnosis, tumor type, and vital status at the end of follow up. Acute lymphoblastic leukemia (43.4%) and lymphomas (24.5%) were the largest tumor type groups.

During the period of observation, 2,745 men (81.4%) and 1,888 women (70.7%) had never married nor had started a live-in relationship; 736 (12.2%) subjects had a total of 1,064 liveborn children: 263 men (7.8%) had 367 children, and 473 (17.7%) women had 697 children.

Within-cohort comparisons

Figure 1 shows differences in the cumulative incidence of marriage for different tumor types among both men and women (Gray's test: P=0.001 and P<0.001, respectively). Restricting the analysis to married or cohabiting subjects, there were differences in the cumulative incidence of the first live birth for different tumor types among spouses of men (Gray's test: P=0.026) but not among women (P=0.175) (Figure 2).

The median age at first marriage was 28.1 years: interquartile range (IQR): 25.6-31.0 in men and 25.1 years (IQR: 22.2-28.0) in women. For all subjects (married and unmarried), the median age at birth of the first child was 29.8 years (IQR: 27.0-33.1) for men and 26.3 years (IQR: 22.2-29.4) for women.

Comparisons between the cohort and the general population

Table 2 shows the O/E ratios of the number of marriages by age and era of diagnosis for different tumor types and for the two genders. CNS tumor survivors had the lowest ratio of marriages (O/E ratio 0.18; 95% CI: 0.07-0.36 among men; 0.26 95% CI: 0.12-0.50 among women). A statistically significant decreasing trend of marriage frequency by calendar year of diagnosis was present for all tumor types combined in both genders, and for acute lymphoblastic leukemia in males only.

Table 3 shows the O/E ratios of the number of live births among women by age and period of diagnosis, for different tumor types. Considering all women of the cohort (Table 3a), all tumor types showed a significant fer-

Table 1. Off-Therapy Registry 1960-1998. Marital status of long-term childhood cancer survivors by gender, age at diagnosis, period of diagnosis, tumor type and vital status.

	Never married and never lived as married		Ever married or ever lived as married		Unknown marital status		Total	
	N	% (row)	N	% (row)	N	% (row)	N	% (column)
Gender								
Men	2745	81.4	591	17.5	38	1.1	3374	55.8
Women	1888	70.7	751	28.1	31	1.1	2670	44.2
Age at diagnosis								
0-4	1805	80.8	414	18.5	15	0.7	2234	37.0
5-9	1487	74.4	488	24.4	24	1.2	1999	33.1
10-14	1341	74.0	440	24.3	30	1.7	1811	30.0
Period of diagnosis								
1960-1979	899	52.9	777	45.7	24	1.4	1700	28.1
1980-1989	2436	82.6	477	16.2	37	1.3	2950	48.8
1990-1998	1298	93.1	88	6.3	8	0.6	1394	23.1
Diagnostic groups								
Acute lymphoblastic leukemia	1992	75.9	603	23.0	29	1.1	2624	43.4
Acute non-lymphobastic leukemia	167	76.6	49	22.5	2	0.9	218	3.6
Hodgkin's disease	570	66.8	268	31.4	15	1.8	853	14.1
Non-Hodgkin's lymphoma	475	75.9	142	22.7	9	1.4	626	10.4
Central nervous system tumors	278	92.4	19	6.3	4	1.3	301	5.0
Sympathetic nervous system tumors	293	80.9	67	18.5	2	0.6	362	6.0
Renal tumors	409	76.9	119	22.4	4	0.8	532	8.8
Malignant bone tumors	107	92.2	8	6.9	1	0.9	116	2.0
Soft-tissue sarcomas	248	80.3	59	19.1	2	0.7	309	5.1
Other tumor types	94	91.3	8	7.8	1	1.0	103	1.7
Vital status								
Alive	4374	76.9	1307	23.0	5	0.1	5686	94.1
Dead	234	91.8	20	7.8	1	0.4	255	4.2
Unknown	25	24.3	15	14.6	63	61.2	103	1.7
Total	4633	76.7	1342	22.2	69	1.1	6044	100.0

tility deficit, with the lowest O/E ratio for women who had a CNS tumor (0.21; 95% CI: 0.08-0.43). A statistically significant decreasing trend of fertility by calendar year of diagnosis was present for CNS tumors. Yet, fertility deficits disappeared completely or lost statistical significance when the analyses were restricted to married or cohabiting women (Table 3b: O/E for all tumor types = 1.08; 95% CI: 0.99–1.17), and a statistically significant increasing trend of fertility by calendar year of diagnosis was present for several tumor types. These findings confirm a strong association between marrying and having children in the cohort.

Figure 3 shows the cumulative incidence of marriage among childhood cancer survivors ("observed") and in the general population ("expected") in the period 1980-2004. Initial difference was reduced by approximately 50% between age 30 and 38 in women; a similar tendency to catch up with the general population was observed also in men, but based on small numbers and only after the age of 40.

Offspring

Overall, the liveborn offspring gender ratios (M/F) were 1.34 (95% CI: 1.16-1.53) and 1.27 (95% CI: 1.14-1.40) for male and female survivors, respectively; this value is higher than the 1.06 value observed for the general Italian population.[35] When analyses were restricted to the first live birth, in order to account for the possible bias depending on the decision not to have further children after the first when he/she is of the desired gender, the offspring gender ratios only marginally changed: 1.34 (95% CI: 1.13-1.56) and 1.25 (95% CI: 1.11-1.41) for male and female survivors, respectively.

Discussion

We found that in Italy, childhood cancer survivors were less likely to marry and have children than the general population. These findings are in accordance with previous studies in Piedmont,[13,20] in the US[10,14] and in England

Figure 1. Off-Therapy Registry 1960-1998. Cumulative probability of marriage for childhood cancer survivors, by gender and tumor type. Time-to-first marriage was calculated from the date of 18th birthday to the start of the relationship. Gray's test: men *P*=0.001, women *P*<0.001.

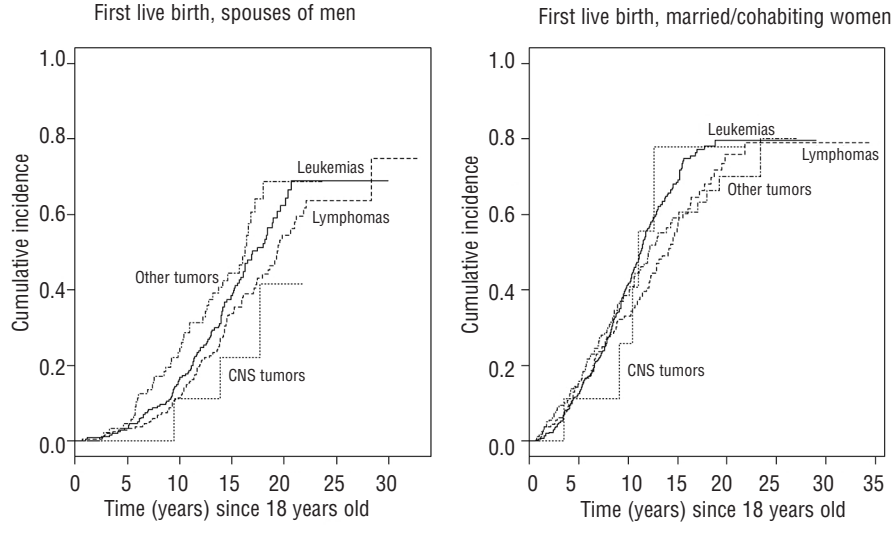

Figure 2. Off-Therapy Registry 1960-1998. Cumulative probability of having a first liveborn child for childhood cancer survivors (married or cohabitants) by gender and tumor type. Time-to-first birth was calculated from the date of 18th birthday to the date of birth of the first child. Gray's test: spouses of men *P*=0.026, women *P*=0.175.

and Wales.[11] They confirm that, in some aspects, the social life of these subjects retains some significant difference, or even limitations, in comparison with that of their peers.

Strengths of this study are the long recruitment period (from 1960 to 1998), the high level of completed follow up, and the low proportion of missing data (1.7% for vital status and 1.1% for marital status information). Moreover, information on vital and marital status were retrieved from the Register Offices, removing the need to contact the patients and minimizing selection and information biases that affect questionnaire data.

However, limitations have to be considered in interpreting our results. Detailed information on treatment, such as irradiation site and dosage and chemotherapy dosage, were not available, hampering any causal inference on the risk of treatment-induced infertility. Administrative data did not allow us to distinguish adopted children, which could result in fertility overestimation, whereas artificial fertilization should not pose any problem since all biological children (however conceived) are included in reference statistics. On the other hand, fertility underestimation might result from the calculation of the total number of children from the current family composition, since some information would be lost for children who are deceased, or who no longer live with their parents. This underestimation should be negligible in our study given the young age of the offspring. Moreover, the administrative data used to assess the probability of parenthood in our cohort did not allow us to assess adverse pregnancy outcomes, miscarriages, proportion of stillbirths or prevalence of birth defects among the offspring.

CNS tumor survivors are the subset at highest risk for reduced marriage rates. This finding confirms that of other previously published reports and may depend on the wide use of radiotherapy and surgery, causing relevant handicaps, including growth deficiency and neuro-cognitive problems.[5,6,14,36]

The apparent disadvantage in establishing stable social relationships and having offspring, observed in survivors of any type of childhood cancer, could be partly explained

Table 2. Off-Therapy Registry 1960-1998. Ratio of observed (O) to expected (E) number of marriages for selected tumor types in 1980-2004 and corresponding 95% Confidence Interval (CI) by gender, age and period of diagnosis.

	All tumor types		Acute lymphoblastic leukemia		Acute non-lymphobastic leukemia		Hodgkin's disease		Non-Hodgkin's lymphoma		Central Nervous System tumors		Other tumor types	
WOMEN	**n=2584**		**n=1244**		**n=103**		**n=270**		**n=170**		**n=123**		**n=674**	
	O/E	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**
Age at diagnosis														
0-4	0.64	0.56-0.73	0.60	0.50-0.72	0.43	0.05-1.55	0.93	0.40-1.84	1.24	0.34-3.18	0.23	0.03-0.82	0.71	0.56-0.88
5-9	0.74	0.64-0.84	0.68	0.57-0.82	0.84	0.42-1.51	0.83	0.54-1.23	1.14	0.72-1.71	0.15	0.00-0.81	0.75	0.52-1.05
10-14	0.73	0.63-0.84	0.91	0.73-1.13	0.70	0.32-1.32	0.75	0.58-0.95	0.57	0.34-0.91	0.33	0.12-0.71	0.56	0.33-0.89
Period of diagnosis														
1960-1969	0.92	0.59-1.37	1.15	0.46-2.38	-	-	0.41	0.09-1.21	-	-	0.95	0.02-5.30	1.10	0.59-1.89
1970-1979	0.76	0.68-0.85	0.73	0.63-0.84	0.66	0.21-1.54	1.03	0.76-1.36	0.83	0.47-1.38	0.39	0.11-0.99	0.75	0.58-0.95
1980-1989	0.62	0.54-0.70	0.62	0.51-0.74	0.89	0.51-1.45	0.67	0.48-0.91	0.88	0.56-1.32	0.11	0.01-0.40	0.52	0.36-0.73
1990-1998	0.67	0.49-0.89	0.83	0.47-1.37	0.19	0.00-1.08	0.57	0.25-1.13	0.66	0.26-1.35	0.45	0.05-1.62	0.76	0.42-1.28
Test for trend	P=0.015		P=0.243		P=0.449		P=0.204		P=0.671		P=0.375		P=0.114	
Total	**0.70**	**0.65-0.76**	**0.69**	**0.62-0.77**	**0.72**	**0.45-1.09**	**0.78**	**0.64-0.95**	**0.82**	**0.60-1.10**	**0.26**	**0.12-0.50**	**0.69**	**0.58-0.82**
MEN	**n=3276**		**n=1309**		**n=109**		**n=542**		**n=434**		**n=169**		**n=713**	
	O/E	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**	**O/E**	**95% CI**
Age at diagnosis														
0-4	0.49	0.41-0.58	0.50	0.39-0.64	0.54	0.07-1.95	0.59	0.34-0.95	0.48	0.22-0.92	0.11	0.00-0.62	0.46	0.32-0.64
5-9	0.60	0.52-0.69	0.61	0.48-0.77	0.52	0.17-1.21	0.55	0.41-0.71	0.69	0.48-0.97	0.26	0.07-0.67	0.74	0.47-1.11
10-14	0.58	0.50-0.67	0.60	0.45-0.80	0.65	0.28-1.28	0.60	0.46-0.77	0.54	0.37-0.76	0.13	0.02-0.47	0.75	0.45-1.19
Period of diagnosis														
1960-1969	0.73	0.49-1.04	0.90	0.47-1.57	-	-	0.29	0.08-0.75	1.01	0.21-2.94	-	-	0.96	0.48-1.72
1970-1979	0.61	0.54-0.69	0.62	0.52-0.74	0.68	0.27-1.40	0.68	0.55-0.84	0.57	0.39-0.80	0.22	0.07-0.52	0.61	0.44-0.83
1980-1989	0.48	0.41-0.56	0.45	0.34-0.59	0.56	0.24-1.11	0.50	0.36-0.68	0.61	0.43-0.84	0.13	0.02-0.48	0.43	0.25-0.68
1990-1998	0.36	0.19-0.61	0.40	0.08-1.18	-	-	0.25	0.03-0.91	0.38	0.08-1.12	-	-	0.52	0.17-1.22
Test for trend	P=0.001		P=0.012		P=0.451		P=0.296		P=0.595		P=0.360		P=0.073	
Total	**0.56**	**0.51-0.61**	**0.57**	**0.49-0.65**	**0.58**	**0.33-0.96**	**0.58**	**0.48-0.68**	**0.59**	**0.46-0.74**	**0.18**	**0.07-0.36**	**0.58**	**0.46-0.73**

by a delay effect, suggested by the tendency of our cohort to catch up with the general population (Figure 3). Such a delay may also explain the observed decreasing trends of the marriage O/E ratios by calendar period of diagnosis, probably representing a lower tendency of marriage among the most recent cohorts of survivors (also much younger), rather than reflecting more serious late effects of the most recent treatments.

The marriage deficits in our study were greater than those reported in North America[14] and in the UK.[11] Such differences cannot be entirely explained by differences in defining "ever married". Although in the American study[14] "ever married" included those living as married, in the UK,[11] as well as in our study, "ever married" included only legally married couples, and yet the British marriage deficit was lower than that found in our cohort.

Our population not only had a lower probability of getting married but also to have children. Our estimates of fertility deficits range from 38% for non-Hodgkin's lymphoma survivors to 79% for CNS tumor survivors. However, such an unfavorable comparison of fertility between our cohort and the general population is likely to be due to a much higher proportion of married women in the general population. Married women are expected to be more inclined to have children than unmarried women:[37] by applying the reference fertility rates to the women of our cohort, where the marriage deficit was estimated to be 30%, we expect part of the observed fertility deficit to be due to the lower proportion of married women. This effect, which unfortunately we cannot evaluate since data on the general population fertility rates are not available separately for married and unmarried women, would add to a potentially impaired reproductive capacity. We, therefore, repeated the analysis applying the reference fertility rates (from both married and unmarried women of the general Italian population) to the sub-

Table 3. Off-Therapy Registry 1960-1998. Ratio of observed (O) to expected (E) number of liveborn children for selected tumor types in 1979-2004 and corresponding 95% Confidence Interval (CI) by age and period of diagnosis among women. Analyses include (a) all women of the cohort of survivors; (b) only married or cohabitant women of the cohort of survivors.

	All tumor types		Acute lymphoblastic leukemia		Acute non-lymphobastic leukemia		Hodgkin's disease		Non-Hodgkin's lymphoma		Central Nervous System tumors		Other tumor types	
(a) ALL WOMEN	n=2589		n=1248		n=103		n=271		n=170		n=123		n=674	
	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI
Age at diagnosis														
0-4	0.57	0.49-0.65	0.56	0.46-0.67	0.59	0.12-1.74	0.57	0.23-1.18	0.56	0.07-2.01	0.35	0.07-1.02	0.59	0.46-0.75
5-9	0.60	0.52-0.68	0.55	0.46-0.65	0.57	0.26-1.09	0.74	0.50-1.07	0.78	0.48-1.19	0.15	0.00-0.86	0.67	0.46-0.93
10-14	0.56	0.48-0.64	0.76	0.62-0.93	0.46	0.18-0.94	0.45	0.34-0.59	0.51	0.30-0.81	0.16	0.03-0.47	0.42	0.22-0.72
Period of diagnosis														
1960-1969	0.59	0.40-0.85	0.87	0.46-1.48	-	-	0.25	0.05-0.73	-	-	1.14	0.14-4.12	0.55	0.28-0.96
1970-1979	0.59	0.53-0.66	0.59	0.51-0.68	0.61	0.24-1.25	0.63	0.48-0.83	0.54	0.31-0.87	0.32	0.09-0.83	0.60	0.46-0.76
1980-1989	0.54	0.47-0.62	0.57	0.46-0.69	0.58	0.30-1.01	0.45	0.30-0.64	0.70	0.42-1.09	0.06	0.00-0.35	0.60	0.42-0.83
1990-1998	0.57	0.39-0.80	0.97	0.53-1.62	0.00	0.00-0.96	0.44	0.14-1.04	0.70	0.26-1.52	0.00	0.00-1.01	0.49	0.20-1.01
Test for trend	*P*=0.410		*P*=0.969		*P*=0.276		*P*=0.595		*P*=0.469		*P*=0.006		*P*=0.871	
Total	**0.57**	**0.53-0.62**	**0.60**	**0.54-0.67**	**0.53**	**0.32-0.82**	**0.53**	**0.42-0.64**	**0.62**	**0.45-0.85**	**0.21**	**0.08-0.43**	**0.59**	**0.49-0.70**
(b) MARRIED OR COHABITANT WOMEN	n=729		n=369		n=27		n=110		n=52		n=9		n=162	
	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI	O/E	95% CI
Age at diagnosis														
0-4	1.18	1.02-1.35	1.29	1.06-1.56	1.72	0.35-5.02	0.82	0.33-1.68	0.77	0.09-2.79	1.23	0.25-3.59	1.07	0.84-1.36
5-9	1.07	0.93-1.22	1.03	0.86-1.23	0.95	0.41-1.88	1.29	0.86-1.85	1.13	0.70-1.73	0.75	0.02-4.17	1.07	0.73-1.52
10-14	1.00	0.87-1.16	1.20	0.97-1.46	0.82	0.33-1.69	0.76	0.57-0.99	1.22	0.73-1.93	0.61	0.13-1.78	1.28	0.65-2.21
Period of diagnosis														
1960-1969	0.80	0.54-1.15	1.05	0.56-1.79	-	-	0.59	0.12-1.71	-	-	1.14	0.14-4.12	0.66	0.34-1.16
1970-1979	0.97	0.87-1.08	1.01	0.88-1.16	1.04	0.38-2.27	0.85	0.64-1.11	0.80	0.46-1.31	0.76	0.21-1.94	1.01	0.78-1.28
1980-1989	1.30	1.12-1.49	1.43	1.16-1.73	1.05	0.54-1.83	0.88	0.59-1.27	1.36	0.82-2.12	0.72	0.02-3.99	1.69	1.14-2.41
1990-1998	2.53	1.71-3.61	4.63	2.47-7.92	0.00	0.00-2.60	2.17	0.70-5.06	3.02	1.11-6.58	0.00	0.00-13.4	1.95	0.72-4.25
Test for trend	*P*<0.001		*P*<0.001		*P*=0.458		*P*=0.183		*P*=0.007		*P*=0.531		*P*=0.001	
Total	**1.08**	**0.99-1.17**	**1.15**	**1.03-1.29**	**0.96**	**0.57-1.53**	**0.88**	**0.71-1.08**	**1.14**	**0.82-1.55**	**0.80**	**0.32-1.65**	**1.09**	**0.90-1.31**

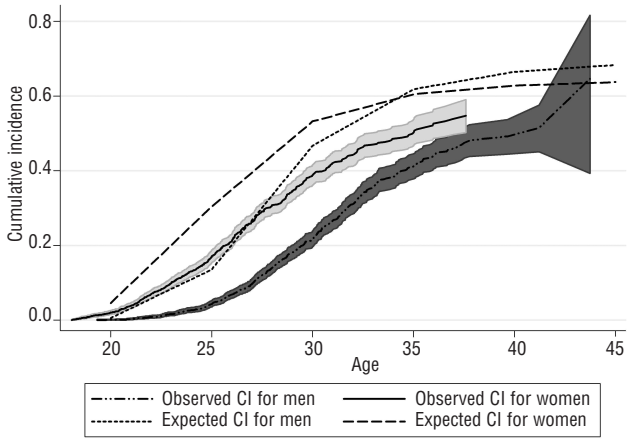

Figure 3. Off-Therapy Registry 1960-1998. Cumulative incidence (CI) of marriage in childhood cancer survivors (observed) and in the general population (expected) by gender in 1980-2004, with 95% confidence limits.

cohort of married women. In this way, assuming that married women are more likely to have children, the O/E ratio in our cohort would be overestimated. But, if the fertility deficit persisted, we could conclude that it may not be entirely attributable to the observed marriage deficit. The results of the analysis (Table 3b) show that the fertility deficit either disappeared completely (as for married survivors of acute lymphoblastic leukemia, for whom we find an increased fertility with respect to the general population) or was strongly reduced and lost statistical significance. In particular, the 79% fertility deficits for CNS tumor survivors decreased to a non-statistically significant 20%. This result suggests that childhood cancer survivors in Italy who were "competent" to get married (probably because of a lower residual morbidity) were as likely to have children as their healthy peers. Our results are consistent with US studies that found high fertility rates in married survivors.[38]

In this study, there was a significant excess of male offspring that persisted also after adjusting for birth order. This finding is consistent with those of previous studies conducted in Piedmont[13,20] (the Piedmont cohort is included in the present study and represents 9.7% of the OTR cohort) but has not been observed in other studies.[39-44] We can speculate that a wider use of assisted reproduction treatments, which are known to influence the gender ratio of children, might explain this finding.

In conclusion, our results confirmed that young adults who survived a childhood cancer in Italy have a reduced chance of forming a family. Given the increasing proportion of patients who are expected to be cured and thus to become active adults in the coming years, these features should be carefully considered by childhood cancer specialists engaged in the continuous process of refining treatment.[45,46] In addition to devising more effective and less harmful therapeutic modalities, the inclusion of counseling in the strategies of management and long-term surveillance of childhood cancer patients could be very beneficial to survivors as they approach adulthood.

Appendix

Chairpersons of AIEOP Centers (as of 2010): Cordero di Montezemolo L (Torino), Fagioli F (Torino), Bona G (Novara), Dini G (Genova), Carnelli V (Milano), Biondi A (Milano), Zecca M (Pavia), Conter V (Bergamo), Porta F (Brescia), Fedeli F (Milano), Massimino M (Milano), Nespoli L (Varese), Roncarolo MG (Milano), Carli M (Padova), Cesaro S (Verona), Memo L (Belluno), Colleselli P (Vicenza), Battisti L (Bolzano), Tamaro P (Trieste), Mascarin M (Pordenone), Nocerino A (Udine), Izzi G (Parma), Pession A (Bologna), Paolucci P (Modena), Borgna Pignatti C (Ferrara), Vecchi V (Rimini), Abate ME (Bologna), Aricò M (Firenze), Acquaviva A (Siena), Favre C (Pisa), Aversa F (Perugia), Pierani P (Ancona), Felici L (Pesaro), Visani G (Pesaro), Fioritoni G (Pescara), Foa R. (Roma), Riccardi R (Roma), Frega G (Roma), Clerico A (Roma), Locatelli F (Roma), Casale F (Napoli), Poggi V (Napoli), Amendola G (Nocera Inferiore), Filosa A (Napoli), Ladogana S (San Giovanni Rotondo), Presta G (Tricase), Pozzi S (Lecce), De Mattia D (Bari), Consarino C (Catanzaro), Nobile F (Reggio Calabria), Sperlì D (Cosenza), D'Angelo P (Palermo), Marino S (Catania), Gallisai D (Sassari), Targhetta R (Cagliari).

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