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An estimate of the number of people in Italy living after a childhood cancer.

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Abstract

Cancers diagnosed in children below the age of 15 years represent 1.2% of all cancer cases, and survival after a childhood cancer has greatly improved over the past 40 years in all high income countries. This study aims to estimate the number of people living in Italy after a childhood cancer for all cancers combined and for a selection of cancer types. We computed 15- year prevalence using data from 15 Italian population- based cancer registries (covering 19% of Italian population) and estimated complete prevalence for Italy by using the CHILDPREV method, implemented in the COMPREV software. A total of 44,135 persons were alive at January 1st, 2010 after a cancer diagnosed during childhood. This number corresponds to a proportion of 73 per 100,000 Italians and to about 2% of all prevalent cases. Among them, 54% were males and 64% had survived after being diagnosed before 1995, the start of the observation period. A guarter of all childhood prevalent cases were diagnosed with brain and central nervous system tumors. a guarter with acute lymphoid leukemia, and 7% with Hodgkin lymphoma. Nearly a guarter of prevalent patients were aged 40 years and older. Information about the number of people living after a childhood cancer in Italy by cancer type and their specific health care needs may be helpful to health- care planners and clinicians in the development of guidelines aimed to reduce the burden of late effect of treatments during childhood.

Introduction

Cancers diagnosed in children below the age of 15 years represented 1.2% of all cancer cases worldwide, in 2012. <u>1</u> A lower proportion was reported in the United States (0.6%) and Europe (0.4%); in both areas, approximately 150 cases per million children were diagnosed yearly. <u>1</u>, <u>2</u> In the same year, the annual mortality rate was 20 to 30 cases per million children in Europe and the United States, respectively. In Italy, a significant constant decrease of approximately 3% per year since 1970 has been observed.<u>3</u>

Survival after a childhood cancer has greatly improved over the past 40 years in all high income countries. In Europe, children in ages 0–14 diagnosed with cancer during 1999–2007 show a 78% overall 5-year survival. **4** The 5-year survival is even higher (82%) for cases diagnosed in Italy in 2003–2008. **2** Notably, 15-year survival is about 4% lower than 5-year survival, suggesting that cure is now the outcome for most childhood cancer patients, **2** and the number of long-term childhood cancer survivors is expected to increase. **5**-**8**

These patients not only represent an extremely relevant issue in terms of social life and public health but they also form an interesting subgroup of patients with respect to cancer type, biological features, and long-term outcome. **9** Many of these patients are now adults, and there is growing awareness that the therapies they underwent may be associated with a potential long-term risk, **10** as cancer treatments may adversely affect the survivors' future physical, cognitive, and/or psychosocial health. **8**, **11**, **12** Nevertheless, studies reporting estimates of complete prevalence after a childhood cancer are only a few, **5**-**8**, **13**even if it is well known that persons living after a cancer diagnosed at any age represent >4% of the whole population, in high income countries. **14**-**17**

The aim of this study was to estimate the number of people living in Italy after a childhood cancer for all cancers combined and for a selection of cancer types, chosen according to frequency in childhood ages (*i.e.*, the 3 most frequent) and for expected late effects in adolescents and adults. These results could provide helpful information to researchers, clinicians and survivors, in order to contribute to optimal long-term care. **10**

Materials and Methods

Data sources

This study included data from 15 population-based cancer registries (CRs), members of the Italian Association of Cancer Registries (AIRTUM), with at least 15 years of cancer registration as of 2010 and follow-up for vital status as of December 31, 2013. The 15 CRs cover >11 million people (*i.e.*, 19% of the entire Italian population in 2010) and 1.5 million children aged <15 years (Table <u>1</u>).

Estimates were provided for all cancer types combined but skin non-melanoma (all types; C00-43, 45–96) and for the three most frequent cancer types in children, selected according to the following ICDO3<u>18</u> codes: acute lymphoblastic leukemia (ALL; M9727-9729, M9835-9837), brain and central nervous system cancer (CNS; C70-72), Hodgkin lymphoma (HL; M9650-9667). For comparison purposes, benign and uncertain behavior tumors of CNS were excluded.

The Childhood Cancer Registry of Piedmont (CCRP), which covers the whole Piedmont region since 1976 (7% of the Italian pediatric population), contributed to the study for validation purposes only, since complete prevalence calculations require the availability of incidence for all age groups. Italian national population by age at January 1st, 2010 was provided by the Italian National Statistics Institute.

Statistical methods

Estimation of complete prevalence was obtained by applying the CHILDPREV

method, <u>20</u> implemented in the COMPREV software. <u>21</u> The CHILDPREV method requires estimation of incidence and survival parameters from all ages. For each CR, we computed 15-year limited duration prevalence (15-year LDP) of cases diagnosed during childhood (ages 0–14) and at any age, based on incident cases diagnosed in the 15-year period 1995–2009 and followed-up for vital status to December 31st, 2009. Furthermore, we estimated the complete prevalence at any age, which included unobserved cases diagnosed before 1995.

Finally, we applied the age- and sex-specific complete prevalence rates to the entire Italian population. For 15-year LDP calculations only, four CRs with last year of registration other than 2009 were shifted either one year backward (Napoli and Reggio Emilia) or 1 or 2 years forward (Veneto and Genova, respectively).

Both relative survival and incidence functions were estimated by means of parametric models using data from the long-term Italian CRs, which provided an 18-year or longer data series within the period 1985–2009 (Table <u>1</u>), and were used to estimate the proportion of childhood cancer survivors diagnosed before 1995. The 15-year LDP counts were obtained using the counting method implemented in SEER*Stat software.<u>22</u>

In this study, prevalent cases were fully observed for ages at prevalence 0 to 14 years, partially observed for ages 15 to 29 years (because some of these cases were diagnosed before 1995) and not observed from age 30 years and thereafter. The incidence model implemented in CHILDPREV was a 6-degree polynomial in age 23 applied separately by sex and cancer type. The survival model was a parametric cure model assuming that a proportion of individuals with cancer are bound to die (fatal cases) with a survival following a Weibull distribution, while the remaining proportion (cured fraction) has the same mortality rate as the general population with the same age and gender stratification, when time tends to infinity.24-26 The parameters of the survival model were stratified by age class (0-14, 15-44, 45-54, 55-64, 65-74, 75+ years). A period effect was included at the exponential of the survival function of fatal cases. An additional time trend parameter bounding survival trends before the year 1973 was used for cancer type specific estimates (ALL, HL, CNS); the value of this parameter was based on the historical Connecticut Cancer Registry data. 6, 20 Survival was modelled separately by sex and cancer type. Age-, sex-, and cancer type-specific proportions of prevalence estimates in CRs included in this study were applied to the Italian national population by age at January 1st, 2010 to obtain the corresponding national prevalence estimates.16

Since prevalence is a function of both incidence and survival, we compared incidence and 5-year relative survival rates in the pool of 15 Italian CRs (1995–2009) included in the study with CCRP (1976–2009), and with model-based incidence and survival rates used in the model implemented in CHILDPREV.

Results

Table <u>1</u> lists the CRs involved in the study, together with the number of incident cases in the period 1995–2009 by cancer type. ALL represents 26% of all cases, CNS 16%, and HL 8%. The time trends of incidence (1995–2009) and survival (1994–2008)—the major determinants of cancer prevalence—of children diagnosed between 0 and 14 years of age in the pool of 15 Italian CRs are presented in Figures <u>1</u> and <u>2</u>. Throughout the 1995–2009 period, overall incidence rates were 188 per million boys and 160 per million girls, with a peak in 2001–2003 in boys and in 1998–2000 in girls. Thereafter, a slight decline was observed in both sexes in the late 2000s, mostly driven by ALL and CNS trends (Fig. <u>1</u>).

For all cancer types, five- year survival slightly increased from 1994–1996 (77%) to 2006–2008 (82%) in both sexes, mainly driven by ALL, from 84% to 93% (96% in females), while no relevant changes emerged for CNS and HL survival (Fig. <u>2</u>).

We estimated a total of 44,135 persons alive in Italy at January 1st, 2010 after a cancer diagnosed in childhood (Table <u>2</u>). This number corresponded to a proportion of 73 per 100,000 Italians (0.07%). Of them, 54% were males and 46% were females. The CHILDPREV method allowed prevalence to be estimated for patients diagnosed before 1995 (the start of the observation period), that is, 64% of the estimated total prevalence.

The cancer types with the largest number of survivors were CNS (10,677, 24% of all prevalent cases), ALL (10,199, 23%), followed by HL (3081, 7%).

In 2010, 23% (10,366) of prevalent patients were aged 40 years or older and only 3% (1488) of all childhood cancer cases were aged 60 years or older (Table $\underline{2}$). The distribution by age group of complete prevalence varies by cancer type (Fig. $\underline{3}$). Prevalent patients younger than 30 years were 65% when the diagnosis was ALL, 57% for HL, and only 32% for CNS.

For validation purposes incidence, survival and prevalence rates from the long-term Italian CRs, in the CCRP and model-based were compared. We found a good agreement for both incidence and survival rates (Appendices A and B, respectively). Comparison of complete prevalence and 34-year limited duration prevalence (34-year LDP) in CCRP, showed a good agreement in ages 0–19 years and an overestimation in ages 20–34 years (Appendix C).

Discussion

Childhood cancer survivors are individuals potentially exposed to late effects of cancer treatments received.² Cancer treatments could adversely affect survivors' lives with often long latencies before the occurrence of side effects. Recent epidemiological studies suggest that over 40% of childhood cancer survivors treated from the 1960s to the early 1990s have experienced at least one chronic disease, often of severe nature.²⁶⁻²⁸

Information about the number and specific health care needs of childhood cancer survivors in Italy is poor, and this study was developed within the framework of a research project supported by the Italian Ministry of Health aimed at the evaluation of a specific surveillance program for childhood cancer survivors, to prevent and timely treat possible late effects of childhood cancer.

We estimated that >44,000 persons living in Italy at the beginning of 2010 had had a cancer diagnosis during childhood. They represented 0.07% of the Italian population and 1.7% of prevalent cases diagnosed at any age for any type of cancer.<u>16</u> The three most frequent cancer types in children (ALL, HL and CNS) corresponded to more than half of all prevalent cases. In addition, 46% was 30 years or older, and this fraction included patients diagnosed >15 years before.

The age distribution of prevalent cases reflects the different historical trends in cancer prognosis: before 1960 ALL survival was <6 months for almost all patients $\underline{8}$, $\underline{29}$; after 1960 improvements in treatments caused an increase in survival for ALL and HL. On the other hand, almost 40% of children diagnosed with CNS cancers in the 1960s survived >5 years, $\underline{6}$, $\underline{7}$ which explains the higher proportion of CNS survivors at older ages. Furthermore, the prevalence after childhood cancer still slightly changed in recent years because of the decline of late mortality due to the decrease of potentially life-threatening effects of the first cancer therapy. The high doses of radiation and chemotherapy, used in the treatment of HL in the period 1980–1990, have been drastically reduced or replaced with less toxic agents in more recent years to avoid the survivors' risks of secondary leukemia.

From a collaborative research in childhood cancer survivorship,<u>**30**</u> it can be inferred that prevalence estimates vary between 0.04% and 0.10% of the national populations. In particular, in

the Nordic countries and in the United States, prevalence is estimated at about 0.10% of the national population. **7**, **8**

Despite the difficulties in comparing numbers and proportions of prevalent cases after childhood cancer among countries, related to differences in length of cancer registration, age groups considered, and statistical methods used, overall estimates in Italy are comparable to those reported in the literature.

This study provides the first published estimates of complete childhood cancer prevalence in Italy. Its most relevant strength is the size of the population included, which makes estimates reliable. However, the application of CHILDPREV method is challenging, as it requires assumptions on incidence and survival trends over unobserved time. In our analysis, the majority of prevalent cases were not observed (Table <u>2</u>), and the number was estimated through statistical modelling.<u>20</u> We estimated prevalence for cases diagnosed in ages 0–14 years, and included all CRs with at least 15 years of observation, which is the minimum length required by the method. The validation of incidence, survival, and prevalence by comparison with CCRP is reasonably reassuring: even though we observed an overestimation of prevalence in young adults (ages 20–34), the average difference between the CCRP and the complete prevalence is <10%. The completeness index method, as presently implemented in the COMPREV software, does not include adjustments for changes in incidence rates. Thus backward projection of incidence rates may lead to a possible overestimation of complete prevalence for cancer types with increasing incidence.<u>2</u>

The classification of histological types in children, as well as in adults, presents specific challenges, due to different spectrums of diagnostic subtypes in adults and children. The use of the International Classification of Diseases for Oncology, third edition (ICDO-3), instead of the International Classification for Childhood Cancer grouping<u>31</u> is due to a statistical reason, as the CHILDPREV method requires the computation of prevalence data at any age. This choice produces two consequences: benign or uncertain behavior CNS tumors, representing 7% of pediatric tumors,<u>2</u> were excluded; 5% of all lymphoid leukemias in children were not captured by the ICDO-3 classification.

Conclusions

This is the first attempt to estimate the number of people living after a childhood cancer in Italy. As this number is expected to keep increasing, it is important to assess its public health implications. Therefore, the estimates of number and characteristics of persons living many years after childhood cancer diagnosis may be helpful to health-care planners and clinicians in developing guidelines aimed to improve long-term follow-up of survivors in order to reduce the burden of late effects of treatments in these patients. <u>32</u>

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