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Original Research

Late mortality and causes of death among 5-year survivors of childhood cancer diagnosed in the period 1960–1999 and registered in the Italian Off-Therapy Registry

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Abstract ***Introduction:*** Advances in paediatric oncology led to the increase in long-term survival, revealing the burden of therapy-related long-term side effects. We evaluated overall and cause-specific mortality in a large cohort of Italian childhood cancer survivors (CCSs) and adolescent cancer survivors identified through the off-therapy registry.
Materials and methods: CCSs alive 5 years after cancer diagnosis occurring between 1960 and 1999 were eligible; the last follow-up was between 2011 and 2014. Outcomes were reported as standardised mortality ratios (SMRs) and absolute excess risks (AERs).
Results: Among 12,214 CCSs, 1113 (9.1%) deaths occurred. Survival at 35 years since diagnosis was 87% (95% confidence interval [CI]: 86–88) and at 45 years was 81% (95% CI: 77–84). CCSs had an 11-fold increased risk of death (SMR 95% CI: 10.7–12), corresponding to an AER of 48 (95% CI: 45–51). Mortality decreased by 60% for survivors treated most recently (1990–1999). The most frequent causes of death were recurrence of the original cancer (56%), a subsequent neoplasm (19%) and cardiovascular diseases (5.8%). Among those who survived at least 15 years after diagnosis, a secondary malignancy was the leading cause of death.
Conclusions: This study confirms the impact of recent advances in anticancer therapy in reducing mortality, mainly attributable to recurrence but also to other causes. However, overall mortality continues to be higher than in the general population. A long-term follow-up is needed to prevent late mortality due to secondary neoplasms and non-neoplastic causes in CCSs.

1. Introduction

Important advances in paediatric oncology have been made in the past decades, with cure rates improving from less than 30% in the 1960s to more than 75% for children treated in the early 2000s [1]. This resulted in a substantial increase in the population of long-term survivors, usually defined as patients living more than 5 years after cancer diagnosis [2]. However, several studies have shown that childhood cancer survivors (CCSs) experience late morbidity and mortality at higher rates compared with their peers in the general population [3–9]. Besides the recurrence of the original cancer, other causes of death have been reported in excess among CCSs based on the type of original tumour, type and era of treatment. Most studies are based on CCS cohorts from the US or North Europe [10–18], whereas information is scarce about survivors treated in Southern Europe [19,20]. This study aims to evaluate the overall and cause-specific long-term mortality of a large Italian cohort of CCSs.

2. Materials and methods

2.1. Registry and population

The study cohort was identified from the off-therapy registry (OTR) of the Associazione Italiana di Ematologia ed Oncologia Pediatrica established in 1980 to prospectively enrol children with cancer who have reached the elective end of their therapy plan in the absence of clinical signs of active disease [21]. At the start of the registry, prevalent cases were also included with the first patient being diagnosed in 1960. The following tumour

types were considered at that time: acute lymphoblastic leukaemia (ALL), acute non-lymphoblastic leukaemia (ANLL), Wilms' tumour (WT), Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and neuroblastoma (NB). In 1986, the registry was expanded to include soft-tissue sarcomas (STSs) and central nervous system (CNS) tumours. Since 1989, all other tumour types are included through linkage to a centralised electronic archive [22]. For this study, only subjects diagnosed before 2000 were eligible for analysis.

The OTR collects information on patients' demographics, their primary cancer, its treatment, the clinical course of the disease and major clinical events (relapse, subsequent neoplasms, death and cause of death) occurring after the elective end of therapy. A follow-up is periodically updated either through treating institutions or census bureaus. To allow comparison with other similar cohorts in the literature, only subjects alive 5 years after cancer diagnosis were eligible for this study.

2.2. Ascertainment of vital status and cause of death

As part of the European Union–funded PanCareSurFup project [23], in the period 2011–2014, the vital status of each subject was updated via postal survey with census bureaus and/or the national health system registry. For cases not traced, the last clinical follow-up available in the OTR was retained.

For each deceased subject, the death certificate was requested from the municipality where the event occurred. In some circumstances, only one cause of death was reported, whereas, in others, the complete death certificate with up to four consecutive and contributing causes of death was provided. Each underlying cause of death was then defined based on the death certificate and on clinical data available in the OTR. If the cause of death based on clinical data was different from the one derived from the death certificate, we used the cause derived from clinical information. All causes of death were coded in accordance with the International Classification of Diseases, 9th (ICD-9) or 10th revision (ICD-10). Causes of death were grouped into six categories as per Eurostat [24] (Supplementary Table 1). Deaths due to neoplasm (ICD-9: 140–239; ICD-10: C00-D48) were divided in two groups consisting of recurrence of the primary tumour and subsequent malignant neoplasms (SMNs).

The OTR protocol was approved by the ethics review board of each participating institution. The PanCareSurFup protocol was also approved by the Gaslini Hospital ethics board.

2.3. Statistical analysis

The probability of survival was estimated based on the Kaplan–Meier method allowing for left truncation for prevalent cases at the start of OTR [25]. Greenwood standard errors were used. To compare survival with that of the Italian general population, the expected number of deaths adjusted for age and sex was calculated for each year since diagnosis by the indirect standardisation method [26] using national statistics [27], yielding the expected survival probabilities. In brief, the indirect standardisation method allows to calculate the expected numbers of deaths in the study population by multiplying the person-years for each sex, age and calendar year by the corresponding mortality rates in the general population.

Standardised mortality ratio (SMR—i.e. the ratio between observed and expected number of deaths) and absolute excess risk of death (AER—i.e. observed minus expected number of deaths, divided by the number of at risk person-years multiplied by 10,000) of the CCS were calculated, and the corresponding 95% confidence intervals (CIs) were estimated, assuming a Poisson distribution for the number of observed events [26]. Only deaths with known causes were included in the calculation of cause-specific SMRs and AERs.

SMRs and AERs were stratified based on sex, age at diagnosis (0–4, 5–9,10-14 and 15–21 years), calendar year of diagnosis (1960–79, 1980–89 and 1990–99), tumour type, treatment (chemotherapy [CT] plus radiotherapy [RT], RT, CT, neither CT nor RT) and years since diagnosis (5–9, 10–14, 15–19, 20–24, 25–29, 30–34 or >34 years). To evaluate the simultaneous effect of those factors on overall and cause-specific mortality, multivariable regression models were applied such as the Cox proportional hazard model to derive the hazard ratios (HRs) of death and the Poisson regression model to calculate relative risk of SMR (RR-SMR) or of AER (RR-AER) [28].

Cause-specific mortality curves were estimated by the crude cumulative incidence method [29], overall and by calendar year of diagnosis. Causes of death other than the one under study were treated as competing risks.

All tests were two-tailed and a p value < 0.05 was considered statistically significant. All analyses were performed by using Stata (Stata Statistical Software, Release 13.0; StataCorp, College Station, TX, Stata Corporation, 2011).

3. Results

From the original cohort of 13,485 children and adolescents included in the OTR, 1271 (9.4%) were excluded either because they had died (n = 1161) or had their last follow-up within 5 years since diagnosis (n = 110). This left 12,214 five-year survivors eligible and evaluable for this study (Supplementary Table 2). Among eligible survivors, there were more male survivors (56%) and the most common cancer was ALL (39%). Most children (39%) were younger than 5 years at diagnosis; more than half (53%) were diagnosed in the most recent chronologic period (1990––1999), and 51% received combined treatment with CT and RT, and 40%, CT only (Table 1 and supplementary Table 3).

Table 1
Vital status, standardised mortality ratio, absolute excess risk and relative rate of mortality because of all causes of death by potential explanatory factors in 5-year survivors diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry.

Characteristics	N (%)	Person-years	Alive	Dead	Expected	Univariable analysis		Multivariable analysis		
						SMR (SE)	AER (SE)	RR-SMR[a] (SE)	RR-AER[a] (SE)	HR[a] (SE)
All patients	12,214	211,830	11,101	1113	98	11 (0.34)	48 (1.6)	–	–	–
Sex										
Male	6788 (56)	117,020	6114	674	75	9.0 (0.35)	51 (2.2)	reference	reference	reference
Female	5426 (44)	94,810	4987	439	24	18 (0.89)	44 (2.2)	2.0 (0.13)	0.83 (0.06)	0.79 (0.05)
First primary neoplasm										
ALL	4779 (39)	88,124	4330	449	39	11 (0.54)	46 (2.4)	reference	reference	reference
HL	1237 (10.1)	23,379	1085	152	16	9.3 (0.75)	58 (5.2)	1.6 (1.2–2.2)	1.6 (0.28)	1.6 (0.26)
NHL	995 (8.2)	17,876	939	56	10.5	5.3 (0.71)	25 (4.1)	0.91 (0.09)	0.80 (0.10)	0.96 (0.10)
WT	1028 (8.4)	19,761	979	49	7.5	6.5 (0.93)	21 (3.5)	0.55 (0.08)	0.39 (0.09)	0.58 (0.09)
NB	998 (8.2)	17,744	919	79	6.2	13 (1.4)	41 (5.0)	0.59 (0.09)	0.48 (0.10)	0.59 (0.09)
CNS	931 (7.6)	12,436	788	143	5.3	27 (2.2)	111 (9.6)	1.2 (0.18)	1.1 (0.19)	1.1 (0.17)
Soft tissue sarcoma	618 (5.1)	10,118	555	63	4.5	14 (1.8)	58 (7.8)	2.5 (0.29)	2.6 (0.32)	2.5 (0.29)
ANLL	511 (4.2)	7678	458	53	3.3	16 (2.2)	65 (9.5)	1.3 (0.18)	1.2 (0.20)	1.3 (0.18)
Bone tumour	364 (2.9)	4465	313	51	2.1	25 (3.6)	109 (15.9)	2.6 (0.49)	2.7 (0.54)	2.6 (0.51)
Other[b]	753 (6.2)	10,249	735	18	3.2	5.6 (1.3)	14 (4.1)	0.60 (0.19)	0.46 (0.19)	0.60 (0.19)
Age at diagnosis, y								0.88 (0.03)[c]	1.2 (0.05)[c]	1.2 (0.05)[c]
0–4	4797 (39)	85,555	4479	318	30	11 (0.61)	34 (2.1)	reference	reference	reference
5–9	4080 (33)	73,222	3646	434	35	12 (0.59)	54 (2.8)	1.1 (0.09)	1.5 (0.13)	1.5 (0.12)
10–14	2584 (21)	42,340	2307	277	26	10.5 (0.63)	59 (3.9)	0.77 (0.07)	1.5 (0.17)	1.6 (0.16)
15–21	753 (6.2)	10,713	669	84	7.2	12 (1.3)	72 (8.5)	0.75 (0.11)	1.8 (0.29)	1.9 (0.27)
Years since diagnosis								0.61 (0.02)[c]	0.64 (0.02)[c]	–
5–9	–	51,948	–	536	14	38 (1.6)	100 (4.4)			
10–14	–	55,475	–	250	21	12 (0.74)	41 (2.8)			
15–19	–	43,300	–	106	22	4.7 (0.46)	19 (2.4)			
20–24	–	28,250	–	72	16	4.5 (0.53)	20 (3.0)			
25–29	–	18,078	–	72	11	6.6 (0.77)	34 (4.7)			
30–34	–	9959	–	50	7.5	6.7 (0.94)	43 (7.1)			
>34	–	4820	–	27	5.7	4.7 (0.91)	44 (10.7)			
Year of diagnosis										
1960–1979	1,952[d] (16)	54,078	1615	337	37	9.2 (0.50)	55 (3.4)	reference	reference	reference
1980–1989	3760 (31)	78,945	3342	418	37	11 (0.55)	48 (2.6)	0.80 (0.06)	0.66 (0.06)	0.73 (0.06)
1990–1999	6502 (53)	78,807	6144	358	25	14 (0.77)	42 (2.4)	0.70 (0.07)	0.42 (0.05)	0.45 (0.05)
Treatment[e]										
No RT, no CT	751 (7.1)	10,609	730	21	3.4	6.1 (1.3)	17 (4.3)	reference	reference	reference
CT only	4239 (40)	66,095	4043	196	26	7.6 (0.54)	26 (2.1)	1.8 (0.44)	2.3 (0.69)	1.9 (0.45)
RT only	229 (2.2)	4525	191	38	3.0	12 (2.1)	77 (13.6)	2.2 (0.63)	2.7 (0.95)	2.4 (0.67)
RT and CT	5367 (51)	107,855	4652	715	57	12 (0.47)	61 (2.5)	3.2 (0.75)	4.4 (1.3)	3.3 (0.78)

Numbers were reported with two decimals for numbers< 1.05; one decimal for numbers up till 10.5 and no decimals above 10.5.
SE = standard error; ALL = acute lymphoblastic leukaemia; HL= Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; WT= Wilms' tumour; NB = neuroblastoma; CNS = central nervous system; ANLL = acute non-lymphoblastic leukaemia; RT = radiotherapy; CT=chemotherapy; AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry; SMR = standardised mortality ratio; AER = absolute excess risk; RR = relative risk.

[a] Subjects without treatment information were excluded from analysis.

[b] Other: Langerhans cell histiocytosis\malignant histiocytosis (n = 258); germ cell\neoplasms of gonads (n = 217); retinoblastoma (n = 100); hepatic tumours (n = 62); other solid (n = 116).

[c] Considered as a continuous variable.

[d] Only 121 survivors diagnosed in the period 60–69 contribute to the treatment era category 1960–79.

[e] Data on treatment were not available for 1628 (22,746 person-years) survivors.

3.1. Overall mortality

Only 184 (1.5%) survivors were not traced; death was documented for 1113 (9.1%) subjects. The overall cohort comprised 211,830 person-years, and the median follow-up of the censored patients was 22 years (interquartile range, IQR, 17–29) after diagnosis. As shown in Fig. 1, the probability of long-term survival at 25, 35 and 45 years since diagnosis was 91% (95% CI: 90–91), 87% (95% CI: 86–88) and 81% (95% CI: 77–84), respectively. If all the 13,485 off-therapy patients were considered regardless of their minimum follow-up of 5 years, the probability of survival at 25, 35 and 45 years was 82% (95% CI: 81–83), 79% (95% CI: 78–80), and 73% (95% CI: 70–77), respectively. Only 98 deaths were expected in a comparable Italian population (Table 1), leading to a more than 10-fold increased risk of death among CCSs (SMR = 11, 95% CI: 10.7–12),

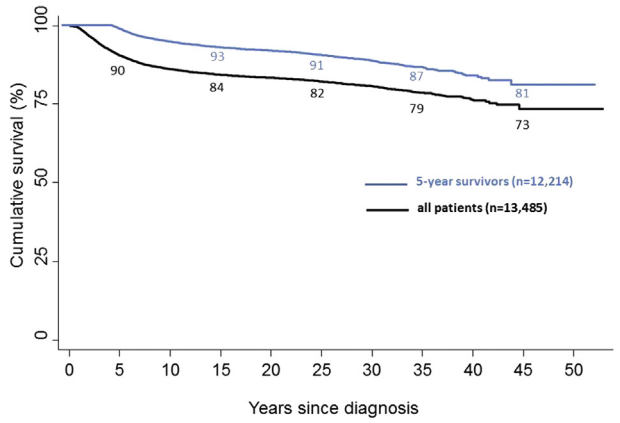

Fig. 1. Probability of survival among patients diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry. Black line refers to all the registered patients, blue line refers only to those who survived at least 5 years since diagnosis. AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR, off-therapy registry. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

corresponding to 48 extra deaths (AER = 48, 95% CI: 45–51) per 10,000 person-years. Fig. 2 shows the difference in the observed overall survival by gender compared with that expected in an age-, year- and sex-matched Italian population. It is apparent that the survival estimate among CCSs was always lower than that of the background population.

The highest SMRs (Table 1 and Supplementary Table 3) were observed among survivors of CNS tumours (27, 95% CI: 23–31) and bone tumours (25, 95% CI: 19–33), the lowest among those treated for NHL, WT and other tumours. In the multivariable analysis adjusting for all other risk factors and considering time as a continuous variable, the risk of death among CCSs decreased with increasing age class at diagnosis (RR-SMR = 0.88, 95% CI: 0.82–0.96) as well with increasing period since diagnosis (RR-SMR = 0.61, 95% CI: 0.58–0.64). Compared with those treated before 1980, patients treated in the 1980s had a 20% reduced mortality (RR-SMR = 0.80, 95% CI: 0.69–0.93) that further decreased to 30% for those treated in the 1990s (RR-SMR = 0.70, 95% CI: 0.57–0.84). This trend is shown in Fig. 3 in which, at 15 years since diagnosis, the cumulative risk of death for survivors treated before 1980 was 11% (95% CI: 9.7–13), whereas that of those treated in the 1980s was 7.8% (95% CI: 6.5–8.7) and only 5.1% (95% CI: 4.6–5.7) for those treated in the 1990s, $p < 0.001$.

Finally, as compared with CCSs treated with only surgery (no RT, no CT in Table 1 and supplementary Table 3), those treated with combined RT and CT had a significant three-fold increased risk of death (RR-SMR = 3.2, 95% CI: 2.1–5.0), those treated with RT alone had a RR-SMR = 2.2 (95% CI: 1.3–3.9) and those treated with CT alone had a RR-SMR = 1.8 (95% CI: 1.1–2.9).

If AERs or HRs were considered, results were consistent with those of SMR with the exception of gender where female survivors had lower risk of death than male survivors and of age at diagnosis for which an increasing trend in deaths was observed with increasing age (Table 1 and supplementary Table 3).

3.2. Cause-specific mortality

Causes of death were available for 1024 (92%) of the deceased subjects (details in Supplementary Table 1); and in 42 cases (4.1%), the available clinical information led to the recoding of the official cause of death (Supplementary Table 4). Table 2 reports on SMR and AER by specific cause of death. Recurrence of the

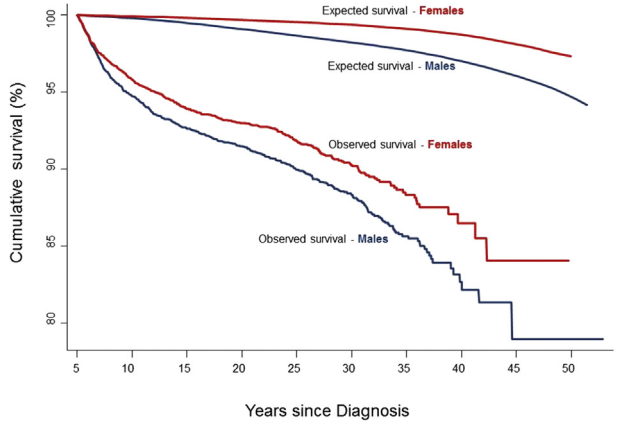

Fig. 2. Overall survival by gender of 5-year survivors diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry, compared with the expected survival in an age-, year- and sex-matched Italian population. AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry.

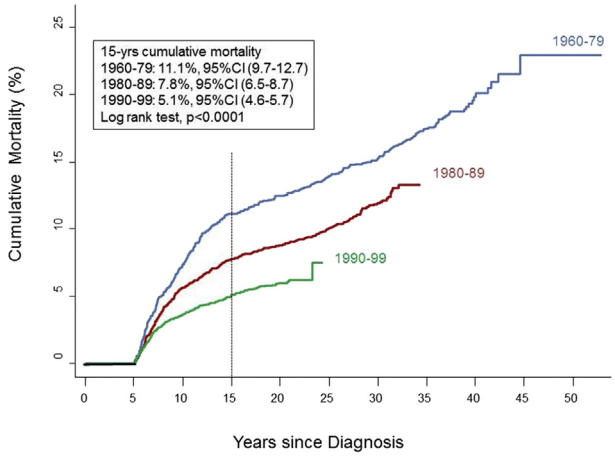

Fig. 3. Overall cumulative mortality by era of diagnosis of 5-year survivors registered in the Italian AIEOP-OTR registry. AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry; CI = confidence interval.

Table 2
Standardised mortality ratio and absolute excess risk by specific cause of death among 5-year survivors diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry.

Causes	Person-years	Observed (%)	Expected	SMR (95% CI)	AER (95% CI)
All causes	211,830	1113 (100)	98	11 (10.7–12)	48 (45–51)
Recurrence	210,806	624 (56)	–	–	30[a] (27–32)
Subsequent neoplasm	210,806	216 (19)	18	12 (11–14)	9.4 (7.8–10.5)
Cardio vascular disease	210,806	64 (5.8)	8.3	7.7 (6.0–9.8)	2.6 (1.7–3.2)
Other causes	210,806	50 (4.5)	20	2.4 (1.8–3.2)	1.4 (1.00–2.3)
External causes	210,806	44 (3.9)	47	0.94 (0.70–1.3)	NA
Respiratory disease	210,806	26 (2.3)	1.9	13 (8.9–19)	1.1 (0.73–1.7)
Unknown causes[b]	1024	89 (8.0)	–	–	–
All causes except recurrence	210,806	400 (39)	97	4.1 (3.7–4.5)	14 (12–15)

Numbers were reported with two decimals for numbers< 1.05; one decimal for numbers up until 10.5 and no decimals above 10.5.
AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry; SMR = standardised mortality ratio; AER = absolute excess risk; CI = confidence interval.
[a] Crude rate may be interpreted as an AER.
[b] No death certificate available.

original cancer accounted for the majority of deaths (56%), with a crude AER of 30 (95% CI: 27–32) per 10,000 person-years. The second most frequent cause of death was an SMN (19%), with an SMR of 12 (95% CI:11–14) and an AER of 9.4 (95% CI:7.8–10.5). Cardiovascular system–related deaths accounted for 5.8% of all deaths and caused 2.6 (95% CI: 1.7–3.2) excess deaths per 10,000 person-years. All other causes of death were associated with excess risks, except that for external causes, whose SMR was similar to that of the general population (SMR = 0.94; 95% CI 0.70–1.3). When we looked at causes of death in accordance with the first malignant neoplasm, recurrence was the most frequent cause of death for all tumour types, except for HL and NHL among whom the most frequent cause was an SMN (Supplementary Figure 1).

Panel A in Fig. 4 shows the cumulative cause specific mortality in our cohort. At 30 years since diagnosis, mortality due to the recurrence of the primary cancer was 5.6% (95% CI: 5.1–6.0), due to a SMN was 2.5% (95% CI: 2.1–2.9), due to diseases of the cardiovascular system was 0.77% (95% CI: 0.55–1.04), due to respiratory diseases was 0.41% (95% CI: 0.26–0.64), due to other causes was 0.58% (95% CI: 0.41–0.80) and due to external causes was 0.51% (95% CI: 0.36–0.71). The cumulative incidence of deaths because of recurrence continued to increase sharply in the first 15 years after diagnosis and become less frequent in the following years, whereas, in the first years, those due to SMN or other causes were less frequent but continued to increase over time. This observation is shown in Fig. 4 panel B in which the cumulative probability of death is reported considering only subjects that had survived at least 15 years since diagnosis.

In panel C of Fig. 4, the cumulative mortality among CCSs considering separately deaths due to recurrence and those due to all other causes is compared with the expected mortality in the Italian sex- and age-matched general population. At 40 years since diagnosis, the cumulative mortality among CCSs because of all causes except recurrence was 8.5%, whereas only 2.1% was expected based on rates from the general population.

Table 3 reports results of multivariable regression models to estimate the relative mortality rates because of recurrence and those because of all other causes. Female survivors had lower risk of death because of recurrence (RR-AER 0.77, 95% CI 0.64–0.91) but higher risk of death because of other causes. Using ALL survivors as the reference, those treated for ANLL, HL and NHL had a significantly lower mortality rate because of recurrence, whereas significant higher rates were observed among survivors of bone tumours and NB. Considering all other causes, a significant increased risk was observed for survivors of ANLL, HL, NHL, CNS tumours, STS and bone tumours. More recent treatment era was significantly associated with a significant reduction in deaths due to recurrence (Table 3 and Fig. 5 panel A). A trend for a similar effect was observed also when other causes of death were considered, although it was not significant when SMRs were calculated (Table 3), it was significant in the analysis of cumulative incidence of death (Fig. 5 panel B).

4. Discussion

This study is the first study from a Southern European country analysing long-term mortality in a large cohort of CCSs. Compared with the general Italian population, we showed that both male and female survivors die at higher rates than expected, but their late mortality reduced steadily over the decades between 1960 and 1999. Recurrences of the original cancer continued to be the main cause of mortality in the first 15 years from diagnosis but reduce steadily, whereas other causes of death, especially deaths from second malignancies,

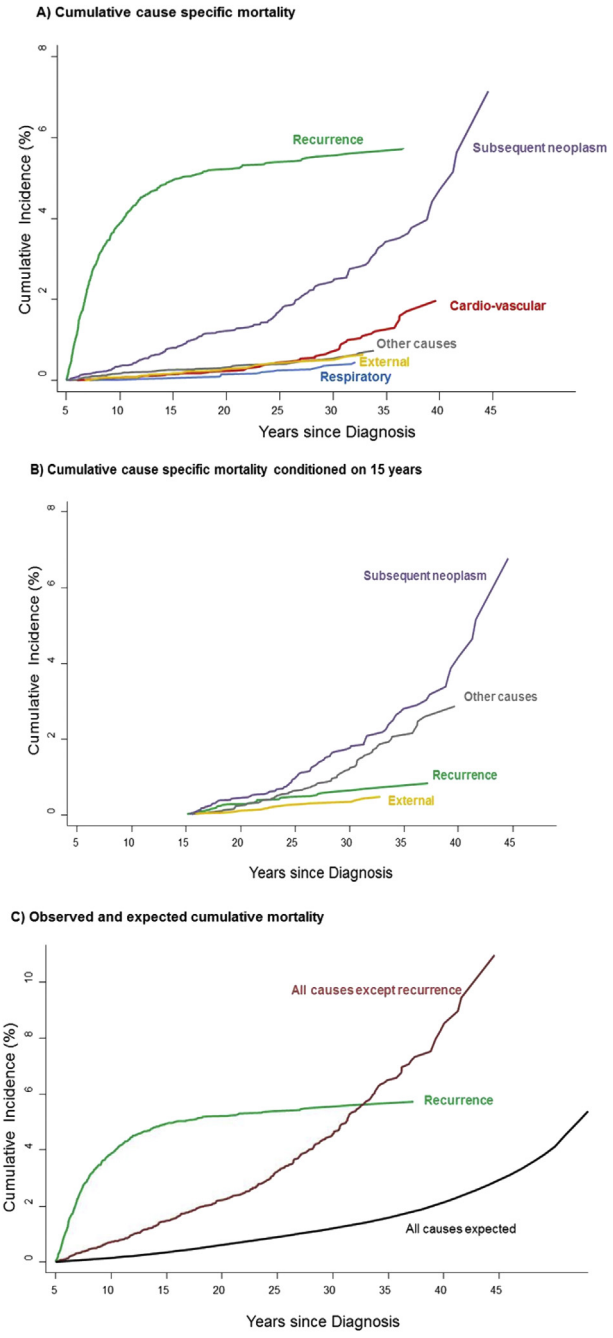

Fig. 4. Cumulative cause-specific mortality of 5-year survivors diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry. (A) Mortality due to recurrence of cancer, subsequent neoplasm, cardiovascular disease, respiratory causes, external causes and all other causes; (B) mortality due to recurrence of cancer, subsequent neoplasm, external causes and all other causes conditioned on survival at 15 years; (C) mortality due to recurrence of cancer and to all other causes and expected mortality based on rates from the general Italian population. AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry.

increase as time elapses since diagnosis. Our findings are broadly similar to those reported from other European and North American countries that described an excess risk of deaths among CCSs as compared with their peers in the general population [10,12,13,15]. Our SMR estimate of 11.3 is slightly higher than that reported in other large cohorts (>10.000) of survivors (Supplementary Table 5); however, cohorts are not fully comparable because of differing time periods of diagnosis and duration of the follow-up.

In Italy, as in other countries, long-term survival improved significantly in children treated more recently [8,13–15] mainly because of the reduction in deaths both from the original cancer and from other causes [11]. These improved results are likely to be related to changes in treatment [30,31]. In fact, in the early periods considered in our study, childhood cancer diagnosis had quite often an unfavourable prognosis and multimodal therapy was available only in few centres. At that time, the main objective was to obtain 'cure at any cost', thus often accepting the risk of possible early or late complications. With the improvement of survival rates together with the identification of new genetic, molecular and or clinical risk factors, it became possible to move to the 'cure at the least cost possible' paradigm. For instance, the trend for several recent therapeutic protocols has been towards reducing treatment exposures while maintaining cure level in selected patients (e.g. cranial RT given only to selected leukaemic patients and at reduced dose; reduction of RT volume and dose in HL patients without requiring a significant escalation in cytotoxic CT), or better results with more aggressive treatments in children for whom, in previous years, the outcome was quite poor (e.g. stem cell transplantation in leukaemic as well in high-risk neuroblastoma patients) [30,31]. As of today, patients are treated with modern therapeutic strategies, including personalised medicine, we can expect further mortality reductions immediately after treatment; however, long-term follow-up studies are needed to monitor their potential late effects.

We also confirm other reports [10,11,15,16] that the excess of deaths is mainly attributable to recurrence of the original cancer. In fact, although deaths due to recurrence steadily increase during the first 10–15 years since diagnosis, they subsequently became quite rare. In our study, the rate of the recurrence-specific mortality in people who survived at least 15 years from diagnosis (Fig. 4B) was based on only 19 deaths among 6719 subjects still at risk at that time (0.28%). Those very late events occurred mostly among survivors from leukaemia or lymphoma (13 cases) and in few cases of WT, NB and CNS tumours. In exceptional cases, late relapses of childhood cancers may occur [32]; however, we share the concern documented by Möller *et al.* [14] that the original cancer can be erroneously coded as the cause of death and thus may inflate reporting of recurrence on the death certificate. This source of error will be carried over into epidemiologic studies, unless reviews of death certificates are carried out, as was partially performed in this study.

Table 3
Multivariable Poisson regression model to estimate the relative mortality rates among 5-year survivors diagnosed in the period 1960–1999 and included in the Italian AIEOP-OTR registry, considering separately deaths due to recurrence and those due to all other causes except recurrence.

Characteristics	Recurrence[a]	All causes except recurrence[a]	
	A) RR-AER[b] (95% CI)	B) RR-SMR (95% CI)	C) RR-AER (95% CI)
Sex			
Male	reference	reference	Reference
Female	0.77 (0.64–0.91)	2.3 (1.9–2.8)	1.1 (0.87–1.5)
First primary neoplasm			
ALL	reference	reference	Reference
ANLL	0.30 (0.21–0.44)	2.2 (1.3–3.8)	2.7 (1.3–5.3)
HL	0.13 (0.06–0.27)	2.5 (1.8–3.3)	3.4 (2.3–5.1)
NHL	0.35 (0.21–0.58)	1.6 (1.1–2.4)	1.8 (1.1–3.1)
WT	1.4 (1.01–2.1)	1.00 (0.63–1.6)	0.94 (0.50–1.8)
NB	2.1 (1.5–2.8)	0.75 (0.41–1.4)	0.53 (0.19–1.5)
CNS	0.82 (0.54–1.2)	2.6 (1.7–4.1)	3.4 (2.1–5.9)
Soft tissue sarcoma	1.2 (0.78–1.8)	2.1 (1.3–3.2)	2.5 (1.4–4.3)
Bone tumour	2.1 (1.3–3.3)	3.9 (2.1–7.8)	5.6 (2.5–12.4)
Other	0.42 (0.17–1.04)	0.91 (0.36–2.3)	0.58 (0.09–3.9)
Age at diagnosis, y	1.4 (1.2–1.5)[c]	0.83 (0.72–0.94)[c]	1.01 (0.86–1.2)[c]
0-4	reference	reference	reference
5-9	1.8 (1.5–2.3)	0.81 (0.62–1.1)	0.91 (0.64–1.3)
10-14	2.1 (1.6–2.7)	0.65 (0.49–0.90)	0.99 (0.67–1.5)
15-21	2.6 (1.8–3.8)	0.59 (0.37–0.92)	1.1 (0.60–1.9)
Year of diagnosis			
1960–1979	reference	reference	reference
1980–1989	0.64 (0.52–0.79)	1.04 (0.81–1.3)	0.82 (0.61–1.1)
1990–1999	0.41 (0.31–0.53)	0.91 (0.64–1.3)	0.51 (0.32–0.81)
Years since diagnosis	0.34 (0.30–0.38)[c]	0.98 (0.91–1.05)[c]	1.15 (1.05–1.3)[c]
Treatment			
No RT, no CT	reference	reference	reference
CT only	3.6 (1.6–7.8)	0.93 (0.46–1.5)	0.95 (0.33–2.7)
RT only	4.3 (1.7–11)	1.4 (0.61–3.1)	1.5 (0.47–4.6)
RT and CT	7.3 (3.4–16)	1.6 (0.78–3.1)	1.8 (0.64–4.9)

Numbers were reported with two decimals for numbers< 1.05; one decimal for numbers up till 10.5 and no decimals above 10.5.
ALL = acute lymphoblastic leukaemia; HL= Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; WT= Wilms' tumour; NB = neuroblastoma; CNS = central nervous system; AnLL = acute non-lymphoblastic leukaemia; RT = radiotherapy; CT=chemotherapy; AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry; SMR = standardised mortality ratio; AER = absolute excess risk; CI = confidence interval; RR = relative risk.
[a] Subjects with not available treatment and/or unknown cause of death were excluded from analysis.
[b] Ratio of the crude mortality rate may be interpreted as an RR-AER.
[c] Considered as a continuous variable.

Subsequent neoplasms were the second most frequent cause of death in the Italian cohort, (SMR of 12 and AER of 9.4) and in other similar studies [10–15] (Table 2). Deaths due to SMNs have a low cumulative incidence initially that continuously increases until at about35 years since diagnosis when mortality exceeds that due to the original cancer (Fig. 4A) [8,10,13,14,16]. It is recognised that a large proportion of these events is due either to RT and/or CT treatment, but underlying genetic predisposition has also been associated [33]. When we looked at second malignancies by type of the first malignancy (Supplementary Figure 1), survivors whose primary cancer was HL or NHL were most likely to die from second malignancies. The explanation may be high doses of RT for HL, but it is unclear for NHL. This observation will be explored in more detail in another publication.

Overall, we showed a significant reduction in non-relapse–related mortality from 2.3% to 1.0% (Fig. 5B) over the eras covered by our study. Because deaths due to SMN are the largest fraction, it is likely that these deaths, as well, decreased over this time period. This has been shown in other studies and can be attributed to better and more targeted use of therapeutic strategies [11,13,14].

Cardiovascular disease is the third leading cause of death, preceded only by primary and secondary cancer [11] (Table 2), and the highest proportion with cardiac deaths was in survivors of ANLL, HL, NHL and WT, consistent with other reports [8,13]. The use of potentially cardiotoxic risk factors, such as anthracycline drugs and RT, is still widespread because of their pivotal role in several treatment protocols; new treatment strategies should further develop alternative treatments with less toxicity. Deaths from respiratory causes occurred with an SMR of 13 based on 26 cases, somewhat more than the SMR reported by Fidler *et al.* [34].

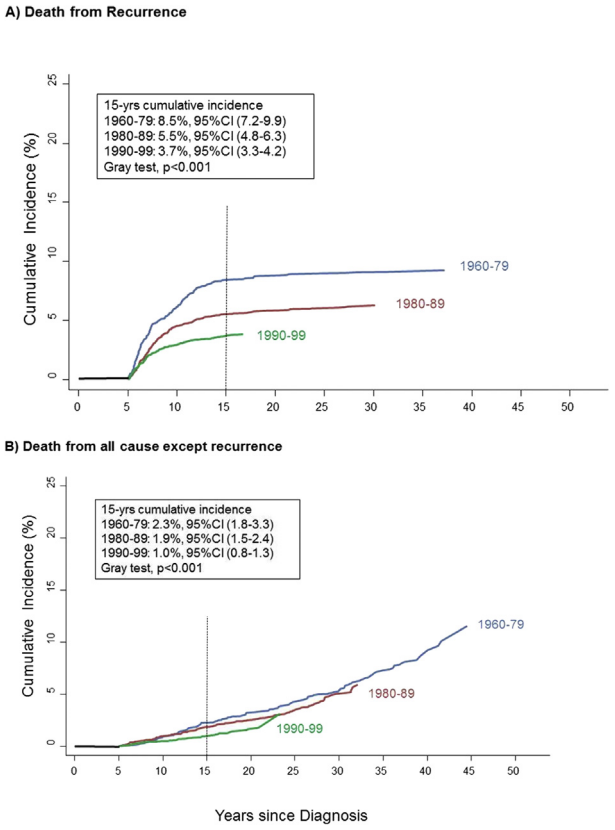

Fig. 5. Cause-specific cumulative mortality according to era of diagnosis of 5-year survivors registered in the Italian AIEOP-OTR registry. AIEOP = Associazione Italiana di Ematologia ed Oncologia Pediatrica; OTR = off-therapy registry; CI = confidence interval.

The number of excess deaths from all causes declined among subjects treated more recently (1990–99), with a reduction of 60% of excess risk compared with the risk in patients treated in 1960–1979 (Table 1). This trend was also observed when deaths from recurrences and deaths from all other causes were considered separately (Table 3; Fig. 5). These results confirm the findings in the North American chilhood cancer survivors study (CCSS) cohort [11] and may be attributable to newer therapies, such as bone marrow transplantation.

As a final general comment, we would like to underline that the results of the study are mainly reported in terms of SMR, the measure most commonly used; however, SMRs can be misleading. For instance, SMR and AER go in different directions for gender and age at diagnosis in Table 1. In particular, the SMR was higher for female survivors because male survivors had a higher expected mortality in the general population. Thus, the relative SMR for female survivors compared with male survivors is 2.0, whereas the relative AER is 0.83 (Table 1). This is because of the different background mortality in the respective strata of each factor.

One of the main strengths of this study is its large size, implying stable estimates for Italian data. In addition, because only 1.6% of subjects were not traced, we avoided potential response bias. One potential limitation of the study is that our cohort is derived from multi-institutional registries and may not include all cancers. However, in Italy, only about 42% of the population is resident in areas monitored by population-based registries, whereas the OTR prospectively identifies 92% of childhood cancers cases expected each year [22]. In common with most other studies, we do not have detailed treatment information, which precluded analyses for the effect of dose–response patterns on risk of death.

These data can be used to persuade policy-makers that CCSs represent a population at risk that needs special care. The risk of premature death does not end at five years after diagnosis but persists into the oldest ages for which we have data when deaths not due to the original cancer continue to increase. This excess mortality can be considered a surrogate marker also for other underlying serious health conditions that can lead to death or severely impact quality of life but that may be preventable. We still need to further continue the longer follow-up and to establish new cohorts of survivors because we have little information on the effects of new agents and on risks occurring on survivors of other diseases characteristic of older ages, such as degenerative conditions [35]. These results will also be used to drive the development of new guidelines to assist survivors and their caregivers in achieving the best quality of life. Current global guidelines are being published, and many more are planned [36–39]. They are an essential part of the Survivorship Passport, an electronic treatment summary that collects detailed demographic and clinical data that, incorporating the guidelines, can lead to an individualised care plan [40]. Screening and surveillance may help in early diagnosis of several chronic conditions and of second malignancies, that if timely treated may further reduce the burden of late mortality in CCSs.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.021.

Appendix B

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