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Adolescent and Young Adult Cancer Survivors: Design and Characteristics of the First Nationwide Population-Based Cohort in Italy

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Purpose: Adolescent and young adult (AYA, 15–39 years) cancer survivors (alive at least 5 years after cancer diagnosis) are less studied than younger and older cancer survivors and research on their late effects is limited. To facilitate research on long-term outcomes of AYA cancer survivors, we established, in Italy, a population-based AYA cancer survivors' cohort. This article describes the study design and main characteristics of this cohort.

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Methods: The cohort derives from population-based cancer registries (CRs). Each CR identified AYA cancer patients retrospectively. Treatment for first primary cancer and all health events from diagnosis to death can be traced through linkage with available health databases, such as hospital discharge records (HDRs), mortality files, and outpatient and pharmaceutical databases.
Results: Thirty-four CRs participated to the cohort which overall includes 93,291 AYAs with cancer and 67,692 cancer survivors. First primary cancer distribution in AYA cancer survivors differs by sex and age groups because of the different cancer types diagnosed in AYAs. Almost 78% of AYA cancer survivors have HDRs and 14.8% also pharmaceutical and outpatient databases.
Conclusion: This cohort will be used to study, for the first time in Italy, the pattern and excess risk of late effects in AYA cancer survivors. HDRs, outpatient and pharmaceutical databases will be used to define primary treatment to assess its impact on AYA cancer survivors' late effects. This cohort exploiting data sources already available at CRs, minimize the data collection effort and it will contribute to assess the feasibility of using administrative database to study cancer survivors' late effects.

Keywords: survivors, late outcomes, population-based data, cohort

Introduction

Survival of adolescent and young adult (AYA) (15–39 years at cancer diagnosis) cancer patients is good[1,2] and it has improved since the last century.[3,4] However, even if these patients survive and are cured from their first cancer, they are still at risk of developing clinical (e.g., second malignant neoplasms and/or other diseases leading to hospitalizations) and socioeconomic (e.g., unemployment, lower attained education, etc.) long-term effects.[5,6]

Research on cancer survivors focused mainly on survivors of childhood cancers[7] and, more recently, also on survivors of adult cancers.[8] However, tumor impact on AYA cancer survivors may differ from other age classes because of several aspects:

1. The spectrum of cancer diagnoses occurring at AYA ages differs from that affecting older and younger people.[9]
2. The biology of AYA cancers is different compared with those affecting children and adults, including biology of similar histological diagnosis.[10]
3. AYA physiology (hormonal), pharmacology (drug clearance), polymorphisms, or genomic properties differ from younger and older persons with respect to cancer susceptibility and treatment.[9]

Furthermore, adolescence and young adulthood are challenging phases for the human growth: they are characterized by physical, emotional, cognitive, and social transitions, such as, for example, the achievement of financial independence. For AYA, cancer diagnosis and treatment may influence negatively these phases[11] and lead to physical, psychological, and social late effects.[12,13]

Considering all these aspects, results coming up from studies on survivors of childhood or adult cancer cannot be directly translated to AYA cancer survivors. Thus, clinical and epidemiological research on late effects deriving from first cancer on the increasing and heterogeneous population of AYA cancer survivors is needed to plan *ad hoc* strategies for long-term management of these patients.[14]

Data on long-term impact of cancer on AYAs are already available from different studies done in United States,[15] Canada,[16] in Europe, Norway,[17] Denmark,[18,19] Netherlands,[20] Scotland,[21] and Switzerland.[22] All these studies however, focused on only one or few outcomes and the information on causes of late effects are limited. Long-term effects may be due to several risk factors interacting together: socioeconomic status, life style, genetic susceptibility, and environmental and occupational exposition.[23] Some of these factors are country specific and so are their impact on cancer survivors. Thus, although cancers in AYA are rare, country-specific research is also needed.

Against this background, in the context of the project ''Adolescent and young adult in Italy'' (Ada), an AYA cancer survivor's cohort was established in Italy to study the pattern of clinical late effects, estimate their excess risk, and create an infrastructure to analyze the causes of late effects. In this article, we describe the study design and the characteristics of this cohort.

Methods

The AYA cancer survivor cohort derives from population-based cancer registries (CRs). In Italy, the first CR was established in 1976 and, as of 2020, 57 population-based CRs are active. Altogether, they cover 70% of the Italian population with an upward trend.[24]

The AYA cohort has a retrospective incident-based design. All Italian CRs were invited to participate. Each CR identified patients with first cancer diagnosis between 15 and 39 years of age in the entire incidence period covered by the CR and linked to these cancer patients all their subsequent tumors and all heath database available at the CR office. The coordinator of the project, the National Cancer Institute of Milan (Istituto Nazionale dei Tumori [INT]), identified centrally the cancer survivors as those alive at least 5 years after the first cancer diagnosis.

Primary tumors were defined using the International Classification of Childhood Cancer, Third Edition (ICCC-3)[25] groups collected into an AYA-specific tumor list adapted from Trama et al.[1] (Supplementary Table S1). International standard checks[26] were used to centrally assess the quality of the data received from each CR contributing to the project. With regard to the other databases, namely, hospital discharge records (HDRs), outpatient and pharmaceutical databases, duplicate records, and records not linked to our

cohort, were removed. For all databases, the completeness and internal consistency of the dates (e.g., date of birth, date of diagnosis; date of first surgery, date of start of chemotherapy, etc.) were checked, as well as the completeness of the main variables: diagnostic and/or treatment code in the HDR and outpatient database; drug AIC in the pharmaceutical database, and cause of death in the mortality registries. For the mortality databases, CRs data were compared with the mortality tables published online by the National Institute of Statistics (Istituto Nazionale di Statistica [ISTAT]).

According to the Italian Association of Cancer Registries (AIRTUM) rules, CRs register and include in the incidence[27]:

- Invasive malignant neoplasms of all sites (with the option not to include basal and squamous cell carcinomas).
- Tumors of uncertain behavior and *in situ* of bladder.
- Tumors benign and of uncertain behavior of central nervous system (CNS), where required by specific protocols of research.[28]

Accordingly, all primary malignant cancers and tumors of uncertain behavior and *in situ* of bladder were included in the cohort, except basal and squamous cell carcinomas because CR data on these cancers are generally incomplete. Tumors benign and of uncertain behavior of CNS were also excluded because only a minority of CRs registered not malignant CNS tumors.

Databases linked to AYA with cancer cohort

Mortality registries. The ISTAT published a mortality table with all deaths occurred on resident population in Italian regions, provinces, municipalities every year. Mortality tables contain information on age at death, place, date, and cause of death, coded through the International Classification of Diseases (ICD) ninth or tenth version.[29,30] Mortality tables by municipality are available since 1992.

Alongside the ISTAT mortality, regional data banks and mortality registers have been created, managed by local health units and regions. It is compulsory for each local health unit to establish and update a registry for each municipality included in its territory containing the list of deceased during

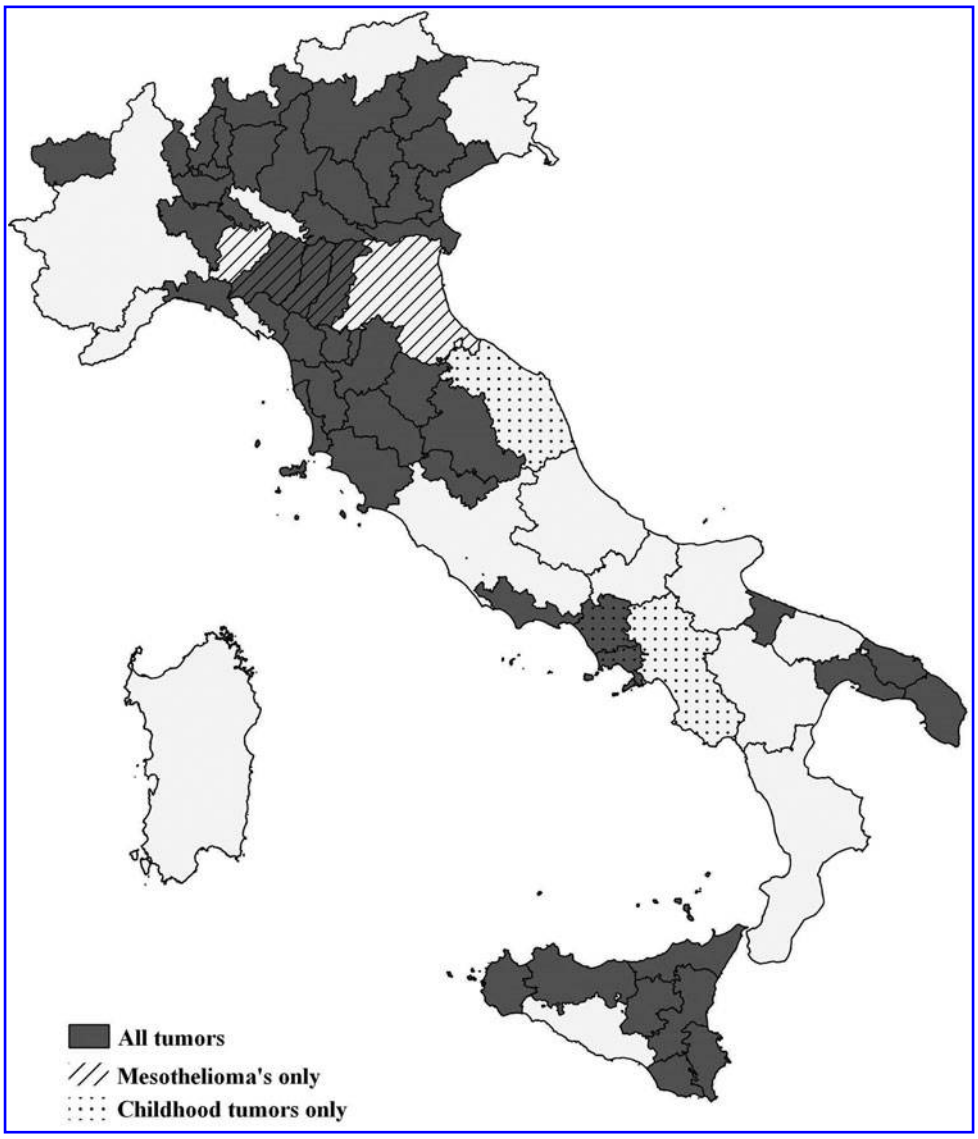

FIG. 1. Geographical coverage of the AYA cancer survivors' cohort. AYA, adolescent and young adult.

Table 1. Number (*N*) and Percentage (%) of Adolescent and Young Adult Cancer Survivors by First Primary Tumors and Sex

	All survivors		*Females*		*Males*	
Primary tumors	N	%	N	%	N	%
Breast tumors	11,328	16.7	11,291	27.7	37	0.1
Thyroid and other endocrine gland tumors	10,922	16.1	8433	20.7	2489	9.2
Lymphomas	10,003	14.8	4714	11.6	5289	19.6
Malignant melanomas	7748	11.4	4754	11.7	2994	11.1
Germ cell tumors	6617	9.8	333	0.8	6284	23.3
Female genital tract tumors	3699	5.5	3699	9.1	—	—
Urinary tract tumors	3298	4.9	1045	2.6	2253	8.3
Leukemias	3126	4.6	1391	3.4	1735	6.4
Digestive organs tumors	2892	4.3	1442	3.5	1450	5.4
Soft tissue sarcomas	2559	3.8	1303	3.2	1256	4.7
CNS tumors	1670	2.5	758	1.9	912	3.4
Head and neck tumors	1350	2.0	550	1.4	800	3.0
Malignant bone tumors	614	0.9	257	0.6	357	1.3
Lung and trachea tumors	480	0.7	238	0.6	242	0.9
Male genital tract tumors	415	0.6	—	—	415	1.5
Other tumors	971	1.4	492	1.2	479	1.8
All first primary tumors	67,692		40,700		26,992	

CNS, central nervous system.

the year and the relative cause of death. The regional registries are available and currently used by CRs and for this cohort.

Hospital discharge records. CRs receive from the regional information system all hospitalizations (occurred inside or outside the area they cover) for all residents in the area covered by the CR. Since 2002, for all hospitals in Italy, it is compulsory to collect data on hospitalizations through the same HDRs, including information on: date of admission and discharge, up to six diagnosis and six procedures (including treatment, i.e., type of surgery, chemotherapy, and radiotherapy) received by the patient during the hospital stay, coded through the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).[30] To this cohort, CRs contributed providing HDRs for cancer patients only.

Outpatient database. Outpatients receive medical treatment without being admitted to a hospital. They are not hospitalized for 24 hours or more but visit hospital, clinic, or associated facility for diagnosis or treatment. Outpatient database contains all outpatient admissions with information on date and the health services (including the type of treatment, e.g., chemotherapy and radiotherapy) received together

Table 2. Number (*N*) and Percentage (%) of Adolescent and Young Adult Cancer Survivors by First Primary Tumors, Age Class at Diagnosis and Sex

	15–19 Years				*20–29 Years*				*30–39 Years*			
	Females		*Males*		*Females*		*Males*		*Females*		*Males*	
Primary tumors	N	%	N	%	N	%	N	%	N	%	N	%
Lymphomas	704	36.0	741	35.0	1724	18.9	1851	22.4	2286	7.7	2697	16.2
Thyroid and other endocrine gland tumors	414	21.2	145	6.8	2466	27.1	723	8.8	5553	18.7	1621	9.7
Germ cell tumors	76	3.9	349	16.5	139	1.5	2679	32.5	118	0.4	3256	19.6
Leukemias	155	7.9	242	11.4	422	4.6	442	5.4	814	2.7	1051	6.3
Malignant melanomas	155	7.9	93	4.4	1426	15.7	731	8.9	3173	10.7	2170	13.0
Breast tumors	4	0.2	0	0.0	792	8.7	6	0.1	10,495	35.4	31	0.2
Female genital tract tumors	43	2.2	—	—	553	6.1	—	—	3103	10.5	—	—
Urinary tract tumors	53	2.7	70	3.3	233	2.6	391	4.7	759	2.6	1792	10.8
Digestive organ tumors	32	1.6	22	1.0	250	2.7	189	2.3	1160	3.9	1239	7.5
Soft tissue sarcomas	100	5.1	124	5.9	402	4.4	321	3.9	801	2.7	811	4.9
CNS tumors	99	5.1	103	4.9	268	2.9	319	3.9	391	1.3	490	2.9
Head and neck tumors	42	2.1	50	2.4	141	1.5	149	1.8	367	1.2	601	3.6
Malignant bone tumors	55	2.8	127	6.0	99	1.1	118	1.4	103	0.3	112	0.7
Lung and trachea tumors	10	0.5	14	0.7	57	0.6	54	0.7	171	0.6	174	1.0
Male genital tract tumors	—	—	16	0.8	—	—	154	1.9	—	—	245	1.5
Other tumors	15	0.8	22	1.0	130	1.4	118	1.4	347	1.2	339	2.0
All first primary tumors	1957		2118		9102		8245		29,641		16,629	

CNS, central nervous system.

with personal data, such as gender, date of birth, and residence. This database is available in Italy from 1996.[31]

Pharmaceutical database. It contains data on innovative expensive drugs; drugs included in the postmarketing surveillance program of the Italian Drug Agency (Agenzia Italiana del Farmaco [AIFA]) and drugs reimbursed by the National Health System. The ''F File'' traces expensive and under postmarketing surveillance drugs across two main suppliers: the hospitals and the local health unit premises. Thus, these drugs can be administered within the hospitals (i.e., to hospitalized patients as well as to outpatients); supplied by the hospital to the patients, at the time of discharge, for their first course of treatment at home; supplied by the local health unit premise to the patients to complete the treatment at home. The other drugs reimbursed by the National Health System are supplied by the community pharmacies and are registered in the community pharmacies' database. For each drug prescription, these databases include information on the drug marketing authorization (Autorizzazione Immissione in Commercio [AIC]) and the quantity prescribed. Our cohort has both databases, that is, ''F File'' and community pharmacies. Pharmaceutical database was established in Italy in 1993.[32]

Thus, the cohort includes all primary and subsequent cancers arising in AYA cancer survivors together with additional database, including information about diagnostic procedures, treatment (type of surgery, excisional biopsy, radiotherapy, chemotherapy) and long-term impact in terms of hospitalizations (to be used as a proxy for a specific disease, e.g., cardiovascular diseases) and mortality.

Comparison population

To estimate the excess risk of AYA cancer survivors, each CR provided also:

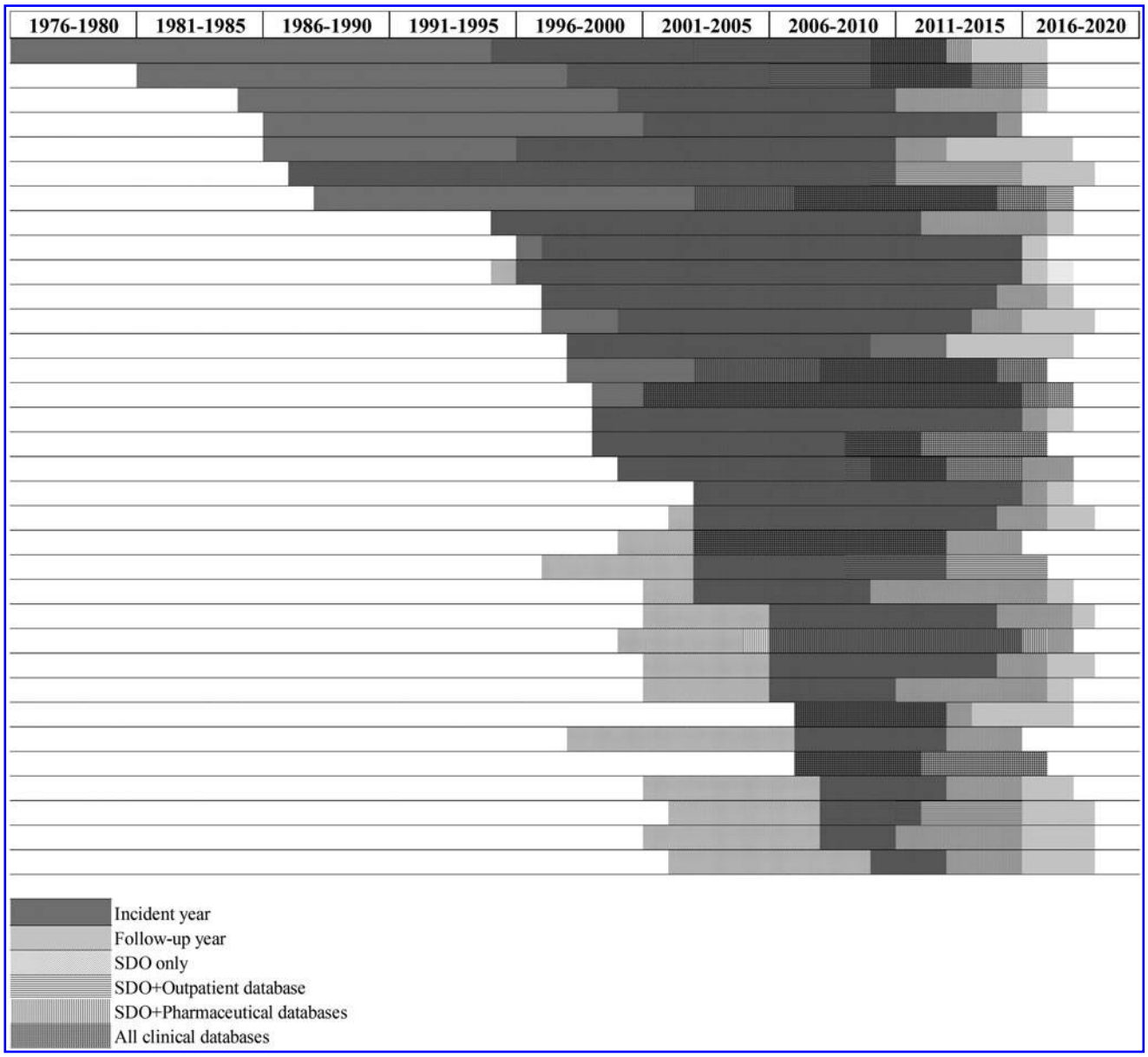

FIG. 2. Incidence, follow-up and database availability in time by CR (lines). CR, cancer registry.

Table 3. Number of Adolescent and Young Adult Cancer Survivors Linked to Hospital Discharge Records, Outpatient and Pharmaceutical Database Starting from Incidence Date

	HDR	*HDR and outpatient databases*	*HDR and pharmaceutical databases*	*HDR and outpatient and pharmaceutical databases*
No. of survivors	52,738	14,226	11,568	10,078
First year of incidence	1987	2000	1999	2000
Last year of incidence	2013	2012	2012	2012
Median time of observation	10 Years	8 Years	8 Years	8 Years
Maximum time of observation	29 Years	16 Years	16 Years	16 Years

HDR, hospital discharge record.

- The complete cancer incidence (in aggregated or individual format) of patients older than 15 years of age for the entire population covered, with details on: age at incidence date, incidence year, sex, tumor topography, and morphology according to ICD-O3 classification.
- The entire mortality tables provided by the regional mortality registries, for all deaths occurred in the area covered by the CR, information on: age at death, place, date, and cause of death, coded according to the ICD ninth or tenth version.

In addition, thanks to a formal agreement with the Italian Ministry of Health, the coordinator received the HDRs for the entire Italian population 15–55 years of age at hospital discharge date, in the period 2002–2016. HDRs of the same patient are linked through a unique anonymous identifier to track all his/her hospitalizations from diagnosis onward.

Results

AYA cancer survivors cohort

As of 2019, 34 out of the 57 Italian population-based CRs agreed to participate to the cohort. Geographical coverage of the survivors' cohort is shown in Figure 1. Gray areas are areas covered by CRs that collect all cancers in the entire population, dotted and slashed areas are areas covered by specialized CRs that collect only certain type of tumors (e.g., mesotheliomas) or tumors of a specific age class (e.g., childhood tumors, patients 0–19 years of age at cancer diagnosis). Altogether, these 34 CRs cover a population of around 26 million people (43% of the Italian population).

We received data on 109,021 patients with first primary tumor incident at 15–39 years of age, between 1976 and 2015. Of these, 15,730 were not included because of tumor exclusion criteria. Thus, we included in the cohort 93,291 AYAs with cancer of which, 67,692 were AYA cancer survivors (around 72.5% of the total incident cohort).

AYA survivors accrued 809,555 person-years of follow-up, with a median time of 12 years (range, 5–40 years) from the first cancer diagnosis. AYA cancer survivors' median age at last follow-up date is 44 years, ranging from 20 to 80 years.

Distribution of AYA cancer survivors by first primary tumor is reported in Table 1. Most common first primary tumors in cancer survivors were breast and thyroid tumors (11,328 and 10,922 cases, respectively), lymphomas (10,003 cases), and melanomas (7748 cases). However, the first primary cancer distribution differs by sex, with breast tumor being the most common in females and germ cell tumors in males.

AYA cancer survivors stratified by first primary tumor, age class, and sex are summarized in Table 2. The most common primary cancers of adolescent (15–19 years at first cancer diagnosis) cancer survivors were lymphomas for both sexes (36.0% in females ad 35.0% in males), followed by thyroid tumors in females (21.2%), and germ cell tumors in males (16.5%).

The most common first primary tumors in survivors of a cancer diagnosed at 20–29 years were thyroid tumors (27.1%) followed by lymphomas (18.9%) and malignant melanomas (15.7%) in females, and germ cell tumors (32.5%) and lymphomas in males (22.4%). The most common first primary tumors in survivors of a cancer diagnosed at 30–39 years were breast (35.4%), thyroid (18.7%), melanomas (10.7%), and female genital tract tumors (10.5%) in females and germ cell tumors (19.6%), lymphomas (16.2%), and melanomas (13.0%) in males.

Data sources within the AYA cancer survivors' cohort

All 34 CRs linked the HDRs, 13 CRs linked also the outpatient database, and 11 CRs linked, in addition to the HDRs, both outpatient and pharmaceutical database. HDRs become available to the majority of CRs in 2002, however, some CRs accessed the HDRs before 2002 and 4 CRs started to collect them only between 2004 and 2009. Outpatient and pharmaceutical databases were established in Italy in the middle '90s, however, CRs started to access to these database in different years from 2001 to 2010 (Fig. 2).

Almost 78% of the AYA cancer survivors (52,738 patients) have HDRs starting from the year of diagnosis with a median follow-up of 10 years (with some patients followed up to 29 years) (Table 3). Fifteen percent of AYA survivors have also the outpatient and pharmaceutical database (10,078 patients) starting from the time of diagnosis with a median follow-up of 8 years, and maximum time of follow-up 16 years (Table 3).

Conclusions

This is the first Italian nation-wide cohort of AYA cancer survivors established exploiting population-based CRs data. As of 2019, evidence on outcomes of AYA cancer survivors in Italy were available only through clinical data.[33,34] Several large cohorts have been established within Europe to study late effects in childhood cancer survivors, including the Nordic Adult Life after Childhood Cancer in Scandinavia study, the British Childhood Cancer Survivor Study, the Dutch Childhood Oncology Group LATER study, and the Swiss Childhood Cancer Survivor Study. These cohorts, similar to the Italian AYA cancer survivors' cohort presented in this article, take advantage of large population-based CRs[35] and through large-scale record linkage techniques,

with health data base, death registries, and hospital registries, provide accurate follow-up information on childhood cancer survivors. Other cohorts, for example, the Childhood Cancer Survivors' Study[36] and the St Jude Lifetime Cohort Study[37] relayed upon self-reported outcomes or built clinically assessed cohort of childhood cancer survivors.

We decided to establish the AYA cancer survivors' cohort taking advantage of the Italian population-based CRs because, with the oldest registries going back to the 1970s, they provide unique opportunities to study lifetime risks. Furthermore, study subjects are identified from CRs, which ensure the inclusion of all AYA cancer incident cases (in the area covered by the CR) and an almost complete follow-up making data less susceptible to lost to follow-up. Furthermore, as information on disease outcomes is obtained from health-related database (DB) (mainly hospital-based DB) and not from self-reports, data will not be influenced by recall bias. Anyway, a drawback of this approach is the paucity of information on diseases not requiring hospitalizations.

This cohort is the result of a collaborative effort of 34 CRs active in different areas of north, center, and south of Italy. It includes a consistent number of AYA cancer survivors with an interesting follow-up time (on average 12 years) and both these elements will be essential to study late effects, as it has been done in similar cohorts.[19–20,22]

Non melanoma skin cancers and benign and *in situ* tumors of CNS were excluded because CRs data on these cancers are generally incomplete unless an *ad hoc* research protocol requires them.[27]

Cancer incidence[4] and survival[1] of AYA cancer patients contribute to explain the distribution of first primary cancers in this cohort. The first primary cancer distribution in our AYA (15–39 years) survivors' cohort is mainly affected by the high proportion of older patients (46,270 patients, 68.3% of the entire cancer survivors' cohort, were diagnosed at 30–39 years of age) and by tumors with high 5-year survival. The latter were breast, cervix uteri[38] and thyroid in females[39]; testicular germ cell tumors[40] in males; and melanomas and lymphomas in both sexes.[1]

The availability within this AYA cancer survivors' cohort of different data sources is an opportunity to study many different clinical long-term effects: second malignant neoplasms, diseases leading to hospitalizations, and mortality. Furthermore, the availability of HDRs for the majority (77.8%) of AYA cancer survivors and of all three health-related DB (HDR, outpatients DB, and pharmaceutical DB) for 14.8% of them will be helpful to define, for at least a part of the cohort, primary treatment, and to assess its role in the long-term effects.

Despite all the strengths previously listed, some limits should also be considered. First, the coding of the outpatient databases differ across CRs because they follow region-specific requirements which differ across Italian regions. Thus, additional work on codes identification and comparison should be done to make homogenous analyses. Second, HDRs are meant for cost reimbursement and this could lead to possible misclassification of the diagnosis and treatment reported. Furthermore, HDRs are available for inpatient admissions only and therefore the full treatment course can be defined only for those AYA survivors with all health-related DB (HDR, outpatient DB, and pharmaceutical DB) available.

Against this background, this cohort will be instrumental to assess the feasibility of using administrative database to study cancer survivors' late effects. In this regard, our checks showed a completeness of the main variables higher than 95% in all the health-related DB considered; a high consistency of number of AYA cancer cases linked to the health DB by year and registry, and a perfect match between CR data with the mortality tables published online by the ISTAT.

Exploiting already available data sources, it will be possible, with a limited effort, to have a critical mass of data to study late effects occurring in survivors of rare cancers such as those affecting AYAs. To this extent, collaborative projects are ongoing. In the context of the Innovative Partnership for Action Against Cancer (iPAAC),[41] we are establishing additional AYA cancer survival cohorts in Spain, Portugal, and Norway since CRs have a long period of follow-up (until 20 years). This will allow to increase the number of cases and their follow-up for current analyses and to assess the feasibility of using health care databases in countries different from Italy.

In the future, to complete the cohort, it will be essential to link it to census data and information on attained education and employment level.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1

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