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Original research

Comparative analysis of 5-year relative survival in adolescents and young adults with cancer relative to both children and adults in Europe (EUROCARE-6): Results from a population-based study

Annalisa Trama [a,*], Silvia Rossi [b], Damien Bennet [c], Charles Stiller [d], Keiu Paapsi [e], Xavier Troussard [f], Fabiola Giudici [g], Henrike E. Karim-Kos [h,i], Francesco Cerza [b], Jan Trallero [j], Rosalia Ragusa [k], Marcel Blum [l], Alexandra Mayer-da-Silva [m], Frederik Peters [n], Fabio Didonè [a,1], Laura Botta [a,1], the EUROCARE-6 Working Group [2]

[a] *Evaluative Epidemiology Unit, Fondazione IRCSS Istituto Nazionale dei Tumori, Milan, Italy*
[b] *Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy*
[c] *Northern Ireland Cancer Registry (NICR), Queens University Belfast, Centre for Public Health, Mulhouse Building, Belfast, Northern Ireland, UK*
[d] *National Disease Registration Service, NHS England, 7–8 Wellington Place, Leeds, UK*
[e] *National Institute for Health Development, Hiiu 42, Tallinn 11619, Estonia*
[f] *Hématologie et Registre Régional des Hémopathies Malignes de Basse Normandie, CHU Caen Normandie, avenue Côte de Nacre, Caen 14000, France*
[g] *Cancer Epidemiology Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy*
[h] *Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands*
[i] *Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands*
[j] *Epidemiology Unit and Girona Cancer Registry, Catalan Institute of Oncology, Directorate Plan of Oncology, Girona Biomedical Research Institute Dr. Josep Trueta (IDIBGI-CERCA), 17004 Girona, Spain; Josep Carreras Leukaemia Research Institute, c/ del sol 15, 17004 Girona, Spain.*
[k] *Catania-Messina-Enna CR, Azienda Ospedaliero Universitaria Policlinico, Catania, Italy*
[l] *Cancer Registry East Switzerland, Flurhofstr, St. Gallen 7 9000, Switzerland*
[m] *Southern Portugal Cancer Registry, Portuguese Oncology Institute of Lisbon Francisco Gentil, Lisbon, Portugal*
[n] *Hamburg Cancer Registry, Germany*

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ABSTRACT

Introduction: In Europe, cancer survival rates are high and improving for children (0–14 years) and AYAs (15–39 years). However, AYAs often have worse outcomes than children but better than adults. Using EUROCARE data, this study analyzes 5-year relative survival rates across age groups, highlighting age-specific differences and survival trends over time to address persistent disparities.

Methods: Data were collected from 95 European population-based cancer registries, covering 57 % of the European population. Analyses included malignant cancers diagnosed between 2006 and 2013. Five-year RS was estimated using the period approach for follow-up between 2010 and 2014. Comparisons between AYAs, children, and adults (40–69 years) were conducted using the Z test for absolute differences. Changes in survival trends over time were analyzed from 2004 to 2013 using the Average Annual Percentage Change (AAPC).

Results: AYAs had lower 5-year RS than children for hematologic cancers, particularly acute lymphoblastic leukemia (61 % vs. 90 %) and Ewing sarcoma (51 % vs. 69 %). Survival gaps were smaller for central nervous system tumors, germ cell cancers, and thyroid carcinoma. Compared to adults, AYAs had higher 5-year RS for

* Corresponding author.
E-mail address: annalisa.trama@istitutotumori.mi.it (A. Trama).

[1] These authors contributed equally and share last authorship

[2] **The EUROCARE-6 Working Group:** Austria: M. Hackl (National CR); Belgium: E. Van Eycken; N. Van Damme (National CR); Bulgaria: Z. Valerianova (National CR); Croatia: M. Sekerija (National CR); Cyprus: I. Gregoriou; A. Demetriou (National CR); Czechia: L. Dušek; D. Krejici (National CR); Denmark: H. Storm (National CR); Estonia: M. Mägi; K. Innos* (National CR); Finland: J. Pitkäniemi (National CR); France: M. Velten (Bas Rhin CR); X. Troussard (Basse Normandie, Haematological Malignancies CR); A.M. Bouvier; V. Jooste* (Burgundy, Digestive CR); N.Vigneron (Calvados, General CR); G. Launoy (Calvados, Digestive CR); S. Dabakuyo Yonli (Cote d'Or, Gynaecologic (Breast) CR); M. Maynadié (Cote d'Or, Haematological Malignancies CR); A.S. Woronoff (Doubs CR); J.B. Nousbaum (Finistere, Digestive CR); G. Coureau (Gironde, General CR); A. Monnereau* (Gironde, Haematological Malignancies CR); I. Baldi (Gironde, Central Nervous System CR); K. Hammas (Haut-Rhin CR); B. Tretarre (Herault CR); M. Colonna (Isere CR); S. Plouvier (Lille Area CR); T. D'Almeida (Limousin CR);

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most cancers, except breast, colon, and prostate cancers. Over time, 5-year RS improved across all age groups, with AYAs showing faster improvement than children but slower progress compared to adults for certain cancers. *Conclusion:* Age-specific disparities in cancer survival persist despite overall improvements. Tailored treatment approaches, specialized AYA oncology programs and collaboration between pediatric and adult oncologists are crucial to bridging survival gaps and improving outcomes for this population.

1. Introduction

Providing cancer care for adolescents and young adults (AYA) is challenging due to the relatively small numbers and the need for age-specific care, which extends beyond the primary cancer diagnosis. Within Europe, it is well recognised that AYAs with cancer have inequitable access to oncology services that provide expert cancer care and consider their unique needs [1]. Despite the high survival (>80 %) of AYAs with cancer [2], previous studies [3–5] have reported worse survival for most AYA cancers compared to children, but better survival compared to adults (40–69 years old), with a few important exceptions (e.g., breast and colorectal cancers).

Using the latest data available in the EUROCARE database, we aim to compare 5-year relative survival (RS) of AYA (15–39 years old) cancer patients with that of children (0–14 years old) and adults (40–69 years old) in Europe. In addition, we aim to compare changes in 5-year RS over time between children, AYAs and adults. Given the substantial variation in distribution of cancer for AYAs compared with children and adults we will develop cancer site-specific analyses considering

cancers typically occurring in AYAs and children and, separately, in AYAs and adults.

Our findings will identify key trends in cancer survival and assess for improvements over time and differences between age cohorts, thus informing priority areas for AYA oncology.

2. Materials and methods

2.1. Study design and data collection

We used the EUROCARE-6 database, encompassing 108 population-based cancer registries (CRs) across 29 European countries, as previously described [2,6,7]. The analysis included all malignant cancers excluding non-melanoma skin cancers and pilocytic astrocytoma due to incomplete registration. Cancers were categorized into diagnostic groups based on International Classification of Disease for Oncology 3rd edition (ICD-O-3), adapted from Barr [8] (Appendix Table 1) which were then grouped into non-carcinoma categories (affecting AYAs and children) and carcinoma categories (affecting AYAs and adults). Regarding tumours of the Central Nervous System (CNS), due to the radical redefinition of gliomas in recent years, it was not possible to adequately classify all tumours according to current standards. We therefore defined clinically relevant and comparable CNS tumours entities. Histologies whose definitions are still recognisable in WHO 2021 classification for CNS tumours are reported individually (e.g., pleomorphic xanthoastrocytomas (PXA), medulloblastomas, germ cell tumours, ependymomas etc.); the remaining malignant glioma histologies are described as a group named ‘other gliomas’ (i.e. astrocytoma, anaplastic astrocytoma, glioblastoma and gliosarcoma, oligodendroglioma and anaplastic oligodendroglioma, malignant glioma). Cases identified through death certificate only (DCO) or autopsy reports, those alive at diagnosis with unknown survival time, and those with invalid data items were excluded from the survival analyses.

2.2. Survival analysis (2010–2014) and difference across age groups

Using the period approach [9], we calculated a 5-year RS for the follow-up period 2010–2014, based on patients diagnosed between 2006 and 2013, with follow-up for vital status at December 31, 2014. RS, the ratio of observed to expected survival in the general population was used to adjust for deaths from causes other than the diagnosed cancer. Expected survival was estimated using the Ederer II method [10].

We compared 5-year RS between age groups, using the Z test for absolute differences. P values below 0.05 were considered statistically significant. A minimum of 40 cases of each cancer was required to compare RS across age groups, resulting in 34 tumours common to AYAs

Footnote continued: F. Molinié; A. Cowppli-Bony (Loire-Atlantique/Vendée CR); S. Bara (Manche CR); A. Debreuve (Marne-Ardennes, Thyroid CR); G. Defossez (Poitou-Charentes CR); B. Lapôtre-Ledoux (Somme CR); P. Grosclaude; L. Daubisse-Marliac; S. Lamy (Tarn CR); Germany: S. Luttmann; A. Eberle (Bremen CR); R. Stabenow (Common CR of 4 Federal States (Brandenburg, Mecklenburg-West Pomerania, Saxony-Anhalt, Thüringen); A. Nennecke; F. Peters (Hamburg CR); J. Kieschke (Lower Saxony CR); S. Zeissig (Rhineland-Palatinate CR); B. Holleczek (Saarland CR); A. Katalinic* (Schleswig-Holstein CR); Iceland: H. Birgisson (National CR); Ireland: D. Murray (National CR); Italy: G. Mazzoleni; F. Vittadello (Alto Adige CR); F. Cuccaro (Barletta-Andria-Trani CR); R. Galasso (Basilicata CR); G. Sampietro (Bergamo CR); S. Rosso (Biella CR); C. Gasparotti; G. Maifredi (Brescia CR); M. Ferrante; R. Ragusa (Catania-Messina-Enna CR); A. Sutera Sardo (Catanzaro CR); M.L. Gambino; M. Lanzoni (Province of Varese and Como CR); P. Ballotari; E. Giacomazzi (Cremona and Mantova CR); S. Ferretti (Ferrara CR); A. Caldarella; G. Manneschi (Firenze-Prato CR); G. Gatta*; M. Sant*; P. Baili*; F. Berrino*; L. Botta; A. Trama; R. Lillini; A. Bernasconi; S. Bonfarnuzzo; C. Vener; F. Didonè; P. Lasalvia; L. Buratti; G. Tagliabue (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan); L. Dal Maso; F. Toffolutti (Centro di Riferimento Oncologico, IRCCS, Aviano for the Friuli Venezia Giulia CR); R. Capocaccia* (Epidemiologia & Prevenzione Board); R. De Angelis*; E. Demuru; F. Cerza; F. Di Mari; C. Di Benedetto; S. Rossi*; M. Santaquilani; S. Venanzi; M. Tallon (Istituto Superiore di Sanità, Rome); L. Boni (Genova CR); S. Iacovacci (Latina CR); C. Genova; L. Benfatto (Liguria, Mesotheliomas CR); A.G. Russo; F. Gervasi (Province of Milan and Lodi CR); G. Spagnoli (Modena CR); L. Cavalieri d'Oro (Monza and Brianza CR); R. Abbate; M.F. Vitale (Napoli 3 South CR); P. Pinna (Nuoro CR); W. Mazzucco (Palermo CR); M. Michiara (Parma CR); G. Chiaranda (Piacenza CR); G. Cascone; E.Spata (Ragusa CR); L. Mangone (Reggio Emilia CR); F. Falcini (Romagna CR); R. Cavallo (Salerno CR); D. Piras (Sassari CR); A. Madeddu; F. Bella (Siracusa CR); A.C. Fanetti (Sondrio CR); S. Minerba (Taranto CR); G. Candela; T. Scuderi (Trapani CR); W. Mantovani; M.A. Gentilini (Trento CR); F. Stracci (Umbria CR); M. Zorzi; S. Guzzinati (Veneto CR); N. Ferrarini (Viterbo CR); Latvia: E. Liepina (National CR); Lithuania: G. Smailyte (National CR); Malta: M. Azzopardi (National CR); N. Calleja (Directorate for Health Information and Research); Norway: T.B. Johannesen* (National CR); Poland: J. Didkowska; U. Wojciechowska (National CR); M. Bielska-Lasota*; Portugal: A. Pais (Central Portugal CR); M.J. Bento; P. Silva (Northern Portugal CR); A. Lourenço; A. Mayer (Southern Portugal CR); Slovakia: C. Safaei Diba (National CR); Slovenia: V. Zadnik; T. Zagar (National CR); Spain: P. Ruiz Armengol (Balearic Islands, Mallorca CR); A. Lopez de Munain; M. De-La-Cruz (Basque Country CR); M. Garrido (Canary Islands CR); A. Vizcaino (Castellon CR); R. Marcos-Gragera; A. Sanvisens (Girona CR, CIBERESP); MJ. Sanchez; D. Redondo-Sanchez (Granada CR, EASP, ibs.GRANADA, CIBERESP); M.D. Chirlaque Lopez; A. Sanchez-Gil (Murcia CR, CIBERESP); M. Guevara*; E. Ardanaz (Navarra CR, CIBERESP); J. Galceran; M. Carulla (Tarragona CR); Switzerland: Y. Bergeron (Fribourg CR); A. Flahault; R. Schaffar (Geneva CR); R. Von Moos (Graubünden and Glarus CR); S. Mohsen Mousavi; M. Blum (Eastern Switzerland CR); A. Bordoni (Ticino CR); The Netherlands: O. Visser* (National CR); UK-England: S. Stevens;J. Broggio (National CR); UK-Northern Ireland: D. Bennett (National CR); A. Gavin*; UK-Scotland: D. Morrison (National CR); UK-Wales: DW. Huws* (Welsh Cancer Intelligence and Surveillance - WCISU); S.Smits (WCISU).

Table 1
5-year relative survival (RS) in european adolescents, young adults (AYAs, 15–39 years) in comparison with RS in children (00–14 years) and adults (40–69 years) for major cancers in the period 2010–2014 along with RS absolute difference between AYAs and children and AYAs and adults.

Tumour	Children				AYAs				Adults				difference AYAs vs children	difference AYAs vs adults
	N	CS	95 % CI		N	CS	95 % CI		N	CS	95 % CI			
Leukemias and related disorders	7,414	86.4	85.5	87.1	9,810	72.7	71.8	73.6	68,798	65.4	65.0	65.8	-13.7*	7.3*
Acute lymphoblastic leukemia (ALL)	5,668	90.1	89.2	90.9	2,282	61.3	59.2	63.3	2,417	30.9	29.0	32.9	-28.8*	30.4*
ALL, B-cell	1,594	91.4	89.9	92.7	559	64.0	59.8	67.8	649	33.3	29.5	37.2	-27.4*	30.7*
ALL, T cell	307	78.2	73.1	82.4	292	59.1	52.9	64.7	158	37.6	30.0	45.2	-19.1*	21.5*
Acute myeloid leukemia (AML)	1,120	70.5	67.6	73.2	3,271	58.1	56.3	59.9	16,078	29.3	28.6	30.0	-12.4*	28.8*
Acute promyelocytic leukemia (APL)	87	90.3	81.4	95.1	427	85.2	81.3	88.3	853	73.3	70.0	76.4	-5.1	11.9*
Chronic myeloid leukemia (CML)	181	82.4	75.5	87.5	1,428	92.8	91.3	94.1	6,509	73.6	72.4	74.8	10.4*	19.2*
Lymphomas	2,962	93.1	92.1	94.0	24,730	89.4	89.0	89.8	122,052	71.5	71.2	71.8	-3.7*	17.9*
Non-Hodgkin lymphomas	1,511	90.1	88.4	91.6	9,851	83.8	83.0	84.5	76,740	75.2	74.8	75.5	-6.3*	8.6*
Lymphoblastic	292	86.8	82.1	90.3	340	63.1	57.6	68.1	373	45.5	39.9	50.8	-23.7*	17.6*
Burkitt	612	92.5	90.0	94.4	613	75.7	72.0	79.0	953	58.3	54.9	61.5	-16.8*	17.4*
Diffuse large B-cell (DLBCL)	176	87.3	81.0	91.6	3,385	82.3	80.9	83.6	25,098	68.1	67.5	68.8	-5.0*	14.2*
Primary mediastinal large B-cell					403	90.6	87.3	93.0	233	86.4	80.9	90.4		4.2
Anaplastic T- and null-cell	122	89.6	82.4	94.0	366	82.8	78.3	86.5	791	57.6	53.8	61.2	-6.8*	25.2*
Follicular					1,533	94.7	93.4	95.8	18,565	89.7	89.2	90.2		5.0*
NK/T-cell	79	78.3	67.1	86.1	510	60.1	55.6	64.4	3,319	40.9	39.2	42.7	-18.2*	19.2*
Mucosa-associated lymphoid tissue (MALT)					646	95.0	92.9	96.5	6,145	89.0	88.0	89.9		6.0*
Other Non-Hodgkin lymphoma Not Otherwise Specified (NOS)	147	89.2	82.1	93.6	1,540	80.9	78.7	82.9	17,940	71.7	71.0	72.4	-8.3*	9.2*
Hodgkin lymphoma	1,118	97.3	96.1	98.1	13,425	94.5	94.1	94.9	9,869	82.0	81.1	82.8	-2.8*	12.5*
Central Nervous System (CNS) tumours	3,263	61.3	59.6	63	8,011	59.3	58.2	60.4	37,089	16.8	16.4	17.2	-2*	-42.5*
Ependymoma	420	73.1	68.3	77.2	629	87.4	84.4	89.8	1,152	77.5	74.7	80	14.3*	-9.9*
Medulloblastoma	825	62.2	58.7	65.4	356	72.1	67	76.5	81	60	48.1	69.9	9.9*	12.1*
Other gliomas	1,426	56.9	54.2	59.5	6,429	54.8	53.5	56	34,633	13.1	12.8	13.5	-2.1	-41.7*
Pleomorphic xanthoastrocytoma (PXA)					82	81.5	70.4	88.7	70	33.8	21.9	46		47.7*
CNS embrional tumors	243	51	44.3	57.2	157	40.9	32.9	48.8	123	21.5	14.5	29.3	-10.1*	19.4*
Meningiomas					134	69.8	61.1	76.9	1,001	69.7	66.3	72.7		0.1
Germ cell tumors of CNS	179	87.1	81.1	91.4	235	87.9	82.8	91.6	42	35.9	21	51.1	0.8	52.0*
Bone sarcomas	1,170	70.2	67.4	72.8	2,824	69	67.2	70.7	4,003	63.6	62	65.2	-1.2	5.4*
Osteosarcoma	558	66.9	62.8	70.6	986	64.2	61.1	67.2	741	45.9	42.1	49.6	-2.7	18.3*
Chondrosarcoma					678	86.6	83.7	89	1,861	74.5	72.2	76.6		12.1*
Ewing sarcoma of bone	478	69.4	64.9	73.4	710	51.1	47.2	54.8	126	32.1	23.9	40.5	-18.3*	19.0*
Soft tissue sarcomas	1,350	72.6	70.1	75	5,034	65.4	64	66.7	25,199	60.2	59.6	60.9	-7.2*	5.2*
Synovial sarcoma	40	97.3	81.6	99.6	223	66.1	59.5	71.9	275	52.4	46.1	58.4	-31.2*	13.7*
Malignant peripheral nerve sheath tumour (MPNST)	50	59.4	44.1	71.7	315	48.3	42.5	53.8	592	47.1	42.8	51.3	-11.1	1.2
Liposarcoma					723	85.6	82.7	88.1	4,661	77.6	76.2	78.9		8.0*
Epithelioid sarcoma					114	63	53.2	71.2	176	45.2	37.1	52.9		17.8*
Leiomyosarcoma					567	74	70.1	77.6	5,410	52.1	50.7	53.5		21.9*
Clear-cell sarcoma					75	51.2	38.6	62.4	73	47.2	34.3	59.1		4.0
Angiosarcoma					144	32.6	24.8	40.5	904	28.3	25.3	31.4		4.3
Undifferentiated high-grade pleomorphic sarcoma					130	67.4	58	75.1	995	54.7	51.2	58		12.7*
Rhabdomyosarcoma	771	69.2	65.8	72.4	401	40.9	36	45.7	440	27.3	23.1	31.7	-28.3*	13.6*
Ewing sarcoma of soft tissue	132	69.2	60.3	76.4	335	53.7	48	59	228	41.5	34.5	48.3	-15.5*	12.2*
Germ cell and trophoblastic of testis	138	96.1	90.7	98.4	23,973	96.7	96.5	97	11,824	95.8	95.4	96.3	0.6	0.9*
Germ cell and trophoblastic of ovary	204	96	92	98	851	95.5	93.8	96.8	280	64.2	58	69.7	-0.5	31.3*
Melanoma of skin	272	94.5	90.8	96.7	25,199	93.3	92.9	93.6	107,707	86.7	86.5	87	-1.2	6.6*
Thyroid carcinoma	332	99.3	97.3	99.8	18,857	99.5	99.3	99.6	47,778	96.2	96	96.5	0.2	3.3*
Carcinoma of breast					33,506	85.8	85.4	86.1	472,856	90	89.9	90.1		-4.2*
Carcinoma of uterine cervix					14,013	85.2	84.5	85.8	37,987	66	65.5	66.5		19.2*
Carcinoma of head and neck					3,529	72	70.5	73.5	122,073	53.8	53.5	54.2		18.2*
Carcinoma of oral cavity					1,455	73.9	71.5	76.2	34,180	52.9	52.3	53.4		21.0*
Carcinoma of nasopharynx					655	74.4	70.8	77.6	3,522	54.8	53	56.5		19.6*
Carcinoma of oropharynx					511	68.5	64.1	72.4	29,952	50.8	50.2	51.4		17.7*

(*continued on next page*)

Table 1 (*continued*)

Tumour	Children			AYAs				Adults				difference AYAs vs children	difference AYAs vs adults
	N	CS	95 % CI	N	CS	95 % CI		N	CS	95 % CI			
Carcinoma of colon excluding appendix				4,682	63.5	62.1	64.9	167,425	64.8	64.5	65.1		-1.3*
Colon neuroendocrine				108	79.4	70.3	86	1,614	54.4	51.8	56.9		25.0*
Colon adenocarcinoma				4,495	63.5	62	64.9	163,057	65.5	65.3	65.8		-2.0*
Carcinoma of rectum				3,135	65.5	63.7	67.2	114,569	65.5	65.2	65.8		0.0
Rectum neuroendocrine				247	97.1	93.8	98.7	1,967	80.4	78.4	82.3		16.7*
Rectum adenocarcinoma				2,827	63.2	61.4	65	110,416	65.7	65.4	66		-2.5*
Carcinoma of prostate				109	86.6	78.2	91.9	313,821	94.3	94.2	94.4		-7.7*
Carcinoma of lung and bronchus				3,352	39.3	37.6	41	290,171	17.2	17	17.3		22.1*
Small cell endocrine lung				297	15.7	11.5	20.4	49,655	7.3	7.1	7.5		8.4*
Non-small cell carcinoma lung				3,055	41.3	39.5	43.1	240,684	19.2	19	19.4		22.1*

*differences are statistically significant.

Note: N corresponds to the mean between the minimum and the maximum number of patients entering in each time intervals contributing to the period analysis, therefore, minimal discrepancies may be possible between the sum of the N of subgroup and the corresponding total

and children and 62 tumours common to AYAs and adults (Appendix Table 1).

Five-year conditional survival (CS), defined as the ratio of 5-year RS to 1-year RS, represents the probability of surviving 5 years considering only those who survived the first year after the primary cancer diagnosis. CS provides information on a risk profile that changes over time. We also used it to generate hypotheses about possible drivers of survival differences between AYA and other age groups.

We excluded childhood cancer registries to achieve a geographically homogeneous dataset across different age groups, so 95 CRs from 29 countries contributed to this analysis, covering approximately 57 % of the European population.

2.3. Survival changes over time

We examined changes in 5-year RS over time by calculating the Average Annual Percentage Change (AAPC). We estimated the 5-year RS with the period approach [9] separately for each year of follow-up from 2004 to 2013. The AAPC was computed as a weighted average of the annual percent change (APC) from the joinpoint model, with weights corresponding to the length of each APC interval [11]. In the absence of a joinpoint, the AAPC is equal to the APC.

To compare trends between AYAs and children, as well as between AYAs and adults, we used the test of parallelism to determine whether the two regression mean functions, represented by joinpoint regression, were parallel [12].

AAPCs were determined by age group for tumours with significantly different RS between age groups in 2010–2014. The 5-year RS point estimates over time and the AAPCs for all these tumours are detailed in Appendices 2 and 3. Due to the large number of tumours analysed, for 5-year RS trend comparisons between AYAs and children in the main text figure we only present tumours with significant 5-year RS increases over time in AYAs; for comparison of trends in 5-year RS between AYAs and adults, we present only tumours with significant differences in AAPCs between the two age groups.

Of the 95 CRs, 69 from 27 countries provided data covering the years of diagnosis 2001–2010 and were included in survival trend analyses.

We used SEER*Stat (version 8.3.9.2) [13] and Joinpoint (version 5.3.0) [14] for our analyses.

3. Results

3.1. Survival across age groups

Table 1 shows 5-year RS in children, AYAs and adults along with absolute differences between age groups.

Appendix Fig. 1 shows RS across all age group (0−69).

3.1.1. Relative survival

AYAs had lower RS for haematological tumours and sarcomas compared to children.

Regarding haematological tumours, RS in AYAs with leukaemia was 73 % compared to 86 % in children. In AYAs, almost half of the patients had ALL and AML and around 14 % had CML, whereas in children more than 70 % of cases had ALL and 2 % CML. Overall, AML and CML were the most common leukaemias in both age groups. AYAs had significant lower RS compared to children also for all types of acute leukaemia, with the exception of acute promyelocytic leukaemia (APL), with the highest differences for acute lymphoblastic leukaemia (ALL) (RS 90 % in children vs 61 % in AYA, around −30 % points) followed by acute myeloid leukaemia (AML) (-12 % points). RS for ALL and AML, varied between AYA age groups, being higher in those aged 15–24 years old (68 % and 60 %, respectively) and lower in the 25–39 age groups (51 % and 57 %, respectively) (Appendix Table 2). In contrast, AYAs had higher RS for chronic myeloid leukaemia (CML) compared to children (+10 % points). In AYAs, RS for lymphoma (overall) was 89 % while in children it was 93 % with HL and NHL corresponding to 94 % and 88 % of lymphoma cases in AYAs and children, respectively. AYAs had lower RS compared to children for HL (95 % vs 97 %) and most of the NHL subtypes, with particularly poorer survival for lymphoblastic lymphoma, NK/T-cell and Burkitt lymphomas. The RS for NHL also varied across AYA age groups, being highest in those aged 15–24 years and lowest in those aged 25–39 years (Appendix Table 2).

Central Nervous System (CNS) tumour RS was 61 % in AYAs and 59 % in children. RS in AYAs with CNS embryonal tumours was 41 % compared to 51 % in children. RS in AYAs with ependymoma and medulloblastoma was higher compared to children (87 % and 72 % vs 73 % and 62 %, respectively).

RS was about 70 % for bone sarcomas (BS) in both AYAs and children. However, within AYA age group, 15–24 years old has a RS of 64 % and 25–39 years old of 74 %, These differences within the AYA age group were mainly due to the subtypes case-mix. Yet, RS for Ewing bone sarcoma (EBS) was lower in AYAs (51 %) than in children (69 %). The difference in RS between AYAs and children for soft tissue sarcoma (STS) was mainly due to rhabdomyosarcoma (RMS) and synovial sarcoma. RMS which had a RS of 41 % in AYAs and 69 % in children; synovial sarcoma had a RS of 66 % in AYAs and 97 % in children. However, RS for synovial sarcoma was 73 % in those aged 15–24 years and 62 % in those aged 25–39 years (Appendix Table 2).

There were no significant differences in RS between AYAs and children for germ cell tumours (GCT), cutaneous melanoma (CM) and thyroid carcinoma (TC) (RS >90 % in these 3 tumours in AYAs and children).

Table 2
5/1-year conditional survival (CS), period analysis 2010–2014 by age classes, along with absolute differences from AYA and child and AYA and adults.

Tumour	Children				AYAs				Adults				difference AYAs vs children	difference AYAs vs adults
	N	CS	95 % CI		N	CS	95 % CI		N	CS	95 % CI			
Leukemias and related disorders	7,176	92.2	91.5	92.8	8,737	83.6	82.7	84.3	57,654	79.3	79.0	79.7	-8.6*	4.3*
Acute lymphoblastic leukemia (ALL)	5,634	94.0	93.4	94.6	1,956	72.5	70.4	74.5	1,420	52.2	49.4	54.9	-21.5*	20.3*
ALL, B-cell	1,600	95.1	93.9	96.1	481	73.9	69.8	77.6	401	53.1	47.7	58.1	-21.2*	20.8*
ALL, T cell	283	84.5	79.8	88.2	237	70.9	64.4	76.4	98	56.2	45.8	65.3	-13.6*	14.7*
Acute myeloid leukemia (AML)	975	82.8	80.2	85.1	2,581	74.8	73.0	76.5	8,822	53.5	52.4	54.6	-8.0*	21.3*
Acute promyelocytic leukemia (APL)	93	95.7	88.9	98.4	401	92.8	89.7	95.0	651	91.6	88.8	93.8	-2.9	1.2
Chronic myeloid leukemia (CML)	165	88.8	82.5	92.9	1,417	95.0	93.7	96.1	5,848	82.2	81.0	83.3	6.2*	12.8*
Lymphomas	2,950	96.9	96.2	97.5	24,456	93.7	93.4	94.0	106,531	82.0	81.7	82.3	-3.2*	11.7*
Non-Hodgkin lymphomas	1,467	95.7	94.5	96.7	9,281	91.7	91.1	92.3	66,873	86.2	85.8	86.5	-4.0*	5.5*
Lymphoblastic	288	91.2	87.2	94.1	306	74.3	68.9	79.0	250	63.2	56.4	69.2	-16.9*	11.1*
Burkitt	601	97.9	96.3	98.8	502	92.7	90.0	94.7	589	90.2	87.1	92.6	-5.2*	2.5
Diffuse large B-cell (DLBCL)	164	96.7	92.2	98.6	3,138	91.1	90.0	92.1	20,073	83.6	83.0	84.2	-5.6*	7.5*
Primary mediastinal large B-cell					387	92.7	89.6	94.8	220	94.3	89.8	96.9		-1.6
Anaplastic T- and null-cell	116	95.6	89.6	98.2	332	92.6	89.0	95.0	565	81.1	77.2	84.4	-3.0	11.5*
Follicular					1,568	95.9	94.7	96.8	17,888	92.2	91.7	92.7		3.7*
NK/T-cell	74	85.7	75.1	92.1	386	79.2	74.6	83.0	2,106	62.4	60.1	64.5	-6.5	16.8*
Mucosa-associated lymphoid tissue (MALT)					621	97.4	95.7	98.5	5,831	92.3	91.4	93.1		5.1*
Other Non-Hodgkin lymphoma Not Otherwise Specified (NOS)	142	97.6	92.5	99.2	1,432	90.7	88.9	92.2	15,803	82.8	82.1	83.5	-6.9*	7.9*
Hodgkin lymphoma	1,175	98.1	97.1	98.8	13,845	95.5	95.1	95.8	9,105	90.0	89.3	90.7	-2.6*	5.5*
Central Nervous System (CNS) tumours	2,776	74.9	73.2	76.5	7,257	67.6	66.5	68.7	20,256	31.2	30.5	31.8	-7.3*	-36.4*
Ependymoma	390	79	74.3	82.9	615	91	88.3	93.1	1,040	87.4	85	89.5	12*	-3.6*
Medulloblastoma	730	72.5	69	75.7	336	78.5	73.6	82.6	61	79.2	66.4	87.6	6*	0.7
Other gliomas	1,172	73.5	70.8	76	5,742	63.4	62.1	64.7	18,092	25.5	24.8	26.1	-10.1*	-37.9*
Pleomorphic xanthoastrocytoma (PXA)					79	85.1	74.3	91.6	50	46.9	30.9	61.3		38.2*
CNS embrional tumors	193	67.7	60.4	74	132	51.2	42	59.6	77	36.9	25.8	48.1	-16.5*	14.3*
Meningiomas					130	76	67.3	82.6	871	80.4	77.2	83.2		-4.4
Germ cell tumors of CNS	169	93.3	88.2	96.3	226	94.5	90.2	96.9	26	53.2	32.7	70	1.2	41.3*
Bone sarcomas	1,144	74.2	71.5	76.7	2,728	74.4	72.6	76	3,322	76.8	75.2	78.3	0.2	-2.4*
Osteosarcoma	551	71	66.9	74.6	963	68.9	65.8	71.8	566	61.7	57.3	65.8	-2.1	7.2*
Chondrosarcoma					671	89.3	86.6	91.5	1,685	82.8	80.7	84.7		6.5*
Ewing sarcoma of bone	465	73.7	69.3	77.6	648	57.8	53.7	61.6	92	45.9	35.1	56	-15.9*	11.9*
Soft tissue sarcomas	1,283	78.6	76.2	80.8	4,537	74.6	73.2	75.9	21,069	73.2	72.5	73.8	-4*	-1.4*
Synovial sarcoma	39	97.3	81.7	99.6	225	70.6	64	76.2	242	61.2	54.4	67.3	-26.7*	9.4*
Malignant peripheral nerve sheath tumour (MPNST)	44	69.7	53.7	81.1	248	61.5	55	67.4	456	64.4	59.4	68.9	-8.2	-2.9
Liposarcoma					712	90	87.5	92.1	4,353	84.4	83.2	85.6		5.6*
Epithelioid sarcoma					96	80.7	70.6	87.6	113	69.3	59.1	77.3		11.4*
Leiomyosarcoma					545	79	75.2	82.3	4,603	62.8	61.3	64.3		16.2*
Clear-cell sarcoma					51	72.2	56.9	82.8	54	62.9	47.7	74.8		9.3
Angiosarcoma					98	50.9	39.9	60.8	515	50.7	46.1	55.2		0.2
Undifferentiated high-grade pleomorphic sarcoma					120	79.7	71	86.1	835	70.5	66.9	73.8		9.2*
Rhabdomyosarcoma	742	74.9	71.5	78	329	51.5	45.9	56.8	266	46.8	40.5	52.9	-23.4*	4.7
Ewing sarcoma of soft tissue	122	75.5	66.7	82.3	290	62.5	56.5	67.9	153	61.3	52.4	69	-13*	-1.2
Germ cell and trophoblastic of testis	135	97.6	92.6	99.2	24,459	98	97.8	98.2	11,400	98.3	97.9	98.6	0.4	-0.3
Germ cell and trophoblastic of ovary	214	97.6	94.2	99	856	98.3	97.1	99	222	82.2	76.1	86.8	0.7	16.1*
Melanoma of skin	269	97.6	94.8	98.9	25,520	95	94.7	95.2	102,133	90.1	89.9	90.4	-2.6*	4.9*
Thyroid carcinoma	336	100	0	0	18,861	99.7	99.6	99.8	46,950	98.3	98.1	98.5	-0.3*	1.4*
Carcinoma of breast					34,073	87.2	86.8	87.5	474,839	91.7	91.6	91.8		-4.5*
Carcinoma of uterine cervix					13,950	89.2	88.7	89.7	34,290	76	75.5	76.4		13.2*
Carcinoma of head and neck					3,309	79.7	78.2	81.1	99,513	67.2	66.9	67.5		12.5*
Carcinoma of oral cavity					1,362	81.7	79.4	83.7	27,526	66.3	65.6	66.9		15.4*
Carcinoma of nasopharynx					636	79.7	76.2	82.7	2,966	67.7	65.9	69.5		12.0*
Carcinoma of oropharynx					451	76.5	72.2	80.2	22,403	65.2	64.5	65.9		11.3*
Carcinoma of colon excluding appendix					4,132	74	72.6	75.4	147,124	75.9	75.6	76.1		-1.9*
Colon neuroendocrine					90	94.3	86.6	97.6	1,151	76.7	73.9	79.2		17.6*

(*continued on next page*)

Table 2 (*continued*)

Tumour	Children			AYAs				Adults				difference AYAs vs children	difference AYAs vs adults
	N	CS	95 % CI	N	CS	95 % CI		N	CS	95 % CI			
Colon adenocarcinoma				3,987	73.7	72.2	75.1	144,642	76	75.7	76.2		-2.3*
Carcinoma of rectum				2,924	71.9	70.2	73.5	103,555	73.8	73.5	74.1		-1.9*
Rectum neuroendocrine				235	99	95.4	99.8	1,673	90.8	89	92.2		8.2*
Rectum adenocarcinoma				2,634	69.6	67.8	71.4	100,397	73.6	73.3	74		-4.0*
Carcinoma of prostate				109	89.2	81.3	93.9	312,647	95.4	95.3	95.5		-6.2*
Carcinoma of lung and bronchus				2,209	61.3	59.1	63.4	135,233	36.4	36.1	36.7		24.9*
Small cell endocrine lung				145	30.9	23.1	39	19,272	19.2	18.6	19.8		11.7*
Non-small cell carcinoma lung				2,064	63.3	61.1	65.4	115,874	39.2	38.9	39.5		24.1*

* differences are statistically significant.

Note: N corresponds to the mean between the minimum and the maximum number of patients entering in each time intervals contributing to the period analysis, therefore, minimal discrepancies may be possible between the sum of the N of subgroup and the corresponding total.

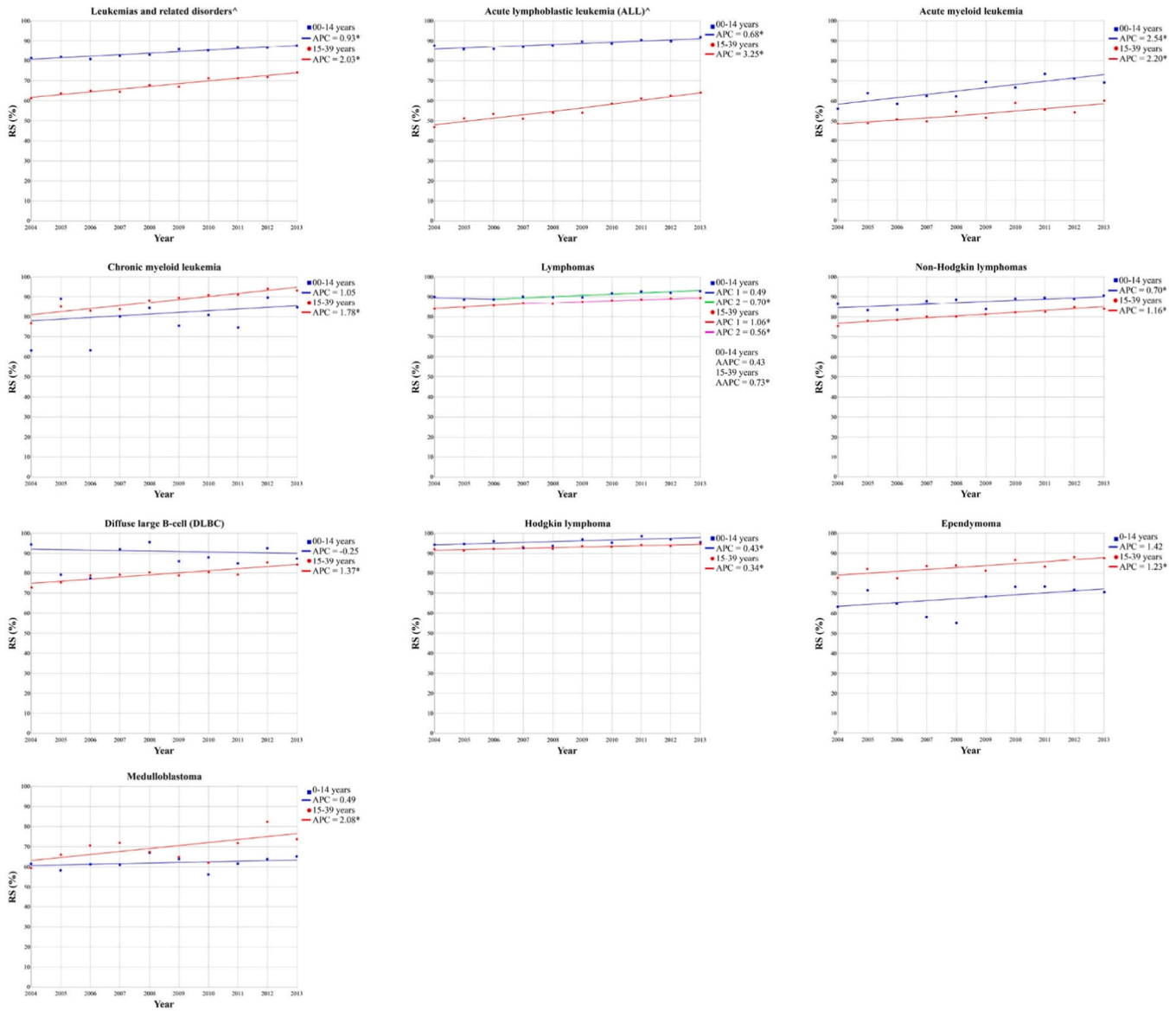

Fig. 1. 5-year relative survival (RS) over time for cancers with significant average annual percent change (AAPCs) in AYA and/or children along with their annual percent changes (APCs) and AAPCs. ^ significant difference in AAPC between children and AYAs. *indicates that the APC and /or AAPC is significantly different from zero at the alpha= 0.05 level. AAPCs where provided in presence of a joinpoint. Represented years are years of follow-up.

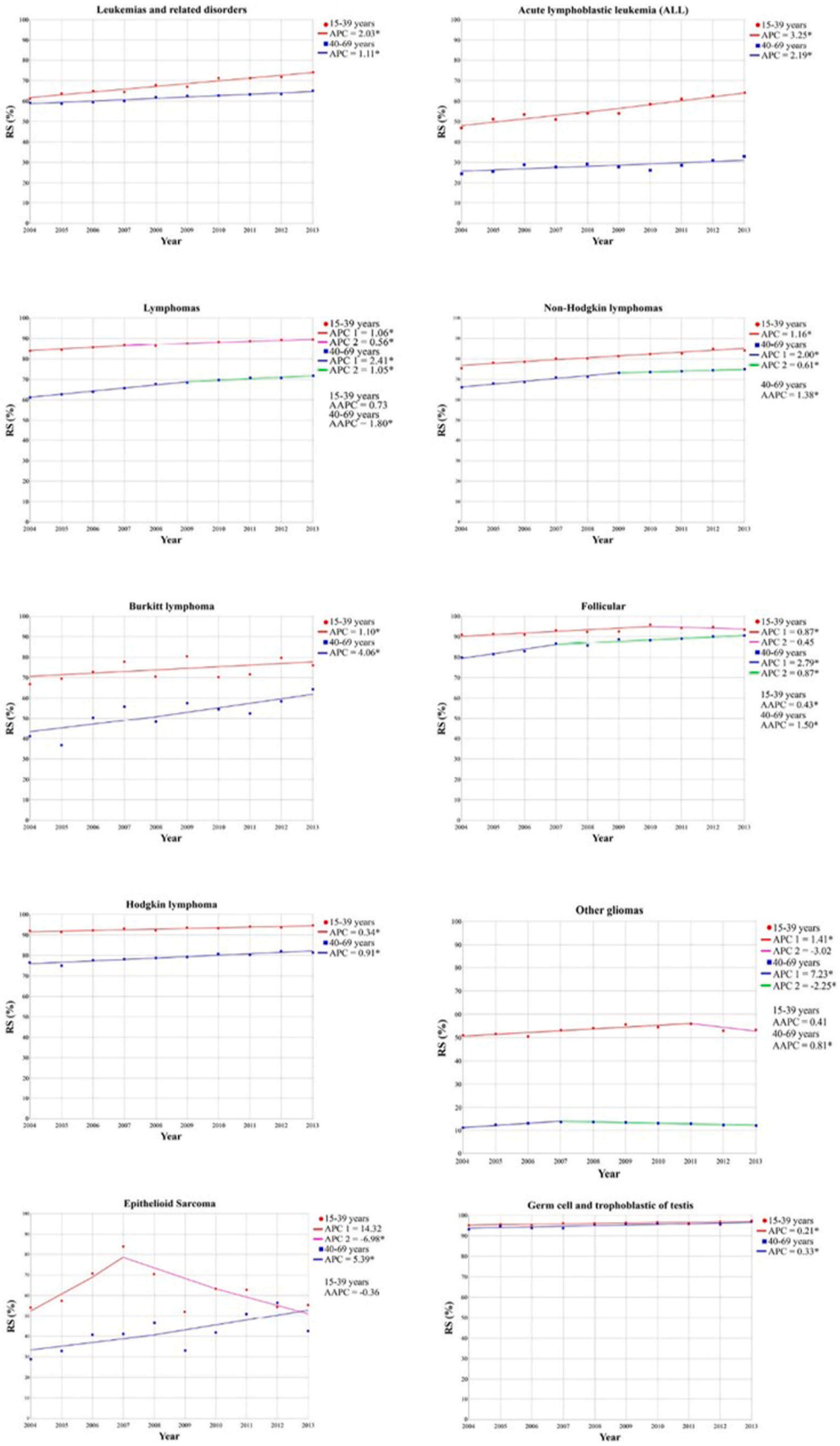

Fig. 2a. 5-year relative survival (RS) over time for cancers with significant different trend in AYA and adults along with their annual percent changes (APCs) and average APC (AAPCs). *indicates that the APC and /or AAPC is significantly different from zero at the alpha= 0.05 level. AAPCs where provided in presence of a joinpoint. Represented years are years of follow-up.

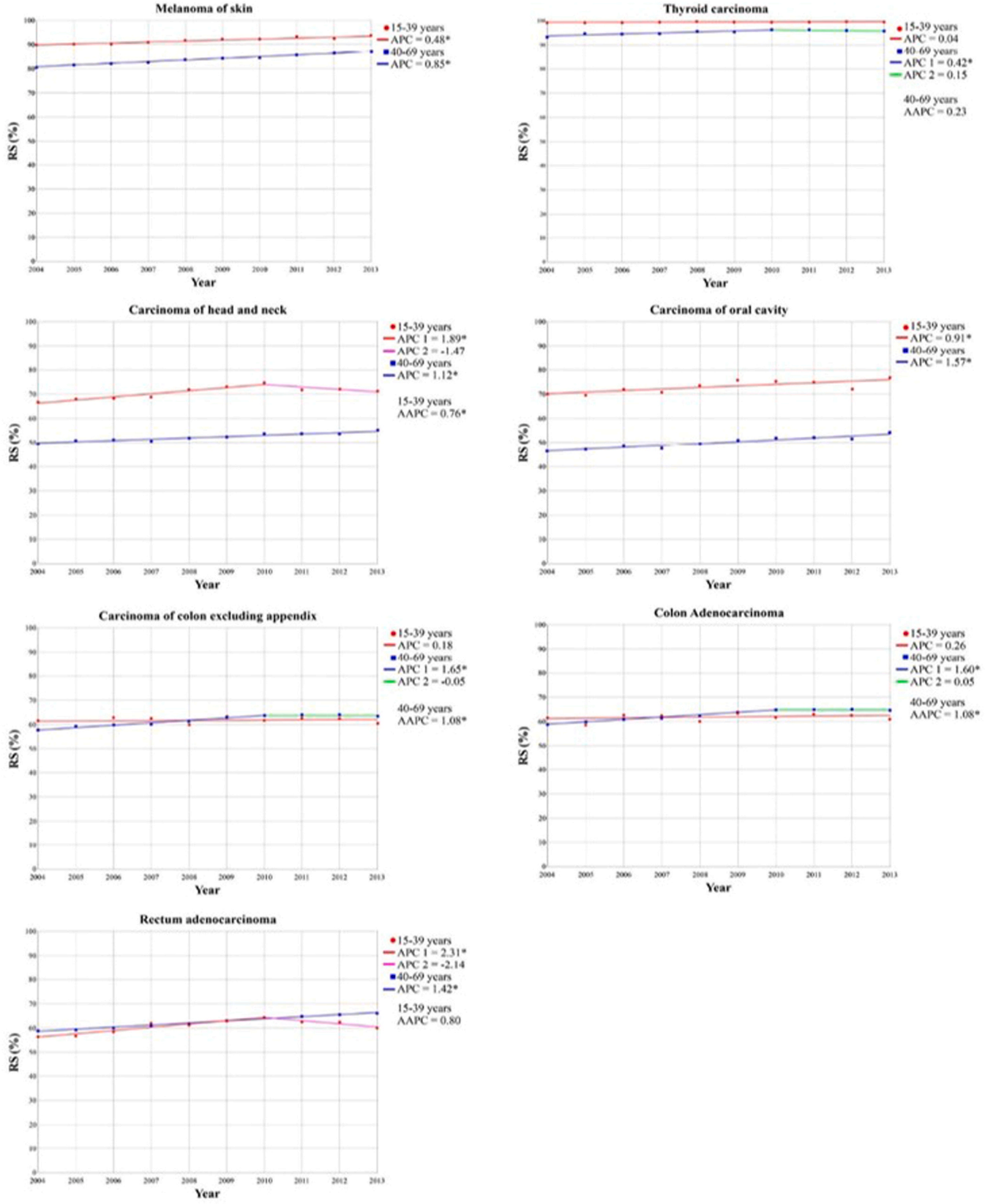

Fig. 2b. 5-year relative survival (RS) over time for cancers with significant different trend in AYA and adults along with their annual percent changes (APCs) and average APC (AAPCs). *indicates that the APC and /or AAPC is significantly different from zero at the alpha= 0.05 level. AAPCs where provided in presence of a joinpoint. Represented years are years of follow-up.

AYAs had higher RS compared to adults for all cancers, except prostate carcinoma (PCa), breast (BC), and colon cancers (CC) where AYAs had lower RS (-8 %, −4 % and −1 %, respectively), although AYAs had higher RS for neuroendocrine neoplasms of the colon compared to adults (79 % vs 54 %). The highest differences in RS between AYAs and adults were found for ALL, AML, CNS tumours, germ cell tumours of ovary (GCTO) (+30 %, +29 %, +42 %, +31 %, respectively).

3.1.2. Conditional survival

Table 2 shows CS in children, AYAs and adults along with absolute differences between age groups.

Compared to children, AYAs had lower CS for ALL, AML, HL and NHL, CNS tumours, EBS, STS, and CM although differences were smaller than those found for RS in Table 1, with few exceptions. For CNS tumours, RS was significantly higher in AYA compared to children (+1,6 %), but CS was significantly lower (-4.9 %). For CM, RS was similar in AYAs and children but CS was significantly lower in AYAs compared to children (-2.6 %). No differences in CS between AYA and children were found for BS, GCT and TC.

Compared to adults, AYAs had higher CS for most cancers, although differences were generally smaller than those found for RS in Table 1, with few exceptions. For BS, CS was 2.4 % points lower in AYAs than in adults, unlike RS, which was 5.4 % points higher in AYAs than in adults. Furthermore, differences in CS between AYAs and adults were accentuated for BC, CC and lung cancers, as these differences were higher than those observed in RS. APL, Burkitt, and germ cell of testis (GCTT) did not show statistically significant CS differences; however, they did in RS.

3.2. Survival changes over time

Fig. 1 shows trends in RS over time in 2004–2013 for cancers with significant AAPCs in AYA and/or children. RS increased over the period for most tumours in both age groups.

Compared to children, AYAs had higher AAPCs for leukemias (2.03 *vs.* 0.93), especially for ALL (3.25 *vs.* 0.68), and also for lymphomas (0.73 and 0.43 in AYAs and children, respectively) (Fig. 1, Appendix Table 3). AAPC was slightly lower in AYAs compared to children for AML, while there was no significant difference between AYAs and children for the remaining tumours. In 2004, RS for CNS tumours in adolescents was significantly lower than that in children, but increased steadily, reaching that of children in 2009. AAPC was higher in AYAs compared to children for medulloblastoma (Appendix Table 3).

Fig. 2 shows RS over time for cancers with significant differences in AAPCs between AYA and adults. Notably, RS increased over time for almost all tumours in both AYAs and adults. However, compared to adults, AYAs had higher AAPCs only for leukaemia (AAPC 2.03 and 1.11) and for ALL in particular (AAPC 3.25 and 2.19). AYAs, in contrast, despite having a higher RS than adults, had a significantly lower AAPCs compared to adults for lymphoma, specific types of NHL (i.e., Burkitt and follicular lymphoma), HL, CNS tumours, GCTT, CM, TC, oral cavity cancers, and colorectal cancers.

RS in BC patients increased overtime in both AYAs and adults and had similar AAPC values (Appendix Table 4), while increasing over time only for adults for CC and PCa.

4. Discussion

Our results confirm that survival differences between AYAs and children and AYAs and adults still persist despite the improved survival. However, this study reveals that these differences are decreasing.

Lower survival for AYA relative to children persists for ALL, AML, RMS and EBS. In AYA, ALL survival still lags behind that of children despite greater AAPC in AYA compared to children; in contrast, for AML, lower survival is also associated with lower AAPC in AYA compared to children. For RMS and EBS, improved survival over time was found for both children and AYA, although not statistically significant.

Survival was lower in AYA compared to adults for BC, CC, and PCa. However, for BC, limited and similar RS improvements were observed in both AYAs and adults, whereas for PCa and CC, AYAs did not experience the survival improvements observed in adults.

The survival gap between AYAs and children is multifactorial and includes differences in clinical management, site of treatment, tumour biology and differences in clinical trial involvement [15]. However, comparing survival between age groups is also necessary in order to consider how the case mix of tumours changes at different ages (e.g., osteosarcoma and EBS are more common in adolescents, chondrosarcoma is more frequent in 30–39 years old; among STS, liposarcoma and leiomyosarcoma are the most common in subjects aged between 30 and 39 years, RMS in children and adolescents) [16].

As with haematological tumours, ALL outcomes have improved with the adoption of paediatric protocols while persisting survival differences in children have been attributed to the more aggressive biologic features of ALL and increased treatment-related toxicities in AYAs [17–19]. For AYAs with AML, paediatric and adult protocols have been reported as sub-optimal [20]. The lack of differences in RS between children and AYAs with APL may be due to the use of all-trans retinoic acid [19]. Children have lower RS than AYAs for CML, as CML in children tends to have a more aggressive clinical presentation than older patients [21].

Regarding sarcomas, paediatric treatment appears to be less effective in AYAs with RMS, suggesting the role of a different RMS biology in AYAs [22]. The poorer survival for AYAs with EBS may be due to intensive treatments whose tolerability decreases with increasing age [23,24]. Survival differences between AYAs and children have been confirmed also across EBS subgroups, based on tissue of origin, tumour site, and disease stage [25].

We found that AYAs had better survival than adults for most cancers and worse RS compared to adults for BC, CC, and PCa. The explanation of the latter is multifactorial, including limited awareness of cancer signs in AYAs, tumour biology, histotype, and stage at diagnosis.

The peculiar aggressiveness of BC in AYAs has been partially attributed to genetic features of AYA BC which predisposes to endocrine resistance and lower prevalence of PIK3CA mutations linked with better prognosis [26], with our findings also showing an increased CS survival gap.

Evidence on prognosis of CC patients with early-onset is conflicting with heterogeneity of studies and variation in age definitions, hindering comparison of results [27]. However, some studies report more aggressive tumour features in AYAs compared with adults (e.g., higher grade, higher proportion of poor prognosis histologies) [27–30]. A distinct biology and prognosis for younger CC patients is suggested by the increase in CS compared to RS for this group. Furthermore, lack of appropriate patient referral to genetic services, delay in diagnosis and clinical management [27,31] and lack of screening in AYAs also explain the observed survival gap.

It is unclear how early age at diagnosis adversely influences outcome in AYAs with PCa, with a limited number of studies reporting non-conclusive results on the clinicopathological and molecular features of PCa in young and adults [32,33]. Our results found worse RS for AYA PCa patients compared to adults and this decreased in CS, supporting the need for additional studies to further understand the biology of PCa in AYAs. Finally, the higher survival in adults may also be due to a higher percentage of early-stage PCa, due to wide access to prostate specific antigen tests.

For all studied cancer sites, clinical information (e.g. on stage at diagnosis, mutational status) would be useful to disentangle age gap in survival using multivariable modelling; this information, however, was not available in our DB.

For nearly all cancers, survival increased over the study period in children, AYAs, and adults. However, over the period, both children and AYAs had somewhat a lesser improvement in survival if compared to adults, which may relate to the much lower RS in older patients at the beginning of the study period in 2004, providing greater room for

improvement over time in adults with these cancers.

Greater improvement in survival in AYAs compared to children may be due to expanded use of paediatric protocols, advances in diagnostics and risk-adapted therapy in AYAs. Across common diagnoses to both AYAs/children and AYAs/ adults, AYAs have superior outcomes when they are treated by a facility/oncologists with a specific knowledge in AYAs and AYAs cancer care [15,34,35]. This has been attributed to the comprehensive care provided, and enhanced access to clinical trials. The upcoming Network of expertise on AYAs will soon define and support developments of AYA programs in each European Member State, which we hope will contribute to improved survival for European AYA cancer patients, in line with their younger and older counterparts.

CRediT authorship contribution statement

Fabio Didonè: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Keiu Paapsi:** Writing – review & editing, Data curation. **Laura Botta:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Xavier Troussard:** Writing – review & editing, Data curation. **Fabiola Giudici:** Writing – review & editing, Data curation. **Annalisa Trama:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Marcel Blum:** Writing – review & editing, Data curation. **Silvia Rossi:** Writing – review & editing. **Alexandra Mayer-da-Silva:** Writing – review & editing, Data curation. **Damien Bennet:** Writing – review & editing. **peters frederik:** Writing – review & editing, Data curation. **Charles Stiller:** Writing – review & editing, Data curation. **Karim-Kos Henrike:** Writing – review & editing, Data curation. **Francesco Cerza:** Writing – review & editing. **Jan Trallero:** Writing – review & editing, Data curation. **Rosalia Ragusa:** Writing – review & editing, Data curation.

Ethics approval

We analysed pseudonymized data collected from 95 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT 73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed on in the EUROCARE-6 protocol, available at http://www.eurocare.it.

Data statement

We are not permitted to share individual data. Aggregated-level data, in the form of counts, rates, or survival proportions, can only be shared upon express permission from the participating registries. These data should be requested by contacting the corresponding author or Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115535.

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