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ORIGINAL RESEARCH

Cancer burden in adolescents and young adults in Europe

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Background: Cancer epidemiology is unique in adolescents and young adults (AYAs; aged 15-39 years). The European Society for Medical Oncology/European Society for Paediatric Oncology (ESMO/SIOPE) AYA Working Group aims to describe the burden of cancers in AYAs in Europe and across European Union (EU) countries.

Patients and methods: We used data available on the Global Cancer Observatory. We retrieved crude and age-standardised (World Standard Population) incidence and mortality rates. We reported about AYA cancer burden in Europe and between 28 EU member states. We described incidence and mortality for all cancers and for the 13 cancers most relevant to the AYA population.

Results: Incidence and mortality varied widely between countries with the highest mortality observed in Eastern EU countries. Cancers of the female breast, thyroid and male testis were the most common cancers across countries followed by melanoma of skin and cancers of the cervix. Variations in cancer incidence rates across different populations may reflect different distribution of risk factors, variations in the implementation or uptake of screening as well as overdiagnosis. AYA cancer mortality disparities may be due to variation in early-stage diagnoses, different public education and awareness of cancer symptoms, different degrees of access or availability of treatment.

Conclusions: Our results highlight the future health care needs and requirements for AYA-specialised services to ensure a homogeneous treatment across different countries as well as the urgency for preventive initiatives that can mitigate the increasing burden.

Key words: adolescents and young adults, cancer, incidence, mortality, population-based cancer registry

INTRODUCTION

In Europe, many estimates of the burden of cancer in adolescents and young adults (AYAs) are derived from single centre or in single country data. Often different definitions of AYAs are used,[1,2] and therefore, the estimates are unreliable for the design of specialised clinical services that can meet their specific needs.[3-5]

Data from EUROCARE have shown lower survival for AYAs than for children or adults for most cancers that affect these groups and modest survival improvements.[6] In Europe, the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOP Europe) founded a Cancer in AYA Working Group, to exchange knowledge and improve the care for AYA patients with cancer.[2] International collaboration is particularly relevant as services vary, the incidence of AYA cancers is increasing and the incidence is at least double in regions with a very high human development index (HDI) than in regions with a low/medium HDI.[7,8]

In this study, the ESMO/SIOPE AYA Working Group aims to describe the burden of cancer in AYAs in Europe in terms of incidence and mortality. These data will form a reference to

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guide health care organisations and collaborations at national and European levels for this underserved population.

PATIENTS AND METHODS

We used the all-inclusive definition of the AYA age range, 15-39 years, that has been accepted in Europe (https://www.siope.eu/encca/) and internationally.

We used data available on the Global Cancer Observatory (GCO) (https://gco.iarc.fr/help). The GCO data were accessed from their interactive web-based platform, provided by the Cancer Surveillance branch of the International Agency for Research on Cancer. The GCO data are only derived from the many European population-based cancer registries (CRs). This provides less biased epidemiological estimates than institutional registers.

We retrieved crude and age-standardised (World Standard Population) incidence and mortality rates. The results are provided for 2020. However, different methods were used to provide the incidence rates for 2020. A brief description follows (for further details refer to Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100744).

Incidence rates

- The most recently observed incidence rates (national or local) were applied to the 2020 population (20 countries).
- Rates were estimated from national mortality data by modelling, using mortality-to-incidence ratios derived from CRs in that country (five countries).
- Rates were estimated from national mortality estimates by modelling, using mortality-to-incidence ratios derived from CRs in neighbouring countries (four countries).
- In Slovakia 2001-2010 incidence rates from a single registry were applied to the 2020 population.

Regarding mortality, the most recently observed national mortality rates were applied to the 2020 population in all the countries included in this study (for further details please refer to Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100744).

We report incidence and mortality for all cancers except non-melanoma skin cancers. We also selected the most common cancers to the AYA population that are available on the GCO website: nasopharynx [International Classification of Diseases (ICD-10) code C11]; colon (C18); rectum (C19-20); liver and intrahepatic bile ducts (C22); melanoma of skin (C43); breast (C50); cervix uteri (C53); testis (C62); central nervous system (CNS) (C70-72); thyroid (C73); Hodgkin's lymphoma (HL) (C81); non-Hodgkin's lymphoma (NHL) (C82-86, C96); leukaemia (C91-95).

To report on the AYA burden in Europe and among the different European countries, we selected the 28 member states of the European Union (EU) in 2018 (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK) and Iceland and Norway within the European economic area with data available in the GCO. We included the UK, although it was then leaving the EU, due to the specific clinical services for AYA in the UK, long-standing research on AYA outcomes and for comparability with previous studies. Age-standardised incidence and mortality rates for Europe were calculated as weighted averages, giving each country a weight equal to the contribution of its population to the total population.

Finally, we retrieved incidence trends from 1998 to 2021 for countries with available data: Bulgaria, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, Switzerland and the UK. Data for 2011-2012 did not include Slovakia and Spain. Data for Austria, Belgium, Cyprus, Finland, Greece, Hungary, Luxembourg, Portugal and Romania were not available for the trend analysis.

RESULTS

In 2020, there were ~112 000 new cancer cases and 12 700 cancer deaths in AYAs in Europe. Overall, AYA cancers represented 5% of the new cancers diagnosed in the European countries selected in 2020.

Figure 1 describes age-standardised incidence and mortality rates (ASR) for all cancers except non-melanoma skin cancers in AYA. Incidence varied widely between countries. Italy was the country with the highest incidence (ASR 79 per 100 000) followed by France, Belgium, Denmark, Hungary, the Netherlands, Portugal and Norway (all with incidence $\geq$64 per 100 000). Malta was the country with the lowest incidence (ASR 36 per 100 000); other countries with low incidence were Iceland (ASR 42 per 100 000) and Estonia (ASR 46 per 100 000). In the remaining countries, incidence ranged from 50 to 64 per 100 000. Mortality also varied between countries with the highest mortality observed in Lithuania, Bulgaria and Romania (ASR ~11 per 100 000) followed by Portugal, Poland and Hungary (ASR ~9 per 100 000). Mortality was $<$5 in Estonia, Spain, Denmark, Iceland, Czech Republic and Slovenia and $<$2 in Malta and Luxembourg. Eastern European countries (e.g. Bulgaria, Romania, Poland) had low incidence rates but high mortality rates, while the other countries from south, centre and north of Europe (e.g. Italy, the Netherlands, Belgium, Norway) had high incidence rates with relatively low mortality rates.

Table 1 describes incidence rates specifically for AYA-relevant cancers in 2020, in both sexes, separately for males and females and compares countries. Cancers of the female breast, thyroid and testis were the most common cancers across countries followed by melanoma of skin and cancers of the cervix. CNS cancers and haematological malignancies were less common across all countries. Colorectal, nasopharyngeal and liver cancers were the rarest across countries. Differences between countries were observed for cancers of the female breast, thyroid, testis, cervix and skin melanoma. Female breast cancer's ASR

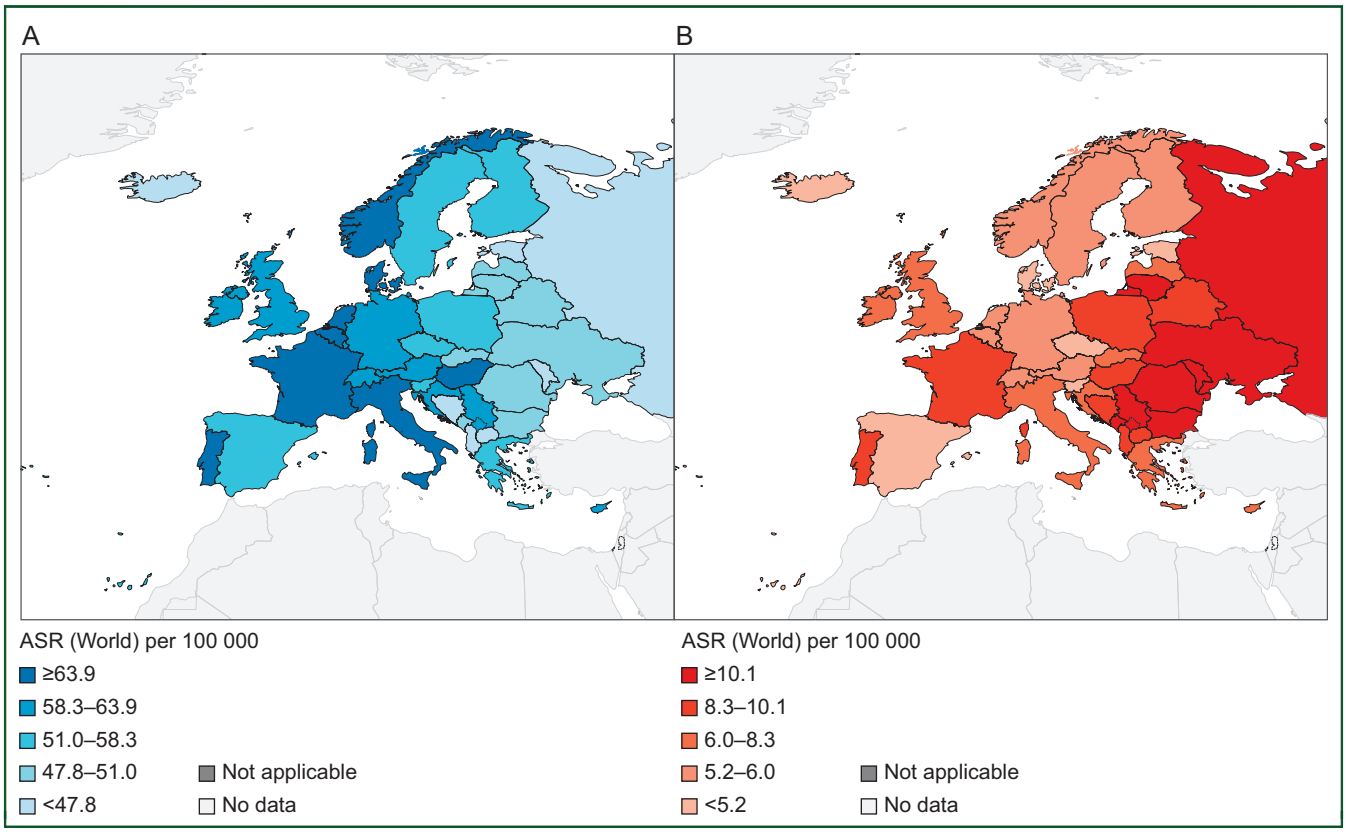

Figure 1. Estimated age-standardised incidence (A) and mortality (B) rates (world) in 2020, all cancers excluding non-melanoma skin cancer, both sexes, ages 15-39 years. ASR, age-standardised rate.

varied from 30 per 100 000 to 13 per 100 000 in France and Slovakia, respectively. The incidence of thyroid cancer was highest in Italy and Cyprus (ASR ∼20 per 100 000) and lowest in Estonia (ASR 2.5 per 100 000). The incidence of testicular cancer was highest in Nordic countries (ASR ∼20 per 100 000) and lowest in Lithuania and Latvia. The incidence of cervical cancer was ∼15-16 per 100 000 in the UK, Hungary, Norway, Latvia and Lithuania, and was lowest in Malta (ASR 2.1 per 100 000). The incidence of skin melanoma varied from 19 per 100 000 in Denmark to 1.3 per 100 000 in Cyprus. The incidence of thyroid cancers and skin melanoma was higher among females than males in all countries.

Figure 2 reports incidence trends for all cancers excluding non-melanoma skin cancers in AYAs by sex. Cancer incidence in AYA is increasing in both sexes and slightly more in females than in males.

Table 2 reports age-adjusted mortality rates for all cancers excluding non-melanoma skin cancers and for AYA-relevant cancers by country. Mortality rates were low for most cancers with the exception of the cancers of the CNS and leukaemia confirming the good prognosis for most cancers of AYAs. Differences in mortality were observed between countries. Eastern European countries (e.g. Bulgaria, Latvia, Lithuania, Poland, Romania) had high mortality rates for many of the AYA-relevant cancers (notably cancers of the cervix, CNS, testis, HL, NHL, leukaemia). Relatively large differences in mortality between countries were observed for testicular and cervical cancers, skin melanoma, HL and NHL. Differences in mortality between countries were relatively small for leukaemia and CNS cancers.

DISCUSSION

Our cooperative ESMO/SIOPE AYA Working Group's article describes, for the first time, the burden of cancers in AYAs in Europe. Our data confirm the rarity of tumours in this population and their increase in the current era and, most importantly, highlights differences in incidence and mortality within European countries, with Eastern European countries having higher mortality from many cancer types.

Variations in cancer incidence rates across different populations may reflect different distribution of risk factors, variations in the implementation or uptake of screening as well as overdiagnosis. We observed that differences in incidence between countries were in five main cancer types, in particular thyroid, breast, melanoma, cervical and testicular cancers.

Thyroid cancer is a common cancer in AYAs, especially in females as our results also confirm. Different use of diagnostic ultrasounds and fine-needle aspiration biopsies (leading to indolent cases)[9] and different distribution of risk factors such as obesity[10] may contribute to explain differences in thyroid cancer incidence between countries and sex.

Breast cancer incidence rates vary widely around the world; however, most factors responsible for the observed

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Table 1. Number of cases and age-standardised incidence rates (world) in 2020, all cancers excluding non-melanoma skin cancers and adolescent and young adults relevant cancers by country, both sexes and by sex, 15-39 years old

Country	Both sexes															Females											Males											
	All cancer excl. non-melanoma skin cancer (number of cases)	All cancer excl. non-melanoma skin cancer ASR	Female breast ASR	Thyroid ASR	Testis ASR	Cervix uteri ASR	Melanoma ASR	CNS ASR	NHL ASR	HL ASR	Leukaemia ASR	Colorectum ASR	Nasopharynx ASR	Liver ASR	All cancer excl. non-melanoma skin cancer (number of cases)	All cancer excl. non-melanoma skin cancer ASR	Female breast ASR	Melanoma ASR	NHL ASR	HL ASR	Leukaemia ASR	Colorectum ASR	Nasopharynx ASR	Liver ASR	All cancer excl. non-melanoma skin cancer (number of cases)	All cancer excl. non-melanoma skin cancer ASR	Thyroid ASR	Testis ASR	Melanoma ASR	CNS ASR	NHL ASR	HL ASR	Leukaemia ASR	Colorectum ASR	Nasopharynx ASR	Liver ASR
Austria	1949	59.6	23.3	9.3	12.3	4.0	10.0	2.8	2.3	2.4	1.9	1.6	0.1	0.3	1239	76.0	23.3	12.9	2.1	2.5	1.5	2.0		0.2	710	43.8	3.7	12.3	7.3	3.0	2.4	2.3	2.4	1.3	0.1	0.4
Belgium	3027	75.2	29.5	7.7	14.3	6.3	13.4	3.0	3.7	4.4	3.4	2.4	0.3	0.4	1937	95.2	29.5	19.5	3.0	3.9	3.3	2.4	0.2	0.4	1090	55.5	2.4	14.3	7.5	3.9	4.3	5.0	3.5	2.4	0.3	0.4
Bulgaria	1150	47.9	20.1	3.6	11.6	10.2	2.5	2.5	2.1	2.5	1.9	1.3	0.2	0.4	763	63.3	20.1	3.4	1.8	2.9	1.8	1.2	0.1	0.2	387	33.5	1.0	11.6	1.6	2.8	2.3	2.1	2.1	1.5	0.2	0.5
Croatia	867	62.1	21.4	10.6	18.8	6.9	4.2	3.3	3.2	3.9	1.6	1.6	0.1	0.2	526	74.3	21.4	4.2	2.7	4.1	1.2	1.8			341	50.3	3.1	18.8	4.1	3.8	3.8	3.7	2.0	1.4	0.2	0.3
Cyprus	322	63.5	24.3	19.3	13.9	3.7	1.3	1.9	2.5	5.9	2.4	1.1	0.2	0.4	202	79.9	24.3	1.2	2.7	6.4	2.7	1.0		0.4	120	47.4	9.9	13.9	1.5	2.6	2.2	5.5	2.2	1.1	0.3	0.4
Czech Republic	2018	54.7	23.9	6.6	14.6	8.1	6.4	2.3	1.8	3.1	2.3	1.5	0.0	0.2	1296	69.9	23.9	8.6	1.5	3.1	1.8	1.7		0.0	722	40.2	2.5	14.6	4.2	2.7	2.1	3.1	2.8	1.3	0.0	0.2
Denmark	1336	69.9	20.6	6.7	18.8	13.0	18.9	1.7	2.6	3.4	1.9	1.0	0.1		847	89.0	20.6	27.4	2.0	3.4	1.6	1.4			489	51.2	3.6	18.8	10.6	1.9	3.2	3.5	2.2	0.6	0.1	
Estonia	231	45.9	15.4	2.5	6.3	11.8	7.1	1.8	4.1	4.3	2.3	0.9			153	61.4	15.4	9.8	2.7	4.9	2.0	0.7			78	31.7	0.8	6.3	4.6	1.8	5.5	3.7	2.6	0.9		
Finland	1036	54.7	14.9	6.7	13.6	6.5	9.9	2.7	2.1	4.4	2.0	2.0		0.1	637	68.1	14.9	14.2	1.4	4.4	1.7	2.1			399	42.1	1.9	13.6	5.9	2.7	2.8	4.4	2.2	1.9		0.2
France	16 415	76.2	30.5	11.8	16.9	6.0	9.6	3.5	3.7	4.8	2.7	2.0	0.3	0.3	10 316	92.7	30.5	11.6	3.2	4.2	2.1	2.6	0.1	0.3	6099	59.0	3.7	16.9	7.7	4.3	4.2	5.4	3.3	1.5	0.4	0.3
Germany	17 540	61.9	24.3	4.1	15.9	7.3	12.1	2.6	2.4	3.1	2.4	3.2	0.1	0.1	10 780	77.0	24.3	16.8	1.7	2.9	2.2	3.7	0.1	0.1	6760	47.8	2.7	15.9	7.7	3.1	3.0	3.4	2.7	2.7	0.1	0.0
Greece	1944	56.7	24.0	7.4	12.7	6.7	4.7	2.6	4.0	3.6	2.6	1.0	0.4	0.3	1154	66.8	24.0	4.6	4.1	4.8	2.3	0.9	0.2	0.2	790	47.3	7.2	12.7	4.7	3.1	3.8	2.5	3.0	1.2	0.6	0.4
Hungary	2211	66.5	22.3	11.7	17.7	16.3	4.2	2.6	2.6	2.6	2.1	2.4	0.2	0.1	1444	86.8	22.3	4.7	2.0	3.0	1.6	2.6	0.2	0.1	767	47.0	2.6	17.7	3.8	3.2	3.2	2.3	2.6	2.1	0.2	0.2
Iceland	56	41.6	18.7	5.2	12.2	13.6	3.9	2.1	0.7	3.9					40	60.1	18.7	6.6		6.6					16	24.0	1.4	12.2	1.3	2.7	1.3	1.4				
Ireland	1146	62.9	20.0	8.8	16.0	10.4	8.7	2.6	2.2	3.7	1.9	1.8	0.0	0.3	762	80.9	20.0	12.6	1.9	3.7	2.4	1.7		0.2	384	44.5	1.2	16.0	4.7	3.0	2.6	3.7	1.5	1.9	0.1	0.4
Italy	14 424	79.2	25.0	20.1	16.7	5.2	9.4	3.5	4.1	5.3	2.6	0.9	0.4	0.4	9270	101.8	25.0	12.0	3.2	5.3	2.7	1.2	0.2	0.3	5154	57.2	5.9	16.7	6.8	5.0	5.0	5.4	2.4	0.5	0.5	0.6
Latvia	326	49.2	15.4	6.1	4.7	14.6	2.5	3.5	2.3	4.2	2.1	1.2	0.1		228	68.7	15.4	3.5	1.4	3.9	2.6	0.8			98	30.5	0.8	4.7	1.6	3.6	3.1	4.5	1.7	1.6	0.2	
Lithuania	458	50.1	16.2	5.4	4.9	14.5	3.9	3.6	2.5	3.3	2.4	1.1		0.1	302	67.4	16.2	4.4	1.5	3.6	2.4	1.3			156	34.1	2.1	4.9	3.4	4.2	3.6	3.0	2.3	1.0		0.2
Luxembourg	149	56.7	23.8	11.0	16.2	3.3	10.5	1.1	1.6	3.7	0.3	0.7			92	70.1	23.8	11.6	1.3	4.5		1.3			57	43.6	4.9	16.2	9.5	2.2	2.0	2.9	0.7			
Malta	65	36.2	13.5	6.8	10.5	2.1	3.2	1.0	4.3	3.6	0.5	0.5			41	47.7	13.5	4.6	5.3	5.0		1.0			24	25.7	1.9	10.5	1.9	1.9	3.3	2.3	1.0			
Norway	1318	65.6	22.4	5.4	21.0	15.0	8.9	2.9	2.1	3.6	2.3	3.4		0.3	796	80.1	22.4	12.6	1.8	3.4	2.1	4.2		0.4	522	52.0	2.6	21.0	5.3	3.7	2.5	3.8	2.5	2.6		0.3
Poland	7614	51.0	27.4	5.6	13.0	5.3	2.2	3.6	2.5	2.3	1.6	1.3	0.2	0.4	4918	65.0	27.4	2.2	2.1	1.9	1.3	1.2	0.1	0.3	2696	38.1	1.6	13.0	2.3	4.4	2.8	2.6	1.8	1.5	0.4	0.4
Portugal	2113	65.7	27.6	10.3	12.2	10.6	3.3	2.9	4.3	3.6	2.3	2.2	0.3	0.3	1359	80.9	27.6	3.9	3.1	3.0	2.1	2.3	0.2	0.1	754	49.6	3.2	12.2	2.7	3.7	5.5	4.2	2.6	2.0	0.4	0.6
Romania	3230	48.5	17.9	6.0	7.6	12.7	2.4	2.3	2.4	1.6	1.9	1.6	0.7	0.5	2084	63.6	17.9	2.5	1.7	1.0	1.8	1.8	0.7	0.5	1146	34.4	0.8	7.6	2.3	3.0	3.0	2.1	2.1	1.5	0.7	0.6
Slovakia	1057	49.9	12.9	4.0	16.6	11.9	3.1	3.3	2.1	3.6	1.9	1.9	0.0	0.2	614	56.1	12.9	3.8	1.9	3.8	1.6	1.9		0.2	443	44.0	1.6	16.6	2.6	4.1	2.2	3.3	2.2	2.0	0.1	0.2
Slovenia	408	57.4	17.2	5.1	21.1	5.3	11.8	2.4	2.5	3.2	1.8	1.0	0.1		234	66.1	17.2	15.1	1.8	3.6	1.9	0.6			174	49.4	1.9	21.1	8.8	2.4	3.1	2.9	1.8	1.3	0.2	
Spain	8198	53.7	25.7	6.3	10.5	4.5	4.0	2.3	3.0	3.9	2.2	1.6	0.5	0.2	5316	67.5	25.7	5.4	2.5	3.8	2.0	1.4	0.3	0.1	2882	39.9	2.2	10.5	2.7	2.7	3.6	4.1	2.4	1.8	0.6	0.3
Sweden	2050	57.2	20.6	5.4	13.7	13.1	9.8	2.1	1.6	2.7	2.1	1.5	0.2	0.4	1318	73.8	20.6	13.2	1.6	2.7	1.8	1.6	0.1	0.4	732	41.3	2.3	13.7	6.6	2.4	1.6	2.7	2.3	1.4	0.2	0.4
The Netherlands	3833	66.5	27.5	3.2	18.9	7.7	12.8	2.4	3.1	3.8	2.2	2.5	0.2	0.3	2287	79.1	27.5	17.0	2.0	3.6	1.9	3.0	0.1	0.3	1546	54.1	1.3	18.9	8.7	2.7	4.2	3.9	2.5	2.1	0.2	0.3
United Kingdom	15 404	62.7	20.3	6.2	12.8	16.6	7.4	2.5	2.7	3.8	2.0	2.9	0.2	0.3	10 051	81.1	20.3	10.0	2.2	3.3	1.7	3.2	0.1	0.4	5353	44.3	2.1	12.8	5.0	2.9	3.3	4.2	2.2	2.5	0.2	0.2
All European countries considered	111 895	63.6	24.4	8.4	14.5	8.5	8.0	2.8	3.0	3.7	2.3	2.0	0.3	0.3	71 006	80.0	24.4	10.5	2.4	3.5	2.0	2.3	0.2	0.2	40 889	47.5	2.9	14.5	5.6	3.5	3.5	3.9	2.5	1.8	0.3	0.3

ASR, age-standardised rate; CNS, central nervous system; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma.

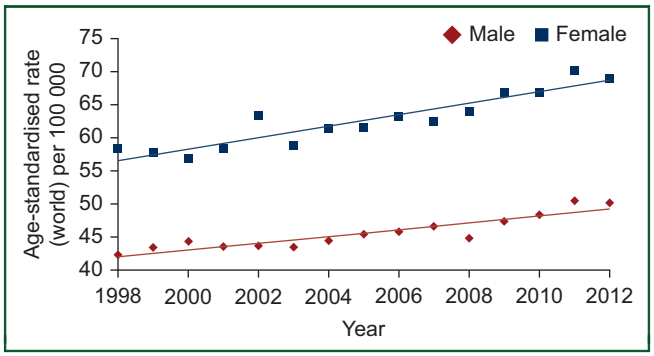

Figure 2. Trend of incidence for all cancers excluding non-melanoma skin cancers, by sex, 15-39 years old.

differences (parity, obesity, use of hormone replacement therapy, mammogram screening) are relevant for postmenopausal women only.[11] Risk factors for breast cancer before age 40 years include family history, age at menarche, age at first birth, breast-feeding habits, low body mass index (<20), use of an oral contraceptive, alcohol intake, etc. Most risk factors in women aged <40 years were similar to those described in breast cancer epidemiology at any age. Previous international comparisons showed that the pattern of these exposures does not closely follow the observed incidence patterns in GLOBOCAN.[11] Among these factors, only the prevalence of underweight varies markedly between European countries. However, this variation in the proportion of underweight women across Europe seems to only loosely follow the incidence patterns we observe.[12] Therefore, the European differences in breast cancer incidence in young women remain poorly explained.

Incidence in cervical cancer is influenced by screening, behavioural risk factors and public health policy between populations. The main risk factor for cervical cancer is human papillomavirus (HPV), which is sexually transmitted and thus associated with sexual behaviour. Smoking, parity and hormonal contraceptive use are also associated with cervical cancer risk. HPV vaccine coverage is low in countries where we observe the highest incidence and screening performance is heterogeneous among European countries.[13-15] In our data, most countries that completed the roll-out of the cervical cancer screening programme (e.g. the Netherlands, Sweden, Slovenia) had the lowest mortality rates, whereas countries with no cervical screening programme or that are rolling out the screening have mortality rates higher than the EU average. Other cervical cancer-associated risk behaviours differ between EU countries.[16-19] Preventive campaigns and vaccination policies should be encouraged for decreasing the impact of HPV-related cancers in Europe.

Breast, cervical and thyroid cancers account for a substantial burden of cancer among AYAs and especially young women as our results confirm. A cancer diagnosis can be catastrophic with repercussions beyond an individual's health, and indeed beyond the individual, especially if it occurs at a young age. Ensuring that young people make informed choices about their health and encouraging policy makers to tailor effective and cost-effective preventive measures would make a great impact on cancer risk and outcomes especially for women.[20]

Differences in melanoma incidence across countries may be due to the different exposure to ultraviolet radiation on sunbeds or natural sun. In addition, different skin pigmentation characteristics may contribute to susceptibility to melanoma.[21] Melanoma is very common in the young adult population, more so in AYA women than in men as our results also confirm. This may be, in part, due to the greater use of risky behaviours among girls in seeking to suntan (using sunbeds or natural sun) which is socially determined.[22]

Testicular cancer is the most common cancer among young men aged 15-39 years. Our data confirmed that incidence tends to be greatest in Northern European countries, while the lowest rates occurred in Eastern European countries. This heterogeneity is not well explained, as there are no strong behavioural, public health or screening factors identified. Birth cohort effect, occupational, environmental and maternal exposure to exogenous toxins have been considered as possible risk factors.[23] Further research using cases collected through national and regional population-based registers and case-control studies are needed together with greater consideration given the public health importance of testicular cancer among young men, and the need for high-quality cancer service delivery to maximise survival prospects and quality of life.[24]

Our study confirmed an increasing incidence of tumours in AYAs. Previous studies have reported that cancers with increasing incidence were those related to obesity (e.g. colorectal cancers, thyroid cancers); thyroid tumours attributed to diagnosis of small low-risk tumours at routine imaging, and cervical tumours attributed to changes in sexual behaviour, while an impact is not yet clearly visible from HPV vaccination. More work is needed to understand the growing incidence of testicular and breast cancers in AYAs, both in Europe and North America.[8]

Our analysis confirmed greater mortality for most AYA cancers, in Eastern Europe more than in Western Europe.[25] This is not unexpected, as Eastern European countries also have lower cancer survival in children and adults.[26,27] Variations in mortality reflect, in part, variations in incidence, but also differences in early diagnosis and available treatment modalities among others.

For many AYA cancers (e.g. testicular, breast, melanoma, HL and NHL), we observed variation in mortality, with higher mortality not always associated with higher incidence, supporting the importance of the health care organisation in providing earlier detection and the most effective treatments. These data concur with previous studies that attributed AYA cancer mortality disparities to variation in early-stage diagnoses, especially where young people are not included in cancer screening protocols, as well as to different public education and awareness of cancer symptoms, different degrees of access or availability of treatment. Many of these are underpinned by different

Table 2. Number of deaths and age-standardised mortality rates (world) in 2020, all cancers excluding non-melanoma skin cancers and adolescent and young adults relevant cancers by country, both sexes, 15-39 years old

Country	All cancers excl. non-melanoma skin cancer (number of deaths)	All cancers excl. non-melanoma skin cancer (ASR)	Female breast ASR	Thyroid ASR	Testis ASR	Cervix uteri ASR	Melanoma ASR	CNS ASR	Colorectum ASR	NHL ASR	HL ASR	Leukaemia ASR	Nasopharynx ASR	Liver ASR
Austria	173	5.2	1.50		0.25	0.66	0.24	1.20	0.08	0.41		0.85		
Belgium	240	6	1.60	0.02	0.23	0.60	0.49	1.30	0.13	0.25	0.14	0.80		0.11
Bulgaria	284	10.9	2.70		1.20	2.00	0.20	1.40	0.14	0.60	0.28	0.84	0.03	0.07
Croatia	115	7.8	1.80		0.83	0.48	0.57	1.50	0.60	0.36	0.12	1.00		0.06
Cyprus	32	6.1	1.40		0.44		0.64	0.80	0.18		0.23	0.34		0.17
Czechia	192	5	1.30		0.69	1.00	0.29	1.00	0.11	0.14	0.09	0.54		
Denmark	97	5.1	1.20		0.32	0.72	0.66	1.20	0.05			0.56		
Estonia	29	5.1	1.10			1.10	0.34	1.20		0.34		0.67		
Finland	116	6	1.20		0.76	0.59	0.15	1.50	0.27	0.22	0.05	0.42		0.09
France	1818	8.3	2.40	0.01	0.50	0.62	0.52	1.40	0.46	0.40	0.18	0.91	0.03	0.19
Germany	1600	5.4	2.00	0.01	0.33	0.60	0.27	0.97	0.29	0.20	0.07	0.59	0.01	0.03
Greece	257	7.4	1.60	0.02	0.72	0.51	0.26	0.93	0.30	0.55	0.21	0.86	0.04	0.18
Hungary	311	9	1.80	0.05	0.96	1.30	0.33	1.10	0.74	0.39	0.13	1.00	0.05	0.10
Iceland	7	5	2.80			1.40		2.10	0.85					
Ireland	127	6.8	2.10		0.26	1.10	0.35	2.00	0.18	0.25		0.57		0.08
Italy	1323	7.1	1.90	0.03	0.48	0.54	0.50	0.89	0.26	0.46	0.32	1.10	0.05	0.10
Latvia	60	8.3	2.10		0.22	2.70		1.80		0.68	0.59	0.68	0.11	0.13
Lithuania	97	11	2.10		0.69	2.60	0.19	2.40	0.98	0.11	0.20	0.67	0.11	0.11
Luxembourg	3	1.4	0.66							0.71				
Malta	2	1.7	1.00											
Norway	117	5.8	1.10			0.49	0.46	1.30	0.48	0.22		0.57		0.13
Poland	1510	9.7	2.70	0.02	1.00	0.89	0.42	1.40	0.50	0.76	0.26	0.92	0.04	0.24
Portugal	325	9.9	2.30		0.58	1.10	0.21	1.40	0.57	0.78	0.20	1.10	0.12	0.15
Romania	702	10.5	1.90	0.02	0.64	2.10	0.29	1.10	0.61	0.57	0.21	1.00	0.19	0.44
Slovakia	167	7.6	1.00		1.20	1.50	0.36	1.40	0.38	0.14	0.38	1.00		
Slovenia	30	3.6	1.40		0.44	0.45	0.46	0.99	0.11					
Spain	797	5.1	1.60	0.01	0.27	0.41	0.26	0.82	0.12	0.28	0.14	0.70	0.04	0.02
Sweden	191	5.3	1.30		0.10	0.58	0.23	1.20	0.40	0.24	0.06	0.62		0.02
The Netherlands	319	5.4	1.70		0.26	0.58	0.47	1.20	0.28	0.35	0.09	0.40		0.06
United Kingdom	1695	6.7	1.90	0.01	0.19	1.30	0.29	1.00	0.86	0.26	0.16	0.44	0.06	0.01
Europe	4790	7.0	1.94	0.02	0.46	0.83	0.36	1.12	0.40	0.37	0.17	0.75	0.05	0.10

ASR, age-standardised rate; CNS, central nervous system; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma.

expenditures on public health systems.[28-31] Different access or administration of available treatment may be particularly relevant for cancers that arise in young people because a cancer in a young person tends to have distinctive clinical features and delivering treatment can be more complex than a similar cancer in an adult. For example, breast cancer in young women is a biologically more aggressive cancer than in older women[29] and often diagnosed at later stages;[32] young-onset skin melanoma has a distinct biology;[33] and colorectal cancer in the young has a distinctive molecular profile, more commonly presents as symptomatic, later stage, mucinous and poorly differentiated disease.[34]

For thyroid and cervical cancers, the variation in incidence outweighed the variation in mortality. For thyroid cancer this may be attributed to the rates of use of ultrasound scans, resulting in diagnosis of tiny incidental nodules which may have never caused life-threatening disease. This is inflating the incidence with tumours with a limited impact on thyroid cancer mortality, which remains similar across countries. Such overdiagnosis will usually lead to treatment, lifelong medical care and adverse effects that can negatively affect the quality of life for a particularly long time in young patients. For cervical cancers, different availability and access to screening or vaccination may explain some of the mortality differences between countries.

In relatively poor-prognosis young-onset cancers included in this analysis, such as CNS cancers and leukaemia, there was little variation in mortality across Europe. Tumour biology may affect mortality together with stage of diagnosis or currently available treatments. Of note, for leukaemia, the mortality differences between countries were lower for patients aged 15-24 years compared to those aged 25-39 years (data available from the corresponding author). This is most likely due to the widespread use of homogeneous treatment protocols by paediatric cancer hospitals.

Cancers are rare in people under 39 years of age, but unlike most rare cancers they can be effectively treated in the majority of cases. To ensure the best outcomes, young people who develop malignancies should be referred to specialist centres and treated in accordance with national or international protocols. Where such protocols are not available, they should be developed. Multi-institutional cooperation and European inter-group cooperative studies have an important role to play in developing treatment protocols, and also in organising and coordinating clinical research in these cancers.

Our study has limitations. Firstly, we reported results for AYAs between the ages of 15 and 39 years. This definition does not allow to compare with previous data from the different ranges of tumours of younger AYA patients (e.g. aged 15-24, 15-29 years). However, our aim was to provide a general burden in Europe from the inclusive definition of AYAs. The European estimates were only calculated from countries with the indicator data available. For a few cancers and indicators (e.g. thyroid and nasopharyngeal cancers), the mortality ASR was based on a small number of countries and therefore, the European ASR must be interpreted with caution. Finally, we only analysed tumours available in the GCO. GCO classifies tumours by ICD, and therefore relevant AYA tumours, such as the heterogeneous group of sarcomas, could not be included in this study.

Finally, variations in data quality and data comparability can vitiate comparison of cancer incidence and survival between populations. CRs included in this paper had good and comparable data quality indicators. The proportion of microscopically verified (MV) cases was $>$90% in most CRs considered; few exceptions with MV% between 80% and 90% were Bulgaria, Croatia, Czech Republic and Italy. The proportion of 'death certificate only' (DCO) cases was very low with few exceptions (e.g. Austria, Bulgaria, Germany and Croatia) for which the % was anyway below 10%. CRs of Belgium, France and the Netherlands do not register DCO cases.

Our study has considerable strengths, such as population-based data, the breadth of coverage and duration of data available. This is the first study providing a comprehensive overview of the burden of cancers in AYAs in different European countries. Our results highlight the future health care needs and requirements for specialised services related to treatment as well as the urgency for preventive initiatives that can mitigate the increasing burden.

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registration fees as invited speaker at international meeting for the presentation of the results from the studies as international PI, receipt of consultancy fee to institution from Ipsen, non-remunerated Co-chair of the Fostering Age inclusive Research (FAIR) trial group of ACCELERATE; non-remunerated member of the Executive Committee of EEC (Euro-Wing Consortium), non-financial interest for leadership role as Chair of the FOSTER Consortium (Fight Osteosarcoma Through European Research) and non-remunerated member of GO-AJA, SFCE, SIOP Europe; FP reports receipt of honoraria for participation in Advisory Board from Roche Diagnostics, receipt of honoraria for providing expert testimony from Ipsen, Merck and non-financial interest for leadership role as Scientific Director of the European School of Oncology; ATo reports receipt of honoraria for participation in Advisory Board from MSD, AstraZeneca, Pfizer, Eli Lilly, receipt of honoraria as invited speaker from Eli Lilly, Novartis and non-remunerated member of AIOM; KS reports receipt of honoraria for participation in Advisory Board from Bayer, Novartis, Novo Nordisk, Roche, non-financial interest for leadership role in PanCare, SPOG, SSPHO and non-remunerated member of Board of Directors of SIOP Europe; GM reports receipt of honoraria for participation in Advisory Board from BMS, Janssen, Roche, Takeda, and receipt of honoraria as invited speaker from Amgen, AstraZeneca, MSD, Novartis, Pfizer; SB reports receipt of honoraria for participation in Advisory Board from Bayer Healthcare, Boehringer Ingelheim, Eli Lilly, Hofmann La Roche, MAP-Biopharma; non-financial interest as principal investigator of the Bayer's larotrectinib study; and non-remunerated member of the European Musculoskeletal Oncology Society (EMSOS), German Pediatric Oncology Society (GPOH); ES reports receipt of honoraria for participation in Advisory Board from AstraZeneca A.E., AstraZeneca UK Ltd., Gilead Sciences Hellas, Merck, Sharp & Dohme, Pfizer Hellas, receipt of honoraria as invited speaker from Amgen Hellas, Pfizer Hellas, receipt of honoraria for providing expert testimony from Ipsen and non-remunerated member of Board of Directors of Hellenic Oncology Research Group, Hellenic Society of Medical Oncology. All other authors have declared no conflicts of interest.

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