Artigo original

Cancer incidence and survival among adolescents and young adults in Hospital Prof. Doutor Fernando Fonseca (2008-2018)

Incidência e sobrevivência de adolescentes e jovens adultos com cancro no Hospital Prof. Doutor Fernando Fonseca (2008-2018)

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Abstract

Introduction: *The incidence of cancer in younger adults carries a high burden. Our goal is to evaluate the incidence and mortality of cancer diagnosed in our hospital in patients, aged 15-39 years from 2008 to 2018.*

Methods: *We analysed 3 age subgroups. We determined the vital status until 2014 and estimate the 5 years survival.*

Results: *A total of 3692 cancer cases were diagnosed: 70 in the 15–24age-group; 455 in the 25-39age-group and 3168 in the 40-59age-group.*

The 5-year overall survival was 93.3% in the 15–24age-group and 74.5% in the 25-39age-group. Lower incidences over time were observed in the >25 years.

The most frequent tumour was Hodgkin's lymphoma in the 15-24age-group and breast carcinoma in the 25-39age-group.

Conclusion: *Comparing with European population, most frequent tumours are similar, incidence rates are lower and survival in the 15–24age-group is higher.*

Keywords: *Neoplasm; Young Adult; Adolescent; Incidence; Survival.*

Resumo

Introdução: A incidência de cancro em adultos jovens tem sequelas. O nosso objetivo é avaliar a incidência e mortalidade de cancro diagnosticado no nosso hospital em pacientes entre 15 e 39 anos, de 2008 a 2018.

Métodos: Analisámos 3 subgrupos etários. Determinámos o estado vital até 2014 e calculamos a sobrevivência a 5 anos.

Resultados: Foram diagnosticados 3692 casos de cancro: 70 com 15-24 anos; 455 com 25-39 anos e 3168 com 40-59 anos. A sobrevivência global aos 5 anos foi de 93,3% no grupo de 15-24 anos e 74,5% no grupo de 25-39 anos. A incidência foi menor ao longo do tempo no grupo >25 anos.

O tumor mais frequente foi o linfoma de Hodgkin no grupo de 15-24 anos e o cancro da mama no de 25-39 anos.

Conclusão: Comparando com populações europeias, os tumores mais frequentes foram semelhantes, obtivemos taxas de incidência mais baixas e maior sobrevivência no grupo de 15-24 anos.

Palavras-chave: Neoplasma; Jovem Adulto; Adolescente; Incidência; Sobrevivência.

Introduction

Cancer research traditionally neglects cancer in adolescents and young adults (AYA)[1], although this trend is changing in the recent years, proven by an increase in the PubMed publications about "cancer in adolescents and young adults"[2].

Despite the lower incidence at these younger age groups, the natural history of these tumours is a bridge between the paediatric and the adult oncology. This spectrum of diseases affects people with a longer-life expectancy, who by their essence are the main drive of any society, consequently affecting a wide range of familial and socio-economic groups. Thus, the importance of investigating the incidence of cancer in these individuals and the implications it entails.[1,3,4]

While there is no consensus on the chronological definition of AYA, the age range set to be encompassed must be appropriate to the physiological, biological, psychological, social, economic, and epidemiological context.[5] According to the Adolescent and Young Adult Oncology Progress Review Group the age defining AYA, ranges from 15 to 39 years. Behind this rationale is the proximity between their biological and physiological maturity, including individuals having passed puberty, but not yet experienced the effects of hormonal decline, with deterioration of the immune response and organ dysfunction associated with chronic health conditions. From a psychosocial perspective, these patients feel more relatable with younger patients than with middle-aged to older patients.[6] Previous studies in Europe opt for the 15-24 age range,[7–9] while worldwide are stated ranges from a 15/20 to 39.[1,3,6]

We set our goal to evaluate the progression of the incidence and mortality of malignant neoplasms diagnosed in our hospital among those aged from 15 to 39 years, during a 10-year period. The collected data was gathered from our hospital's Cancer Registry (ROHFF).

Methods

We conducted a retrospective unicentric study to characterize the malignant neoplasms diagnosed among patients, aged 15-39 years, in a large, public, general hospital. We collected from the ROHFF the data regarding the diagnoses of first primary tumours, among subjects aged 15–59 years, from 1 January 2008 to 31 December 2018. The data included age, sex, residence, diagnosis date, primary tumour topography and morphology, stage at diagnosis, vital status, death date and last contact date.

Eligibility criteria were as follows: diagnosis of cancer (morphology codes with behaviour code 3) according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 2019 version); residents in Portugal (our hospital have cooperation protocols with some Portuguese-speaking African countries for diagnosis and treatment of cancer patients thus we excluded non-residents because they do not represent the real incidence in our geographic area).

We opted to define AYA from 15-39 years following the recommendation of the Adolescent and Young Adult Oncology Progress Review Group. Our definition of AYA was broad, so we decided to divide into subgroups that were more similar between them and were comparable with previous studies. The cases were separated into 3 age groups: 15-24, 25-39, and 40-59 age-groups. The 40-59 age group was added to compare the incidence in that age group because although the biology behind is slightly different, the familial and socio-economic impact is still comparable with the younger groups.

The cases were grouped by specific topography and morphology code combinations according to AYA Site Recode/WHO 2008 Definition- adapted classification scheme for tumours of adolescents and young adults. This reclassification was developed to better define the major cancer sites that affect individuals between 15 and 39 years of age. It is intended to facilitate the reporting of cancer incidence rates and trends.[10]

Age-specific incidence rates per 100.000 population were calculated based on the estimated population from the hospital reference area, obtained from the Portuguese National Institute of Statistics.[11]

The annual average percent change (AAPC) in the crude incidence rates for age groups and by sex and diagnostic group (only diagnostic groups with cases diagnosed in every year were evaluated) was assessed through Joinpoint Regression (Joinpoint Trend Analysis Software[12]), using log-linear models.

The following analyses were only performed in the 15-24 and 25-39 age-groups.

Median follow-up was calculated with the Reverse Kaplan-Meier method.

The survival of cases diagnosed from 2008 to 2014 was estimated using the Kaplan–Meier method, and Breslow test was used to compare differences between sexes. Follow-up for vital status was determined through record linkage to the National Health System Database and from the information reported by the data sources of the registry. Since data by cancer-specific mortality was not available, the endpoint of interest was death by any cause. In cases that could not be linked to the National Health System database, the last contact date was registered. The observed survival in each age group was calculated using the Kaplan-Meier estimation methods.

Results

We retrieved 4014 cases from the ROHFF, 217 were excluded for not having a malignancy diagnosis and 104 were excluded because they were non-residents in Portugal.

In the Hospital Prof. Doutor Fernando Fonseca were diagnosed 3693 (1840 males/1853 females) cases of malignant tumours, between 2008 and 2018, from 15 to 59 years old. The

distribution by age group was 70 (40 males/30 females) in the 15–24 years group, 455 (159 males/296 females) in the 25-39 years and 3168 (1641 males/1527 females) in the 40-59 years.

The absolute frequency by year and sex is shown in **Fig. 1**. The average incidence rates per 100000 individuals, in the 15-24, 25-39 and 40-59 were respectively 10.47, 35.38 and 1764.60. Incidence rates in each year by age groups are shown in **Fig. 2**.

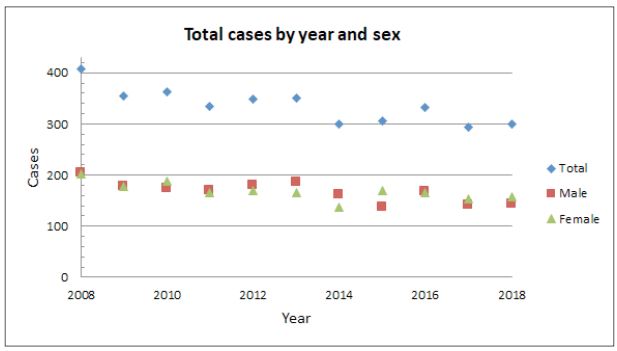


Figure 1. The absolute frequency of cases of cancer by year and sex all (age groups).

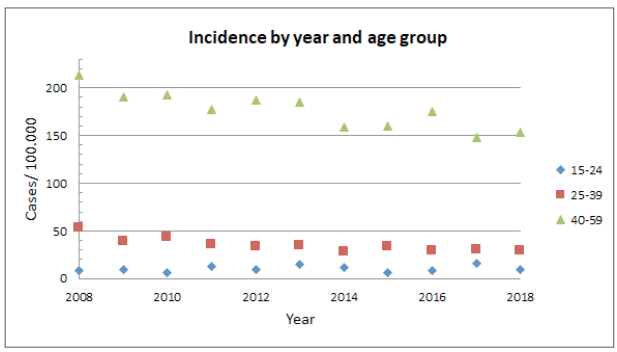


Figure 2. The incidence rates per 100000 individuals, total and by diagnostic groups.

The absolute frequency, distribution, and survival of the tumours by age groups are shown in **Table I**. The most frequent tumours were distinct by age groups: Hodgkin lymphoma, thyroid carcinoma, and testis malignant neoplasm were the most frequent in the 15-24 years age group. Cancer of breast, cervix uteri, and thyroid were the most frequent in the 25-39 years age group. Malignant tumour of breast, respiratory, intrathoracic organs and colon-rectum were the most frequent in the 40-59 years age group. The three most frequent tumours by age and sex are shown in **Fig. 3**.

The trends in incidence rates were better described by a regression model with no joinpoints in both age groups. From 2008 to 2018, the incidence rate for all cancers combined did not change meaningfully among the 15-24 years age group (AAPC: 2.7%; 95% CI: -4.4/9.9), while it decreased significantly among 25-39 (AAPC: -5.4%; 95% CI -7.6/-3.2) and 40-59 years age group (AAPC: -3.0%; 95% CI: -4.1/-1.8). The annual average percent change (AAPC) in the crude incidence rates

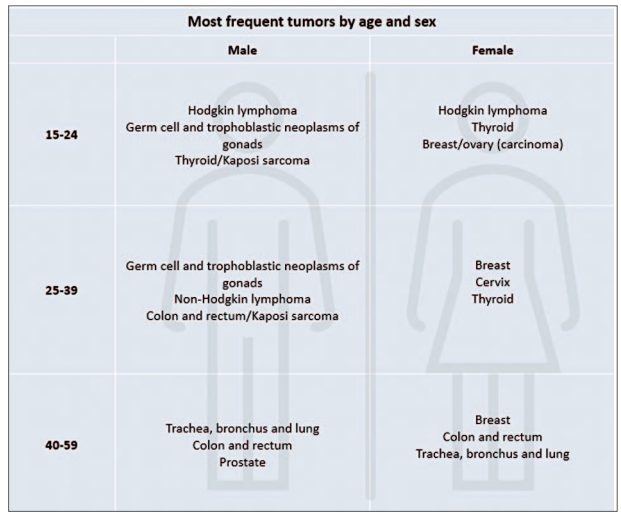
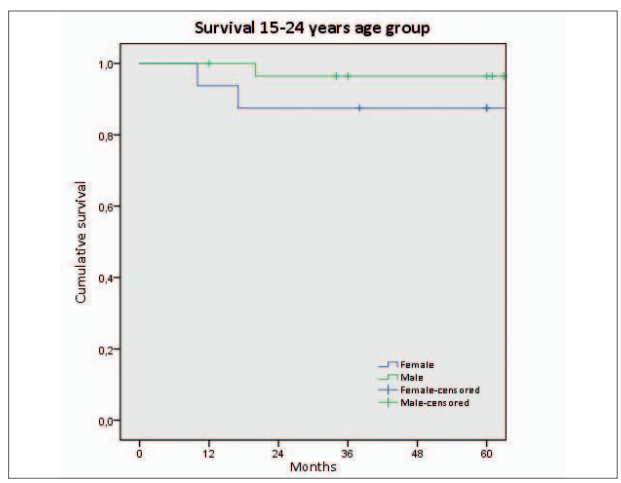


Figure 3. The most frequent tumours by age and sex.

for diagnostic groups are shown in **table II**. Only neoplasms occurring every year are represented.



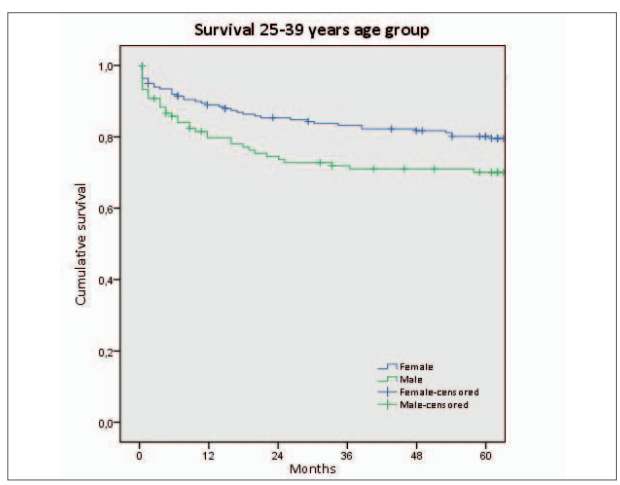


Figure 4. 5-years survival for all cancers combined in the 15-24(a) and 25-39(b) years age group by sex.

Table I. Frequency and distribution by sex of malignant tumors (2008-2018)

Diagnostic Group	15-24			25-39			40-59		
	N (%)	Sex		N (%)	Sex		N (%)	Sex	
		Female	Male		Female	Male		Female	Male
Leukemias									
Acute lymphoid leukemia	_	_	_	3(0,66)	0	3		_	_
Acute myeloid leukemia	1(1,4)	0	1	2(0,44)	0	2	7(0,22)	5	2
Chronic myeloid leukemia	1(1,4)	1	0	1(0,22)	0	1	3(0,09)	2	1
Other and unspecified leukemia	1(1,4)	0	1	2(0,44)	1	1	15(0,47)	6	9
Lymphomas									
Non-Hodgkin lymphoma	4(5,7)	2	2	30(6,61)	12	18	103(3,25)	35	68
Hodgkin lymphoma	21(30)	9	12	20(4,41)	11	9	26(0,82)	4	22
CNS and Other Intracranial and Intraspinal Neoplasms									
Specified low-grade astrocytic tumors	_	_	_	1(0,22)	0	1		_	_
Glioblastoma and anaplastic astrocytoma	_	_	_	2(0,44)	0	2	6(0,19)	1	5
Astrocytoma, NOS	_	_	_	1(0,22)	0	1		_	_
Other glioma	_	_	_	2(0,44)	1	1	3(0,09)	1	2
Ependymoma	_	_	_	1(0,22)	1	0	_	_	_
Medulloblastoma	_	_	_	1(0,22)	0	1	_	_	_
Other specified intracranial and intraspinal neoplasms	1(1,42)	0	1	_	_	_	4(0,13)	1	3
Unspecified intracranial and intraspinal neoplasms	1(1,42)	0	1	_	_	_	1(0,03)	1	0
Osseous & Chondromatous Neoplasms									
Chondrosarcoma	_	_	_	_	_	_	1(0,03)	0	1
Ewing tumour	_	_	_	_	_	_	1(0,03)	1	0
Soft Tissue Sarcomas									
Fibromatous neoplasms	1(1,42)	1	0	2(0,44)	2	0	5(0,16)	1	4
Rhabdomyosarcoma	_	_	_	_	_	_	1(0,03)	0	1
Specified soft tissue sarcoma	_	_	_	3(0,66)	2	1	23(0,73)	16	7
Kaposi sarcoma	3(4,29)	0	3	26(5,73)	13	13	29(0,92)	8	21
Unspecified soft tissue sarcoma	_	_	_	4(0,88)	2	2	8(0,25)	5	3
Germ Cell and Trophoblastic Neoplasms									
Germ cell and trophoblastic neoplasms of gonads	9(12,86)	1	8	32(7,05)	1	31	8(0,25)	2	6
Melanoma and Skin Carcinomas									
Melanoma	_	_	_	6(1,32)	4	2	19(0,6)	11	8
Skin carcinomas	_	_	_	12(2,64)	6	6	54(1,7)	25	29
Carcinomas									
Thyroid	10(14,29)	7	3	42(9,25)	34	8	123(3,88)	107	16
Nasopharyngeal	1(1,42)	0	1	1(0,22)	1	0	20(0,63)	6	14
Other sites in lip, oral cavity and pharynx	1(1,42)	0	1	5(1,1)	2	3	128(4,04)	15	113
Nasal cavity, mid ear, sinuses, larynx other head/neck	1(1,42)	0	1	2(0,44)	0	2	74(2,34)	4	70
Trachea, bronchus and lung	_	_	_	13(2,86)	6	7	410(12,94)	133	277
Breast	3(4,29)	3	0	108(23,79)	108	0	542(17,1)	539	3
Kidney	_	_	_	13(2,86)	3	10	104(3,28)	33	71
Bladder	1(1,42)	0	1	5(1,1)	3	2	80(2,52)	16	64
Gonads	4(0,57)	3	1	5(1,1)	3	2	42(1,33)	42	0
Cervix	1(1,42)	1	0	46(10,13)	46	0	131(4,13)	131	0
Uterus*	_	_	_	2(0,44)	2	0	59(1,86)	59	0
Other and ill-define sites genitourinary	_	_	_	1(0,22)	1	0	240(7,57)	11	229
Colon and rectum	2(2,86)	1	1	27(5,95)	14	13	431(13,6)	169	262
Stomach	1(1,42)	0	1	17(3,74)	8	9	151(4,76)	45	106
Liver and intrahepatic bile ducts	_	_	_	2(0,44)	1	1	44(1,39)	5	39
Pancreas	2(2,86)	1	1	5(1,1)	2	3	75(2,37)	25	50
Other and ill-define sites gastrointestinal tract	_	_	_	2(0,44)	1	1	95(3)	21	74
Carcinoma other and ill-define sites									
Adrenocortical carcinoma	_	_	_	2(0,44)	1	1	2(0,06)	1	1
Carcinoma other and ill-defined sites, NOS	_	_	_	_	_	_	51(1,61)	18	33
Other specified gonadal tumours	_	_	_	_	_	_	2(0,06)	2	0
Myeloma, mast cell, miscellaneous lymphoreticular	_	_	_	4(0,88)	3	1	33(1,04)	11	22
Unspecified Malignant Neoplasms	_	_	_	1(0,22)	0	1	14(0,44)	9	5
Total	**70(100)**	**30**	**40**	**454(100)**	**295**	**159**	**3168(100)**	**1527**	**1641**

* In the original AYA Site Recode/WHO 2008 Definition the uterus and cervix tumors are in the same code, I choose to separate because of the increased incidence of endometrial cancer in the 40-59 age group.

Table II. Annual average percent change 2008-2018 (*P*-value)			
Diagnostic Group	**15-24**	**25-39**	**40-59**
Non-Hodgkin lymphoma	_	_	-7.0(0,1)
Germ cell and trophoblastic neoplasms of gonads	_	5.1(0,5)	_
Carcinoma			
Thyroid	_	-4.9(0,3)	-3.8(0,1)
Other sites in lip, oral cavity and pharynx	_	_	0(1)
Nasal cavity, mid-ear, sinuses, larynx other ill-def. head/neck	_	_	-11.6(0,0) *
Trachea, bronchus and lung	_	_	05(0,3)
Breast	_	-6(0.0) *	-5.0 (0,0) *
Kidney	_	_	-0,3(0,9)
Bladder	_	_	-0,8(0,9)
Gonads	_	_	-4,5(0,3)
Cervix	_	_	-4,2(0,1)
Trachea, bronchus and lung	_	_	-7,5(0,1)
Other genitourinary ill-defined sites:	_	_	5,4(0,0) *
Carcinoma of colon and rectum	_	_	-4,8(0,7)
Carcinoma of stomach	_	_	-0,3(0,9)
Carcinoma of liver and intrahepatic bile ducts	_	_	-14(0,0) *
Carcinoma of pancreas	_	_	-2,2(0,6)
Carcinoma other and ill-defined sites of gastrointestinal tract	_	_	-0,8(0,8)
Carcinoma of other and ill-defined sites, NOS	_	_	-5,7(0,3)
Total	**2,7(0,4)**	**-5,4(0,0) ***	**-3(0,0) ***

* Indicates that the AAPC is significantly different from zero at the alpha=0.05 level.

Table III. Five-year observed Survival (2008-2014)						
	15-24			**25-39**		
Site Group	**N Total**	**N Deaths**	**Survival (%)**	**N Total**	**N Deaths**	**Survival (%)**
Leukemias						
Acute lymphoid leukemia	_	_	_	2	0	100,00%
Acute myeloid leukemia	1	0	100,00%	2	1	50,00%
Chronic myeloid leukemia	1	0	100,00%	1	1	0,00%
Other and unspecified leukemia	1	0	100,00%	1	0	100,00%
Lymphomas						
Non-Hodgkin lymphoma	4	1	75,00%	24	11	54,17%
Hodgkin lymphoma	16	1	93,75%	15	1	93,33%
CNS and Other Intracranial and Intraspinal Neoplasms (all behaviors)						
Specified low-grade astrocytic tumors	_	_	_	1	1	0,00%
Glioblastoma and anaplastic astrocytoma	_	_	_	2	2	0,00%
Astrocytoma: NOS	_	_	_	1	1	0,00%
Other glioma	_	_	_	2	0	100,00%
Ependymoma	_	_	_	1	0	100,00%
Medulloblastoma	_	_	_	1	0	100,00%
Other specified intracranial and intraspinal neoplasms	1	0	100,00%			_
Unspecified malignant intracranial and intraspinal neoplasms	1	0	100,00%			_
Soft Tissue Sarcomas						
Fibromatous neoplasms	_	_	_	2	0	100,00%
Specified soft tissue sarcoma	_	_	_	2	1	50,00%
Kaposi sarcoma	1	0	100,00%	21	11	47,62%
Unspecified soft tissue sarcoma	_	_	_	3	1	66,67%
Germ Cell and Trophoblastic Neoplasms						
Germ cell and trophoblastic neoplasms of gonads	2	0	100,00%	21	0	100,00%
Melanoma and Skin Carcinomas						
Melanoma	_	_	_	5	0	100,00%
Skin carcinomas	_	_	_	7	1	85,71%
Carcinomas						
Thyroid	7	0	100,00%	29	2	93,10%
Nasopharyngeal	1	0	100,00%	1	0	100,00%

Table III. Five-year observed Survival (2008-2014)

	15-24			25-39		
Site Group	**N Total**	**N Deaths**	**Survival (%)**	**N Total**	**N Deaths**	**Survival (%)**
Other sites in lip, oral cavity and pharynx	1	0	100,00%	3	0	100,00%
Nasal cavity, mid-ear, sinuses, larynx other head/neck	_	_	_	2	1	50,00%
Trachea, bronchus and lung	_	_	_	8	6	25,00%
Breast	1	1	0,00%	79	12	84,81%
Kidney	_	_	_	12	2	83,33%
Bladder	1	0	100,00%	5	0	100,00%
Gonads	4	0	100,00%	3	1	66,67%
Cervix	_	_	_	28	7	73,33%
Uterus*	_	_	_	2	1	50,00%
Other and ill-defined genitourinary sites:	_	_	_	1	0	100,00%
Colon and rectum	1	0	100,00%	20	8	60,00%
Stomach	1	0	100,00%	9	7	22,22%
Liver and intrahepatic bile ducts	_	_	_	1	1	0,00%
Pancreas	_	_	_	3	3	0,00%
Other and ill-def. sites gastrointestinal tract	_	_	_	1	0	100,00%
Adrenocortical	_	_	_	1	0	100,00%
Carcinoma other and ill-defined sites						
Myeloma, mast cell, miscellaneous lymphoreticular	_	_	_	3	0	100,00%
Unspecified Malignant Neoplasms	_	_	_	1	0	100,00%
Total	**45**	**3**	**93,33%**	**326**	**83**	**74,54%**

* In the original AYA Site Recode/WHO 2008 Definition the uterus and cervix tumors have the same code; I choose to separate because of the increased incidence of endometrial cancer in the 40-59 age group.

The median follow-up time (2008-2014) was 74.9 months in the 15–24 age-group and 76 months in the 25-39 age-group.

The 5-year overall survival (2008-2014) including the 2 groups (15-39 Years) was 76.8% and 78.2% in females and 74.8% in males. The overall survival in the 15–24 age-group was 93.3%, with no significant differences between males (96.6%) and females (87.5%) **(Fig. 3a)**; in the 25-39 age-group, overall survival was 74.5% with significant differences between males (69.7%) and females (77.5%) ($P = 0.04$) **(Figure 3b)**; survival for each diagnostic group is shown in **table III**.

We also calculated the 5-year overall survival, excluding thyroid carcinoma and Kaposi sarcoma, to correct for overdiagnosis of thyroid cancer and influence of HIV/AIDS in Kaposi sarcoma.[3] In the 15-24 age group the overall survival was 91.9%, 81.8% in females and 96.2% in males; in the 25-39 age group the overall survival was 74.6% with significant differences between males (67.6%) and females 78.9% ($P = 0.01$).

Discussion

The burden of cancer varies by age, sex, and group of tumours.

The changes in incidence in the 10 years evaluated in the 15-24 age group were not meaningful; the incidence is lower than studies from the north of Portugal[7], France[8] and United Kingdom (UK).[13] Cancer in AYAs in the 25-39 age group showed a trend of decreasing incidence, contrasting with previous studies from Korea[14] and the world[4], although time and age group differs. Other limitation when comparing with other studies is that most of the study populations are in the 1990 decade and the 2000 decade,[7-9,14,15] while the most recent studies focus in one specific year.[1,4] The incidence in this age group comparing with the world was lower (35.38 *vs* 43.3).[1]

The most frequent tumours diagnosed in the 15-24 age group were Hodgkin lymphoma, thyroid carcinoma, and germ cell tumours. The same result was reported in the North of Portugal and in other studies.[7] In the 25-39 age group, the most frequent malignant tumours were breast, cervix, and thyroid carcinoma. This pattern is the same as in countries with a high human development index.[1,16] Those cancers arise more or are exclusive of females justifying why women are more affected than men in this age group, contrasting with the other age groups, where men are more affected. This cancers in young patients (15-39) differ, except breast for woman, from the pattern that is observed in cancers in the general population in Portugal,[17] Europe and globally, being most frequent lung, colorectum, breast (women) and prostate (men)[18], a pattern that is also observed in the population in the 40-59 years in our study.

In the 15-24 age group, our hospital has higher survival rates comparing with previous studies from Portugal (1997-2006)7, France (2000-2004)[8] and UK (2001-2005)[13]. This change could represent an improvement in healthcare support, early diagnosis and in treatment, for example in leukaemia[4,19] but it also could be a consequence of the lower number of cases in this age group presented to our hospital. There is a lack of studies that evaluate the 5-year survival in the 25-39 age group more recently, so the following comparisons are not the most appropriate. When comparing the overall 5-year survival (2008-2014) in 15-39 years (76.8%) with other European countries (75%) and the United States of America (USA) (≈78%) in 2006[20],

our hospital has a better performance than other European countries and worse than the USA. Although the incidence is higher in females, males have a lower survival. The differences in survival between sexes are also documented in other studies. Comparing with the USA, the survival (corrected for thyroid tumours and Kaposi sarcoma) in 2007 is lower in males (≈75% vs 73.9) and identical in females (≈80% *vs* 79.7).[4]

The main limitation of this study is that it only represents the reality of the patients diagnosed in our hospital. Not all the population in the region reaches for our hospital, some go to private or for another region for diagnosis and treatment. Also, our hospital does not have all the specialties, for example neurosurgery, dermatology, haematology, so some diseases may be underrepresented. Thus, a regional or national study will give a better understanding of the evolution of cancer in young adults.

The major findings presented by this study were that, while the incidence of cancer in young adults is decreasing, the mortality is still significant. Although the incidence in adolescents and young adults is lower than in older ages, the mortality and the loss of healthy life years could not be ignored.

This study could be important to strengthen prevention strategies and therapeutic approaches in our hospital, and ramp-up future studies in this age group. One of our future goals is to evaluate the survival for a longer time and evaluate the risk factors in this population including comorbidities, genetic and behavioural risk factors.

The high incidence of breast cancer diagnosed before the age of general population screening in Portugal, 50 years old[21], should be an alert and it is important to verify in other studies if these women have some identifiable risk factors that could motivate an earlier screening.

An interesting future point of study could be the evolution of cervical cancer with vaccination for HPV, which was introduced in the national program in 2008. In this study it was not yet possible to see a significant reduction.

Younger patients have a higher-than-expected risk of having a pathogenic or likely pathogenic variants in cancer predisposition genes and so might benefit from genetic testing, irrespective of tumour type. This is especially important given the risk of second primary cancers, the need for an appropriate long-term surveillance, the potential reproductive implications, including prenatal diagnosis and assisted reproduction, the testing of at-risk family members, and potentially provides novel biomarkers and therapeutic targets.[22,23]

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Contributorship Statement / Declaração de Contribuição

CP: conception, acquisition, analysis and interpretation of data; writing the manuscript, critical review and final approval.

NI: data collection, critical review and final approval.

RT: idealização, critical review and final approval.

JT, AP and FP: critical review and final approval.

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