2 The Epidemiology of Malignant Germ Cell Tumors: The EUROCARE Study

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2.1 Introduction

Germ cell tumors (GCTs) comprise a heterogeneous group of tumors in terms of histology, age at diagnosis, anatomical site and prognosis. Here we describe the epidemiology of GCT on the basis of data from European population-based cancer registries (CRs) analysed in the framework of the EUROCARE (European Cancer Registry-based study on survival and care of cancer patients) project, which has monitored cancer patients' survival since 1978 (www.eurocare.it).

2.2 Materials

We have chosen to use the EUROCARE data because, even if CRs collect data on the basis of the International Classification of Diseases for Oncology (ICD-O3) [1] which includes morphology and topography, cancer statistics are usually provided for broad cancer categories, based on the anatomic site of the malignancies. Thus, the current statistics do not provide specific information of germ cell tumors. We have used the morphology and topography data collected by different CRs and analysed by EUROCARE to describe the epidemiology of GCT in Europe. EUROCARE includes only overt malignant tumors, while in situ tumors are requested only for screening-target cancers (breast, cervix, colon-rectum and skin melanoma) and benign tumors are collected only for central nervous system and urinary bladder**.** The International Agency for Research on Cancer (IARC) provides, for selected cancers, the age-standardised incidence rates of microscopically verified cases by histological type and by gender in Cancer Incidence in 5 Continents (CI5X) [2]. Since information on GCT was only available for testis and ovary, in this chapter, we have used CI5X [2] data to analyse testicular and ovarian GCT outside Europe.

EUROCARE is the widest collaborative research project on cancer survival attempted in Europe. The project started in 1989, and the fifth edition, EUROCARE-5, includes data on more than 21 million cancer diagnoses provided by 116 CRs in 30 European countries (www.eurocare.it). The data analysed in this chapter are from EUROCARE-5 and consequently included only malignant tumors. CRs cover the whole national population in European countries such as Austria, Bulgaria, Croatia, Czech Republic, Estonia, Ireland, Latvia, Lithuania, Malta, Finland, Iceland, Norway, Sweden, Slovakia, Slovenia, the Netherlands and the UK, while in

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others CRs cover only one or several regions [3]. In 2000–2007 (the study period of EUROCARE-5), 54,000 GCTs were registered in the countries included in the incident analyses (Table 2.1). Table 2.1 shows the number of GCT cases contributed by the different countries. Please note that the differences by country might be due to the different CR coverage (national vs regional) and to the different incidence years that CR have contributed. Not all included the full period 2000–2007.

Table 2.1 Cancer registration coverage in EUROCARE-5 and the number of germ cell tumor cases registered in the countries included to the incident analyses

	Proportion of population covered by cancer registries included in EUROCARE-5 (%)[a]	Number of germ cell tumor cases registered in 2000–2007
Austria	100	2.610
Belgium (Flanders)	58	1.215
Bulgaria	100	1.457
Croatia	100	900
Czech Republic	100	3.491
Estonia	100	190
Finland	100	944
France	23	1.213
Germany	23	6.950
Iceland	100	79
Ireland	100	1.210
Italy	35	3.450
Latvia	100	267
Lithuania	100	268
Malta	100	76
Norway	100	2.185
Poland	13	904
Portugal	76	698
Slovakia	100	1.683
Slovenia	100	812
Spain	17	778
Switzerland	30	923
The Netherlands	100	5.078
UK	100	16.626
Total		54.007

[a]Cancer registration is continuously improving since EUROCARE-5

GCTs include different histological subtypes, internationally grouped as seminomas and non-seminomas. Throughout this chapter, the generic term seminoma and non-seminoma will be used. Seminoma, dysgerminoma and germinoma are histopathologic equivalent terms for a neoplasm of identical morphology in testis, ovary and extragonadal locations. Seminoma includes all seminoma histological types (ICD-O3 codes 9060–9064); non-seminomas in their turn include embryonal carcinoma (ICD-O3 codes 9070, 9072), yolk sac tumor (ICD-O3 code 9071), choriocarcinoma (ICD-O3 codes 9100, 9102), teratoma (ICD-O3 codes 9080,9082,9083), mixed germ cell tumors (ICD-O3 codes 9081,9085,9101), malignant struma ovarii (ICD-O3 code 9090), cystic teratoma with somatic malignant transformation (ICD-O3 code 9084) and other non-seminomatous germ cell tumors (ICD-O3 codes 9065). Spermatocytic tumor, an exclusively testicular neoplasm, is clinically and pathologically distinct from classic seminoma; thus data are provided separately for this specific type.

2.3 Incidence

The crude and age-adjusted (European standard population) incidence rates of GCT in Europe were both equal to 34/1.000.000 with marked differences between male (64/1.000.000) and female (4/1.000.000). In the USA, the incidence rate was 56/1.000.000 in white males contrasting with 3.2/1.000.000 in white females, over a period of more than 30 years from 1973 to 2007 [4]. In the same country, the incidence in black males was much lower (10/1.000.000), due to a lower incidence of seminomas, while no difference was reported between white and black females [4]. More than 90 % of testicular tumors were indeed GCT. Figure 2.1 shows incidence of testicular cancer across different continents in 2012. White males living in Western industrialised countries, particularly in Northern and Western Europe, showed the highest incidence rates of testicular tumors (12/100.000 in Denmark,

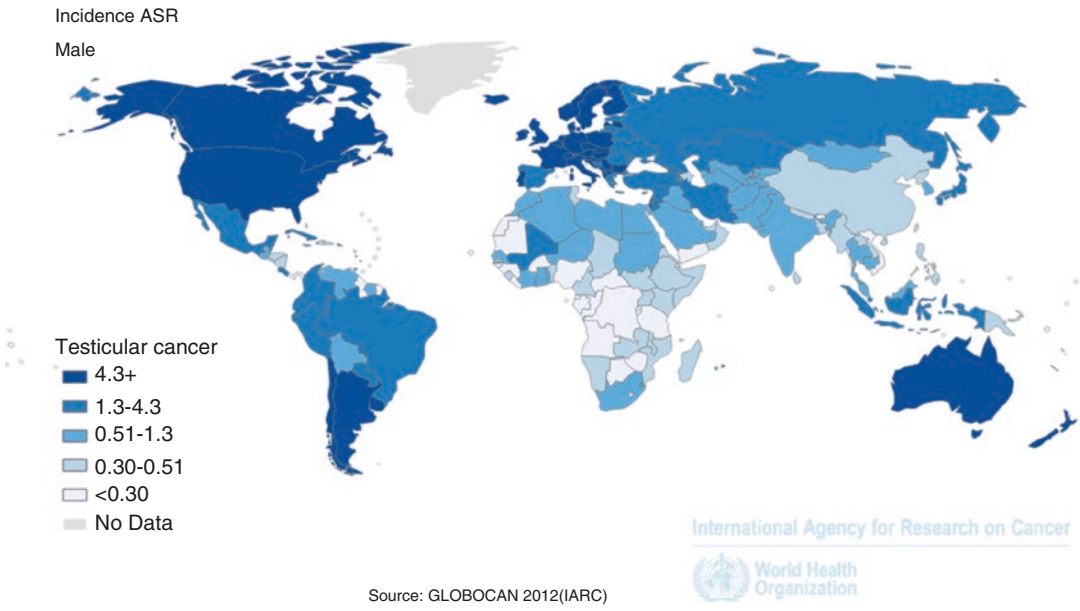


Fig. 2.1 Testicular cancer age-standardised (world) incidence rate per 100.000 (Source http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)

Norway and Switzerland), whereas black males in Africa showed the lowest (<0.5/100.000 in the majority of African countries). In Australia and New Zealand, the incidence was 7/100.000. In North America (USA and Canada), it was 5/100,000; in South and Central America, it was 2/100.000 with differences among countries (Chile 7/100.000, Uruguay 6/100.000, Argentina and Costa Rica 5/100.000, Mexico and Colombia 3/100.000, Brazil 2/100.000 and remaining countries <1/100.000). In Japan, the incidence was 2/100.000; in South, Eastern and Central Asia, it was <1/100.000, being higher in Western Asia, 1.7/100.000, with regional countries (5/100.000 in Israel, 3/100.000 in Georgia and <1 in Oman, Qatar, Iraq and Azerbaijan). In China, the incidence was 0.5/100.000 [5].

Incidence of malignant ovarian GCT was low in all continents: ≤0.9/100.000 in Japan, ≤0.7/100.000 in Central and South America and in China, ≤0.5/100.000 in Australia and Asia, 0.4/100.000 in Canada and <0.4/100.000 in Africa except Malawi where the incidence was 1.3/100.000 [2].

Gonadal GCT (GGCT) Most GCTs arise in the gonads. The incidence in Europe is 33/1.000.000 being substantially higher in males than in females (62/1.000.000 vs 2.5/1.000.000, respectively). Histologic differences are observed between both genders: in males, seminomas are more common than non-seminomas, contrary to women who have more non-seminomas than seminomas (Table 2.2). In males, non-seminomas are mixed germ cell tumors, embryonal carcinoma and teratoma, while in females they are (immature) teratomas and yolk sac tumors (Table 2.2). In males, spermatocytic tumor is very unusual (Table 2.2).

Testicular GCTs have an early incidence peak in the age group 0–4 years followed by a second peak in adolescents and young adults (15–19 and 25–29 and 30–34 years) (Fig. 2.2). The first peak is due to non-seminomas (incidence 1.5/1.000.000 vs 0.07/1.000.000 of seminomas) and mainly due to yolk sac tumour and teratoma, which have an incidence of 1/1.000.000 and 0.3/1.000.000, respectively.

Non-seminomas are more common than seminomas until the age of 30 years; however, the histologic types of those between 15 and 30 years

Table 2.2 (EUROCARE) Gonadal germ cell tumors incidence rate per million, in Europe by histological type, and sex (age adjusted) with 95 % confidence interval (CI)

	Male			Female		
	Rate	95 % CI		Rate	95 % CI	
Germ cell tumors	62.1	61.6	62.7	2.5	2.4	2.7
Seminomas	**36.9**	36.4	37.3	**0.9**	0.8	1.0
Spermatocytic tumor	**0.6**	0.6	0.7	–	–	–
Non-seminomas	**25.3**	24.9	25.6	**1.7**	1.6	1.8
Embryonal carcinoma	**6.8**	6.7	7.0	0.1	0.0	0.1
Yolk sac tumor	1.3	1.2	1.3	**0.4**	0.4	0.5
Choriocarcinoma	0.4	0.4	0.5	>0.1	0.0	0.1
Teratoma	**5.6**	5.4	5.8	**0.8**	0.7	0.9
Mixed germ cell tumors	**10.6**	10.4	10.9	0.2	0.2	0.2
Struma ovarii, malignant	0.0	0.0	0.0	0.1	0.0	0.1
Cystic teratoma with somatic malignant transformation	0.0	0.0	0.0	0.1	0.1	0.2

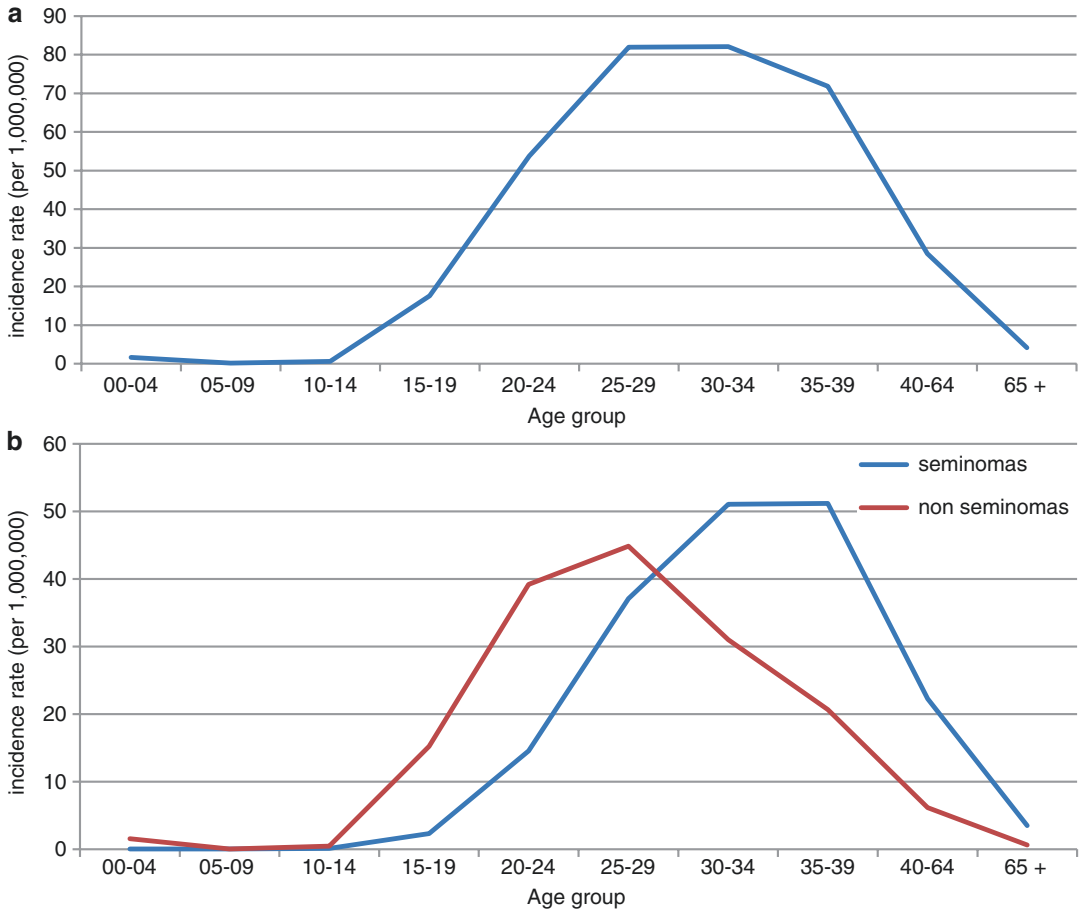


Fig. 2.2 (EUROCARE) Testicular germ cell tumor incidence per 1.000.000 by age group overall (**a**) and by age group and histology (**b**)

are mainly embryonal carcinoma and mixed germ cell tumors and only to a lower extent teratoma and yolk sac tumor.

After the age of 30, seminomas are predominant. Overall, seminomas presented an incidence peak 10 years later than non-seminomas (Fig. 2.2).

Ovarian GCTs have a small peak in children under 5 years and a clear peak in the 15–19-year age group (Fig. 2.3). These results are coherent with those reported in the USA [4]. Both seminomas and non-seminomas have a peak at 15 to 19 years; non-seminomas are more common than seminomas in almost all age groups and in particular in young females (>25 years) (Fig. 2.3). Yolk sac tumour and teratoma represent the most common histologic types in the 0–4-year age group; teratoma incidence increases with age, and it is the most common type in all age groups as from 5 years old.

Extragonadal Germ Cell Tumors (EGGCTs) Only 4 % of all GCTs were extragonadal and arose mainly in midline locations such as the central nervous system (CNS), the mediastinum and the pelvis. Gonadal GCTs were mainly seminomas (59 %

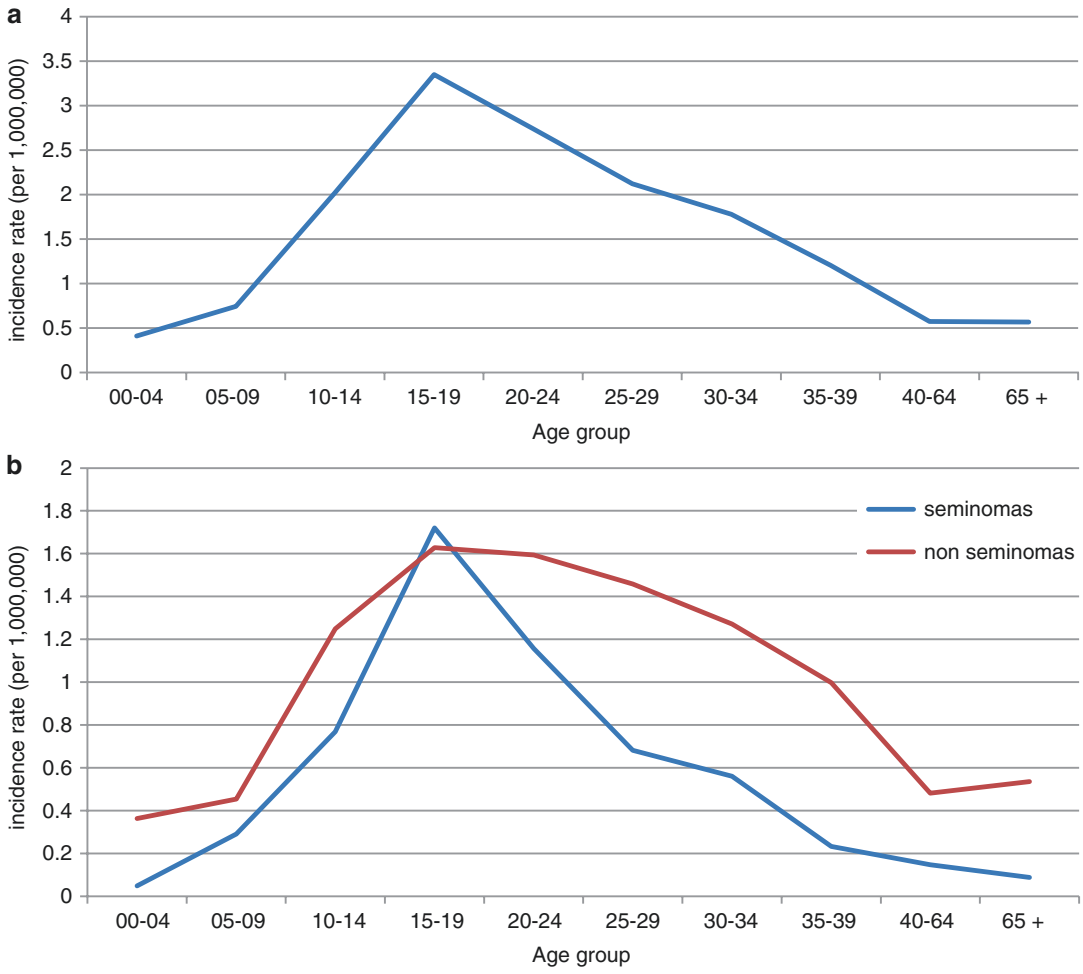


Fig. 2.3 (EUROCARE) Ovarian germ cell tumors incidence per 1.000.000 by age group overall (**a**) and by age group and histologies (**b**)

Table 2.3 (EUROCARE) Incidence rate of germ cell tumors per 1.000.000 by sex (age adjusted), extragonadal sites and histological types with standard error (SE)

	Male						Female					
	All		Seminomas		Non-seminomas		All		Seminomas		Non-seminomas	
	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE
Extragonadal GCTs	1.81	0.05	0.90	0.03	0.91	0.04	1.19	0.04	0.22	0.02	0.97	0.04
Central nervous system	**0.62**	0.03	**0.51**	0.03	0.12	0.01	**0.18**	0.02	**0.14**	0.01	0.03	0.01
Mediastinum and thorax	**0.51**	0.03	**0.21**	0.02	**0.30**	**0.02**	**0.07**	0.01	0.01	> 0.01	**0.05**	0.01
Abdomen and pelvis	**0.38**	0.02	**0.10**	0.01	**0.27**	**0.02**	**0.79**	0.03	0.03	0.01	**0.76**	0.03

seminomas vs 41 % non-seminomas), while 62 % of EGGCT were non-seminomas vs 38 % seminomas. No significant differences in the EGGCT incidence were observed between males and females.

Among males, the most frequent extragonadal sites, in decreasing order, were the CNS, mediastinum and thorax and abdomen and pelvis, while in females locations were the abdomen and pelvis, CNS and mediastinum and thorax. In both sexes, EGGCTs of the brain were mainly seminomas, while in females, non-seminomas were predominant in other sites, especially in the pelvis and abdomen (Table 2.3).

In males, the proportion of EGGCT was lower (3 %) than in females (32 %); in males, the proportion of EGGCT was highest in the 5–14-year age group, while in females, it peaked in the 0–4-year age group (Fig. 2.4).

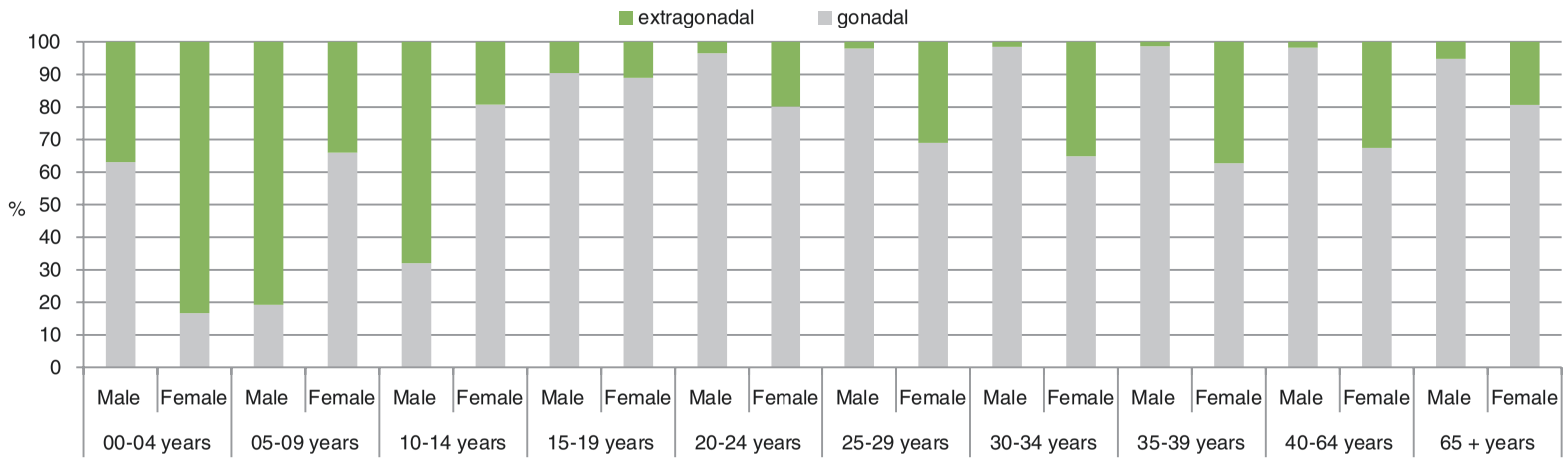
The EGGCT had an early incidence peak in children of less than 5 years; the incidence increased from 5 to 20 years and started to decline again in the older age groups (age older than 30). The first peak was due to GCT of the abdomen and pelvis. The second peak corresponded to GCT of the mediastinum and of the abdomen and pelvis. GCTs of the CNS were the most common in children older than 5 years old and in adolescents from 15 to 19 years (Fig. 2.5). In the extragonadal sites, the age distribution was similar for seminomas and non-seminomas. The age incidence pattern was similar for males and females. Teratoma was the most common non-seminomatous histological type among the extragonadal sites.

2.4 Incidence Trends of Gonadal and Extragonadal Germ Cell Tumors

In the period 1996–2007, there was a statistically significant increase in the incidence of GGCT from 28.6/1.000.000 (95 % confidence interval (CI) 27.2–28.9) to 35.5/ 1.000.000 (95 % CI 34.5–36.5) overall and for both seminomas and non-seminomas (Table 2.4).

Several groups of investigators have reported an increasing incidence of testicular cancer over the last 20 years [4, 6–8]. A recent CR study from the USA revealed a significant increase in the incidence of testicular GCT in both white and black males in the period 1973–2007. Nonetheless, the incidence was much higher among whites. Because of small sample, other ethnic origins were excluded from the study [4]. In Finland, the incidence rates of several histological subtypes of testicular GCT have increased over the last four decades, particularly from 1990 onwards; yet the increasing trend was only seen in men aged 15–44 years [7]. In Germany, the annual incidence rate of testicular GCT increased over the entire period (1998–2008) with seminomas accounting for the majority of the increase [5]. Similar results were reported for the UK for the period 1979–2003 [8]. Our EUROCARE analyses (Table 2.4) are in line with these previous studies.

In comparison with testicular GCT, the overall incidence trends of ovarian GCT differed. In Finland, even if a significant increase in the inci-



Number of cases in male (M) and female (F) by age group

	00-04		05-09		10-14		15-19		20-24		25-29		30-34		35-39		40-64		65 +	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
EGCTs	79	170	42	33	121	45	184	41	202	70	182	102	145	110	114	86	266	142	57	34
GGCTs	135	34	10	64	57	189	1,736	331	5,530	282	8,764	227	9,355	203	8,640	145	14,544	294	1,042	142

EGCTs=extragonadal germ cell tumours

GGCT=gonadal germ cell tumours

Fig. 2.4 (EUROCARE) Age-related variation in the proportion of gonadal and extragonadal germ cell tumors in male and female. *EGCTs* extragonadal germ cell tumors, *GGCTs* gonadal germ cell tumors

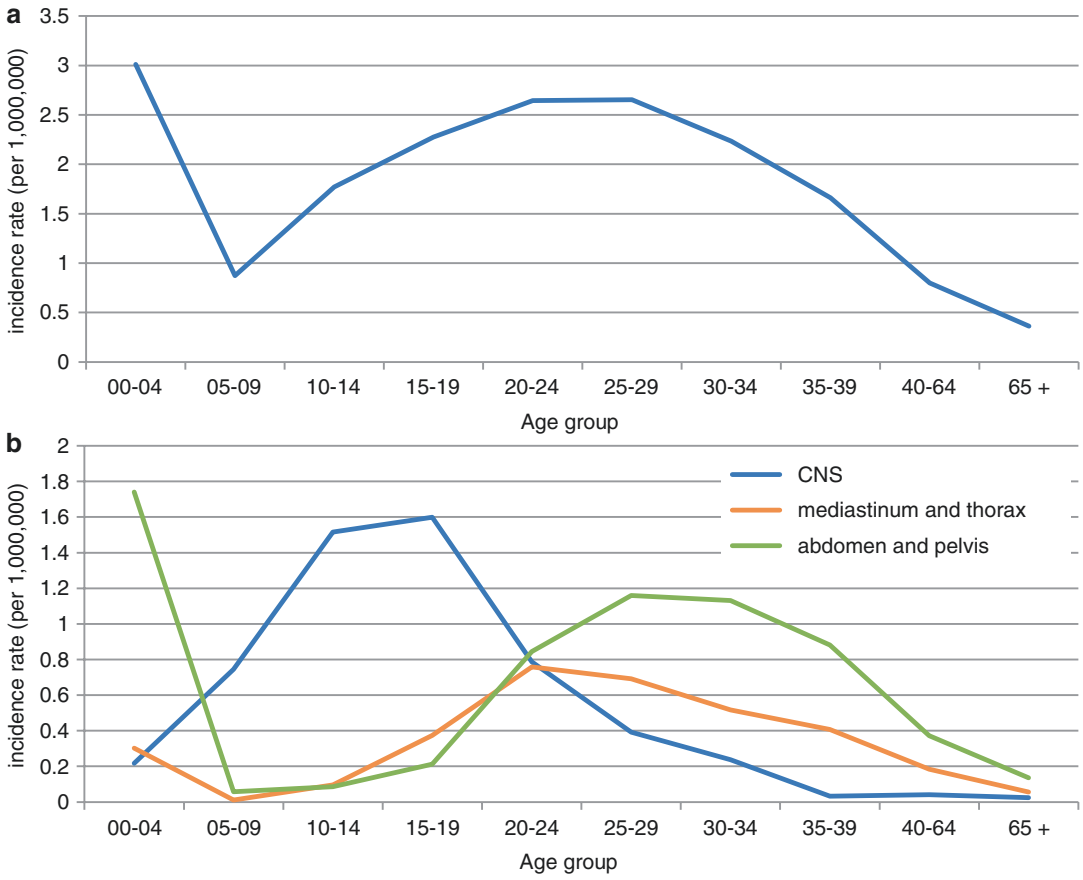


Fig. 2.5 (EUROCARE) Extragonadal germ cell tumors incidence rate (per 1,000,000) by age group overall (**a**) and by age group and extragonadal sites (**b**)

dence of ovarian non-seminomas occurred in the age group of 15–44 years between the first and the last study decade (1969–2008), it remained stable during the last three decades. Similarly, a study on ovarian cancer incidence by histological type carried out in Osaka, Japan, in 1975–1998 [9] reported that the incidence of ovarian GCT also remained stable. In the UK, the incidence of ovarian GCT increased from 1979 to 2003, due to a higher frequency of non-seminomas between the period of time 1980–2000, and in the age group of 10–49 years. However, in the last decade, the incidence has remained stable [8]. In Germany, the incidence of GGCT stayed constant over the period 1998–2008 [6]. In contrast, in the USA, a study covering more than 1200 cases of malignant ovarian GCT concluded that incidence rates have declined over the last 30 years, with the decrease being confined (nearly 30 %) to non-seminomas [10]. Similarly, a more recent study carried out in the USA demonstrated a slight decrease in the incidence of ovarian GCT in both black and white women [4]. We have observed a minor non-significant decline of both seminomas and non-seminomas. Thus, the incidence of ovarian GCT in industrialised countries has not been shown to have increased along with testicular GCT.

Arora et al. [8], taking into account similarities between the shapes of age-incidence curves of GCT and the variation in peak incidence and longitudinal trends by site, hypothesised about a common GCT initiation event in the embryonal period followed by a progression of tumorigenesis conditioned by site-specific events during the foetal and/or postnatal period.

Table 2.4 Gonadal germ cell tumors (GGCTs) per 1.000.000 and age-adjusted incidence (95 % confidence interval), EUROCARE 1996–2007 with average percent change (APC)

	GCTs of testis				GCTs of ovary		
Years	All	Seminomas	Non-seminomas		All	Seminomas	Non-seminomas
1996	26.74 (25.9–27.6)	15.64 (15.0–16.3)	11.09 (10.6–11.6)		1.32 (1.2–1.5)	0.44 (0.3–0.6)	0.88 (0.7–1.0)
1997	27.49 (26.7–28.3)	15.97 (15.4–16.6)	11.52 (11.0–12.1)		1.44 (1.3–1.6)	0.46 (0.4–0.6)	0.98 (0.8–1.2)
1998	28.75 (27.9–29.6)	16.90 (16.3–17.5)	11.85 (11.3–12.4)		1.39 (1.2–1.6)	0.44 (0.3–0.6)	0.96 (0.8–1.1)
1999	29.73 (28.9–30.6)	17.52 (16.9–18.2)	12.21 (11.7–12.8)		1.35 (1.2–1.6)	0.42 (0.3–0.5)	0.93 (0.8–1.1)
2000	29.86 (29.0–30.7)	17.87 (17.2–18.5)	11.99 (11.5–12.6)		1.40 (1.2–1.6)	0.48 (0.4–0.6)	0.92 (0.8–1.1)
2001	30.88 (30.0–31.8)	18.50 (17.8–19.2)	12.39 (11.8–13.0)		1.24 (1.1–1.4)	0.39 (0.3–0.5)	0.84 (0.7–1.0)
2002	30.59 (29.7–31.5)	17.99 (17.3–18.7)	12.60 (12.1–13.2)		1.47 (1.3–1.7)	0.41 (0.3–0.5)	1.05 (0.9–1.2)
2003	31.24 (30.4–32.1)	18.19 (17.5–18.9)	13.05 (12.5–13.6)		1.28 (1.1–1.5)	0.49 (0.4–0.6)	0.80 (0.7–1.0)
2004	32.04 (31.2–32.9)	18.78 (18.1–19.5)	13.25 (12.7–13.8)		1.30 (1.1–1.5)	0.45 (0.4–0.6)	0.85 (0.7–1.0)
2005	33.79 (32.9–34.7)	19.62 (18.9–20.3)	14.17 (13.6–14.8)		1.30 (1.1–1.5)	0.37 (0.3–0.5)	0.92 (0.8–1.1)
2006	34.00 (33.1–34.9)	20.23 (19.5–20.9)	13.77 (13.2–14.4)		1.28 (1.1–1.5)	0.48 (0.4–0.6)	0.81 (0.7–1.0)
2007	34.29 (33.4–35.3)	20.43 (19.7–21.2)	13.86 (13.3–14.5)		1.22 (1.1–1.4)	0.37 (0.3–0.5)	0.85 (0.7–1.0)
APC	2.21[a]	2.28[a]	2.12[a]		–0.9	–0.7	–1.0

[a]The APC is significantly different from zero ($p < 0.05$)

Regarding EGGCT in the period 1996–2007, we found a statistically significant increase in the incidence of GCT of the thymus (APC 2.68) and uterus (an extremely rare location) (APC 1.04). However, the latter result should be considered with caution since uterine mixed mesodermal Mullerian tumors, which are relatively common, are frequently mistaken for teratomas. The incidence was fairly constant for GCT of the brain (APC 0.46), while no changes were observed for GCT of the mediastinum and of retroperitoneum.

Similar results were observed in the UK with an increasing incidence of CNS GCT but not of those of the mediastinum, abdomen and pelvis [8]. In Germany, the incidence of EGGCT in males remained virtually constant, while among females, the incidence of EGGCT declined [6]. Similar results were observed in the USA where the incidence of EGGCT among white males remained fairly constant over the entire time period. The incidence of EGGCT among black males increased from 1973 to 1992 and then reached a plateau before declining in the latest time period; however, rates were based on small numbers, making the interpretation difficult. Among white and black females, incidence rates for EGGCT registered small decreases over time. However, the fluctuation of rates among black females was large, due to small numbers [4].

2.5 Survival

The 5-year relative survival for GCT was very good (93 %), with seminomas having better survival than non-seminomas: 95 % (95%CI 93.5–95.6) and 90 % (95%CI 88–91), respectively.

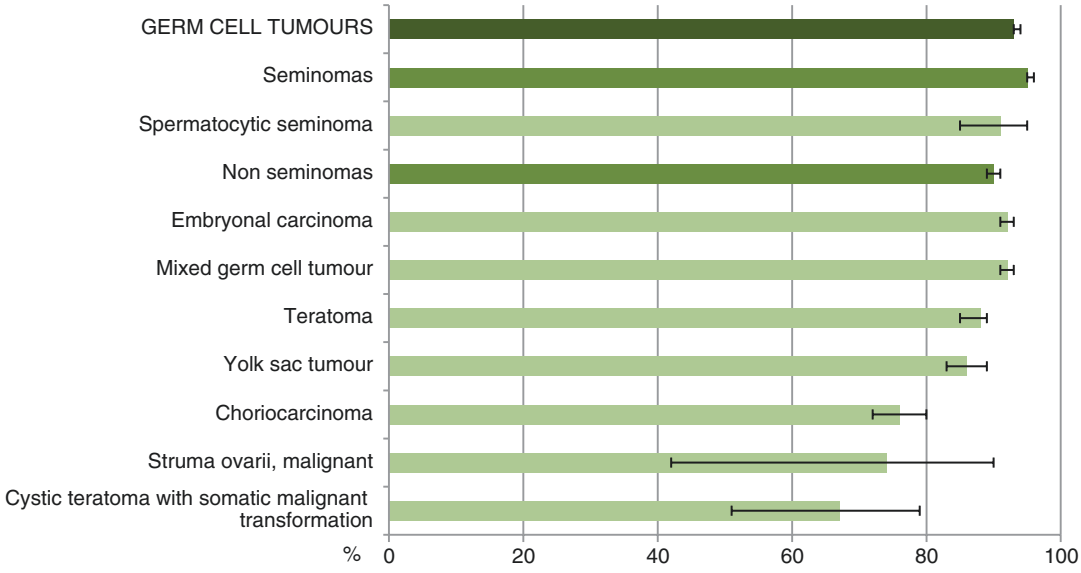


Fig. 2.6 (EUROCARE) Germ cell tumors 5-year relative survival (period 2000–2007) by histotype. Error bars are 95 % confidence interval

Table 2.5 (EUROCARE) Germ cell tumors 5-year relative survival (%) period of diagnosis by site

	Relative survival (%)	95 % CI	
Gonadal germ cell tumors	94.0	93.6	94.3
Testis	94.4	94.0	94.7
Ovary	83.9	81.1	86.3
Extragonadal germ cell tumors	74.2	71.2	76.9
Mediastinum	50.7	43.0	57.9
Retroperitoneum	76.2	64.6	84.4
Brain	81.1	72.0	87.4
Pineal gland	79.9	69.7	86.9
Pituitary gland	96.3	76.2	99.5

Among non-seminomas, the histological type with worst prognosis was mature cystic teratoma with somatic malignant transformation, although the survival estimate must be considered with caution as it was based on a limited number of cases (Fig. 2.6).

Gonadal GCT had better survival than EGGCT: 94 % (95 %CI 93.6–94.3) vs 74 % (95 %CI 71 %–77 %), respectively. Among EGGCTs, survival was good for the brain 81 % (95%CI 72–87), pituitary gland 96 % (95 %CI 76–99), pineal gland 80 % (95 %CI 70–87) and retroperitoneum 76 % (95 %CI 65–84) and lower, 51 % (95 %CI 43–58), for the mediastinum.

Males had better survival than females: 94 % (95 %CI 93.3–94) vs 84 % (95 % 82–86).

Survival decreased with increasing age with the worst survival observed in those older than 40 years for both seminomas and non-seminomas. However, differences were observed between GCT of testis and ovary. For ovarian GCT, survival was 90 % before 40 years of age decreasing to 63 % in the 40–64-year age group and to 29 % in women older than 65. For testicular GCT, survival was 94 % before 40 years and 78 % after 65+ years. These results were in line with those previously published [4, 11].

Interestingly, Verhoeven et al. [12] noted that in 2003–2007, despite the improvements in the relative survival of non-seminoma patients aged ≥50 years, survival remained markedly lower than the survival of seminoma patients of the same age. There is little room for survival improvement among testicular seminoma patients, especially for those aged <50 years. Older testicular cancer patients remain at increased risk of death, which seems mainly attributable to the lower survival of non-seminoma patients [12].

According to the RARECARE [13] definition of rare cancers (incidence <6/100,000), GCTs with an incidence of 34/1.000.000 are rare cancers in Europe. However, germ cell cancer incidence varies considerably in different geographical areas. GCTs include seminomas and non-seminomas and arise mainly in the gonads. However, GCT can be diagnosed also in the CNS, mediastinum, thorax, abdomen and pelvis. The distribution of seminomas and non-seminomas differs by sex and by site of origin. Overall, GCTs are typical tumors of adolescents and young adults and are characterised by a good prognosis, especially gonadal GCT. The incidence is stable except for testicular GCT (Table 2.5).

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