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Incidence patterns and trends of gonadal and extragonadal germ cell tumors in Germany, 1998–2008

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Abstract

Background—Gonadal (GGCT) and extragonadal germ cell tumors [GCT (EGCT)] are thought to originate from primordial germ cells. In contrast to well reported population-based data of GGCTs in males, analyses of GGCTs in females and EGCTs in both sexes remain limited.

Methods—In a pooling project of nine population-based cancer registries in Germany of the years 1998–2008, 16,883 GCTs and their topographical sites were identified using ICD-O morphology and topography for those aged 15 years and older. We estimated age-specific and age-standardized incidence rates.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

Authors' contribution

CR and AS were responsible for the conception, design, analysis, interpretation and preparation of the manuscript. BT contributed to analysis expertise and preparation of the manuscript. AK, JK and KE provided data and contributed to the preparation of the manuscript.

All authors read and approved the final manuscript.

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Results—Among males, the incidence of testicular GCTs increased over time. In contrast, there was no increase in the incidence of EGCTs. Among females, rates of ovarian GCTs were stable, while rates of EGCTs declined over time. The most frequent extragonadal sites were mediastinum among males and placenta among females.

Conclusions—Our results underline different incidence trends and distinct age-specific incidence patterns of GGCTs and EGCTs, as reported recently by several population-based registries. The differences suggest that GGCTs and EGCTs may have different etiologies.

Keywords

Extragonadal germ cell tumors; germ cell tumors; incidence; cancer registry; testicular neoplasms; ovarian neoplasms

Introduction

Malignant germ cell tumors (GCT) in both sexes are thought to originate from primordial germ cells (PGCs). PGCs migrate from the proximal epiblast along the midline of the body through the hindgut to the genital ridge where PGCs are referred to as gonocytes. Depending on the sex-chromosomal constitution and corresponding microenvironment in the gonadal ridge, gonocytes differentiate into either oocytes or pre-spermatogonia [1]. A disturbed migration of PGCs results in misplacement at different sites in the body's midline. Extragonadal germ cell tumors (EGCT) are believed to develop after malignant transformation of these residual PGCs. Different stages of development of the precursor cells and microenvironmental conditions may determine the final histology of the tumors at these sites. This hypothesis might explain the occurrence of GCTs in the sagittal midline of the brain, mediastinum and retroperitoneum [2]. Gain of isochromosome 12p as an important chromosomal marker of both gonadal germ cell tumors (GGCT) and EGCTs in both sexes proposes a common origin [3,4]. However, another hypothesis suggests that metastases of GGCTs in the retroperitoneal space and the posterior mediastinum of adolescent and young adult males are misdiagnosed as primary EGCT after regression of the primary GGCT ('burned out') [5].

Recently, reports of epidemiologic features including incidence and survival of GGCTs and EGCTs among males and females have been published by several population-based registries including the U.S., England, and Finland [6–8]. In contrast to well reported incidences of GGCTs in males, estimates of GGCTs in females and EGCTs in both sexes remain largely unexplored.

The aim of this study was to provide updated incidence rates of GGCTs and EGCTs from Germany using data from population-based cancer registries. We were especially interested in detailed analysis of extragonadal sites.

Material and Methods

With the exception of the upcoming cancer registries of Hesse and Baden-Württemberg, all population-based cancer registries including the registries from Bavaria (BY), Bremen (HB),

Hamburg (HH), Lower Saxony (NS), Northrhine-Westphalia, administrative district of Münster (NW), Rhineland-Palatinate (RP), Schleswig-Holstein (SH), Saarland (SL), and the Common Cancer Registry of the New Federal States (based on population of Mecklenburg-Western Pomerania, Saxony, Brandenburg, abbreviated as MSB) provided individual data of gonadal and extragonadal GCTs.

We used ICD-O-3 (International Classification of Disease for Oncology, 2002) topography and morphology codes to classify the tumors [9]. Among males, morphology codes 9060/3–9062/3, 9064/3 identified seminomas, whereas codes 9065/3–9102/3 identified non-seminomas. Among females, morphology codes 9060/3–9064/3 identified dysgerminomas, the histological equivalent of seminomas, whereas other GCTs were identified by histological type: embryonal carcinoma (9070/3), yolk sac tumor (9071/3), teratoma (9080/3–9084/3, 9102/3), mixed germ cell tumor (9085/3) and choriocarcinoma (9100/3–9101/3). For simplicity, we collectively refer to this grouping as non-dysgerminomas [10]. Topography code C62 identified testicular tumors, whereas code C56 identified ovarian tumors. All other topographical sites were considered extragonadal. Certain extragonadal sites mentioned in prior studies were analysed in detail, including pineal gland (C75.3), pituitary gland (C75.1), brain (C71), thymus (C37.9), mediastinum (C38.1–3), retroperitoneum (C48.0), pelvis (C49.5, 76.3), placenta (C58) and uterus (C54–55). We excluded cases aged 0–14 years as the completeness of registration was too low for a meaningful data analysis. Table 1 presents an overview of the GCT cases in the registries. With the exception of the cancer registry of NS, the proportion of histological verification was generally high, with up to 100% confirmation.

Population data were provided by the statistical offices of the federal states by calendar year and age groups (15–19, 20–24, ..., 80–84, 85+ years). To obtain more precise incidence rate estimates of GCTs, we pooled the case files and corresponding person years at risk of the registries for the period 1998–2008. Stratified by gender and histology, we calculated crude, age-specific and age-standardized incidence rates of GCTs using the European standard population [11].

For the estimation of the annual percentage change (APC) in GCT incidence, we fitted regression lines to the natural logarithm of the age-standardized incidence rates using calendar year as a regressor variable, i.e. $y = a + bx$, where $y = \ln(\text{rate})$ and $x = \text{calendar year}$. The APC is then estimated as $100 \times (e^b - 1)$. These models assumed that the logarithm of the rates changed at a constant rate over the periods. All analyses were run in SAS® version 9.2 (SAS Inc., Cary, NC, USA).

Results

A total of 16,883 GCTs were diagnosed in Germany among persons aged 15 years and older between 1998 and 2008. Among males 1.6% of all GCTs were EGCTs, whereas among females this proportion was 25.9%.

Figure 1 presents age-standardized incidence trends of GCTs. The annual incidence rate of testicular GCTs increased over the entire period (APC: 2.0%; 95%CI: 1.2 to 2.8). The

increase of seminomas (APC: 2.7%; 95%CI: 1.7 to 3.8) accounted for the majority of the increase. In contrast, the incidence of EGCT among males was virtually constant. Among females, the increase in incidence of GGCTs was virtually constant while the incidence of EGCTs decreased by 0.6 per 1,000,000 from 2001 to 2008 (APC: -11.6%; 95%CI: -17.7 to -5.1).

As shown in table 2, in GGCTs among males, the incidence of seminoma was higher than that of non-seminoma. In contrast, among females, non-dysgerminoma was more common. The most frequent extragonadal sites were mediastinum, brain, retroperitoneum and pineal gland among males, and placenta and uterus among females. In particular, GCTs of placenta were exclusively non-dysgerminoma. Among males, the incidence of seminoma in GCTs of brain and pineal gland was considerably higher than that of non-seminoma.

The age-specific incidence patterns of GCTs (ages 15–59) are shown in Figure 2. The incidence of testicular GCTs increased steadily from age 15 year to age 34 years. In contrast, rates of ovarian GCTs decreased in these ages. Among EGCTs, EGCT of the mediastinum in males and EGCT of the placenta in females showed rising incidence from age 15 years to age 29 years, whereas the incidences of GCTs of the brain and pineal gland declined in males during these ages. The observed number of other EGCT sites was too low for meaningful analysis.

Discussion

Our analyses showed that, among males, the incidence of GGCTs increased from 1998 through 2008, while the incidence of EGCTs remained virtually constant. Among females, the incidence of GGCTs stayed constant over times while the incidence of EGCTs declined. Age-specific incidence analyses of GGCTs revealed a steep increase in testicular GCTs and a decrease in ovarian GCTs starting at age 15 years.

As reported recently, the different incidence patterns and trends of GGCTs and EGCTs suggest that their etiology may differ [6–8]. Although it is believed that GCTs originate from primitive germ cells, the developmental potential of germ cells differs according to its stage of maturation and pattern of genomic imprinting [1]. The considerably lower incidence of GCTs among females than males is probably related to the smaller number of germ cells in the ovaries than the testes [12]. Furthermore, in contrast to testicular germ cells, ovarian germ cells do not proliferate after puberty. Finally, sex differences in etiologic factors or mechanisms might explain observed incidence differences between sexes.

Mediastinal and retroperitoneal GCTs occurred overwhelmingly among males. Among males the age-specific incidence pattern of mediastinal GCTs was similar to that recently reported in the U.S. and England [6,7]. Furthermore, that pattern was similar to the pattern of testicular GCTs. The steep increase in incidence of mediastinal GCTs at onset of puberty may reflect a hormone-related promotion of neoplastically transformed germ cells that arose during the embryogenesis.

Among females, GCTs of the placenta were exclusively choriocarcinomas. These choriocarcinomas belong to the group of gestational trophoblastic neoplasia arising from

placental trophoblastic tissue after normal or abnormal fertilisation [13]. The second peak at ages 50–54 (N=8; Rate=0.7; SE=0.3) may be explained as artefact by miscoding topography or morphology.

Intracranial GCTs affected males more frequently than females. Among males, the vast majority of GCTs of the brain and pineal gland (predominantly seminoma) occurred during the second and third decades of life. Registries in the U.S. and England also noted the bulk of intracranial GCTs in these decades [7,14]. Possible reasons for this age pattern are genetics, a change in local hormonal milieu (e.g., in gonads and brain), or more systemic effects.

The pooling of German cancer registries including a large sample size (N=16,883) enabled us to estimate certain extragonadal sites in detail. Nevertheless, there are factors limiting our results. First, a substantial number of EGCTs were registered as having an unknown primary site, complicating the interpretation of the topographical distribution. Even with large numbers overall, several subsite- and histology-specific analyses could not be conducted, as the numbers of cases were too small to allow a meaningful analysis. Second, EGCTs are only rarely registered and can be easily miscoded as gonadal germ cell tumours if the topography coding of tumours is not intensively monitored.

In conclusion, the differences in the incidences of GGCTs and EGCTs among males and females suggest that the etiology of these malignancies differ between the two sexes.

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List of abbreviations

GCT	germ cell tumor
EGCT	extragonadal germ cell tumor
GGCT	Gonadal germ cell tumor
CNS	central nervous system
APC	annual percentage incidence change
95%CI	95% confidence interval
SE	standard error

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Figure 1.

Age-standardized incidence rates of gonadal and extragonadal germ cell tumors in Germany in males (solid line) and females (dashed line) aged 15 years and older, 1998–2008.

Incidence rates of gonadal germ cell tumors in males illustrated by cases per 100,000. The interval on the left side displays the 95% confidence interval with average length, where averaging was performed all years.

Figure 2.

Age-specific incidence rates of gonadal and extragonadal germ cell tumors in Germany in males (solid line) and females (dashed line) aged 15 years and older, 1998–2008. Incidence rates of gonadal germ cell tumors in males illustrated by cases per 100,000.

Overview of the population-based German cancer registries including gonadal and extragonadal germ cell tumors for analyses

Table 1

Period	BY	HB	HH	MSB	NS	NW	RP	SH	SL
From	2002	1998	1998	1998	2003	1999	1998	1999	1998
To	2008	2007	2008	2008	2008	2008	2007	2008	2008
Person years at risk (Mill.)	73.9	5.7	16.5	83.9	40.5	21.8	34.1	23.8	10.0
Registered cases (n)									
Male									
Gonadal	3451	265	759	4381	2521	1278	1663	1354	498
Extragonadal	54	14	17	79	34	18	19	21	10
Female									
Gonadal	81	10	20	97	38	24	27	24	10
Extragonadal	24	1	4	50	6	10	10	7	4
Histological verification (%)	99.9	99.0	98.1	99.9	85.4	98.3	99.0	98.2	100
Death certificate only (%)	0	0.7	0	0	0.3	0.2	0.1	1.0	0

Bavaria (BY), Bremen (HB), Hamburg (HH), Lower Saxony (NS), Northrhine-Westphalia, administrative district of Münster (NW), Rhineland-Palatinate (RP), Schleswig-Holstein (SH), Saarland (SL), and the Common Cancer Registry of the New Federal States (based on population of Mecklenburg-Western Pomerania, Saxony, Brandenburg, abbreviated as MSB)

Table 2

Age-standardized incidence rates (cases per 1 million) of gonadal and extragonadal germ cell tumors by primary site, gender and histological group in Germany, 1998–2008

Topography (ICD-O)	Males						Females					
	Seminoma			Non-seminoma			Dysgerminoma			Non-dysgerminoma		
	N	ASR	SE	N	ASR	SE	N	ASR	SE	N	ASR	SE
Gonadal germ cell tumors	10,549	54.4	0.5	5,621	31.7	0.4	121	0.7	0.1	190	1.0	0.1
Testis (C62)												
Ovary (C56)												
Primary sites of extragonadal germ cell tumors												
Thymus (C37.9)	1	0.01	0.01									
Mediastinum (C38.1–C38.3)	25	0.1	0.03	30	0.2	0.03				5	0.03	0.01
Retropertitoneum (C48.0)	22	0.1	0.03	15	0.1	0.02				2	0.01	0.01
Pelvis (C49.5, C76.3)	1	0.01	0.01	1	0.01	0.01				1	0.004	0.004
Uterus (C54–C55)										8	0.04	0.02
Female genital tract (C57)							2	0.01	0.01	7	0.04	0.01
Placenta (C58)										55	0.3	0.1
Brain, NOS (C71)	32	0.2	0.04	5	0.03	0.01	5	0.03	0.01			
Pineal gland (75.3)	27	0.2	0.03	2	0.01	0.01	1	0.01	0.01			
Pituitary gland (C75.1)	2	0.01	0.01				5	0.03	0.01			
Malignant neoplasm of other and ill-defined sites (C76 excl. C76.3)	5	0.02	0.01	3	0.01	0.01				1	0.002	0.002
Other sites	24	0.1	0.03	25	0.1	0.03	3	0.01	0.01	9	0.05	0.02
Unknown primary site (C80.9)	18	0.1	0.02	28	0.1	0.03	1	0.004	0.004	11	0.05	0.02
All extragonadal germ cell tumors	157	0.9	0.1	109	0.6	0.1	17	0.1	0.03	99	0.6	0.1

ASR: Age-standardized rate; SE: Standard error of the rate