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

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ABSTRACT

Background: Malignant gonadal (GGCT) and extragonal 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 for the years 1998–2008, 16,883 malignant GCTs and their topographical sites were identified using ICD-O morphology and topography for persons aged 15 years and older. We estimated age-specific and age-standardized incidence rates.
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 malignant GGCTs and EGCTs, as reported recently by several population-based registries. The differences suggest that GGCT and EGCT may have different etiologies.

1. 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 malignant GGCTs and EGCTs from Germany using data from population-based cancer registries. We were especially interested in detailed analysis of extragonadal sites.

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2. Material and methods

With the exception of the upcoming cancer registries of Hesse and Baden-Wurttemberg, 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 Diseases 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 9060/3–9062/3, 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]. Spermatocytic seminomas (9063/3) were omitted from the analysis because they are considered to have a distinct pathogenesis [11]. 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 [12].

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 = 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).

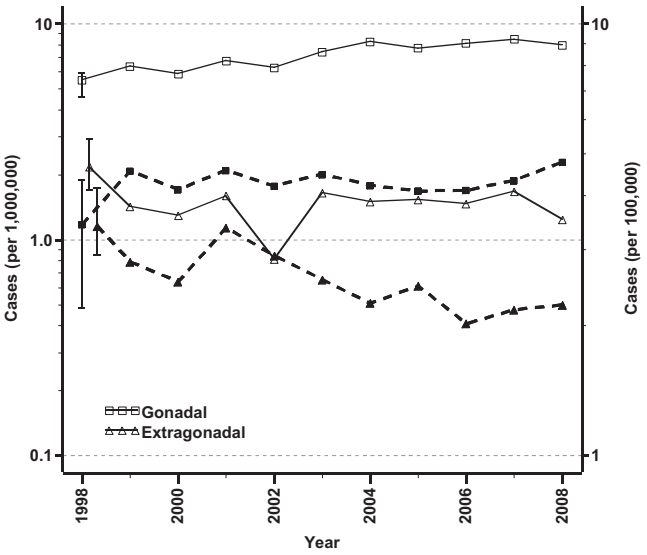

Fig. 1. Age-standardized incidence rates of malignant gonadal and extragonadal germ cell tumors in Germany in males (solid line) and females (dashed line) aged 15 years and older, 1998–2008. Incidence rates of gonadal germ cell tumors in males illustrated by cases per 100,000. The interval on the left side displays the 95% confidence interval with average length, where averaging was performed all years.

3. Results

A total of 16,883 malignant 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%.

Fig. 1 presents age-standardized incidence trends of malignant 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 among 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 nearly constant. Among females, the incidence of GGCTs was 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).

Table 1
Overview of the population-based German cancer registries including malignant gonadal and extragonadal germ cell tumors for analyses.

	BY	HB	HH	MSB	NS	NW	RP	SH	SL
Period									
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).