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Patterns and trends in the incidence of paediatric and adult germ cell tumours in Australia, 1982–2011

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ABSTRACT

Purpose: Germ cell tumour (GCT) aetiology is uncertain and comprehensive epidemiological studies of GCT incidence are few.
Methods: Nationwide data on all malignant GCTs notified to Australian population-based cancer registries during 1982–2011 were obtained. Age- and sex-specific, and World age-standardised incidence rates were calculated for paediatric (0–14) and adult (15+) cases using the latest WHO subtype classification scheme. Temporal trends were examined using Joinpoint regression.
Results: There were 17,279 GCTs (552 paediatric, 16,727 adult). Age-specific incidence in males (all histologies combined) was bimodal, with peaks during infancy for most sites, and second, larger, peaks during young adulthood. Incidence of ovarian tumours peaked at age 15–19. Around half of paediatric tumours were extragonadal, whereas adult tumours were mostly gonadal. Yolk sac tumours and teratomas predominated in infants, whereas germinomas became more frequent towards adulthood. Increasing incidence trends for some adult gonadal tumours have stabilised; the trend for male extragonadal tumours is also declining.
Conclusion: Broad similarities in the shape of age-specific incidence curves, particularly for gonadal, central nervous system, and mediastinal tumours provide epidemiological support for commonalities in aetiology among clinically disparate GCT subtypes. Differences in peak ages reflect underlying subtype-specific biological differences. Declining incidence trends for some adult gonadal tumours accords with the global transition in GCT incidence, and supports the possibility of a reduction in prevalence of shared aetiological exposures.

1. Introduction

Germ cell tumours (GCTs) comprise a diverse group of neoplasms derived from primordial germ cells (PGCs). They arise due to disturbance of normal germ cell maturation during embryogenesis. During normal embryogenesis, PGCs migrate to the midline structures, or gonadal ridge, where they differentiate into oocytes (females) or pre-spermatogonia (males); they may also undergo reprogramming to become pluripotent embryonic germ cells able to form all embryonal and extra-embryonal tissues. Tumours are typically located in the gonads, but can also occur at extragonadal sites along the midline of the body and brain, consistent with the migratory path of PGCs [1]. The spectrum of histologies reflects the stage of maturation and the pluripotential characteristics of the originating PGC [2]. The aetiology of GCTs is not completely understood. Their embryonic genesis provides a mechanism for both genetic predisposition and prenatal environmental factors; the role of postnatal factors in pathogenesis is unclear.

Abbreviations: APC, annual percent change; ASR, age-standardised rate; CI, confidence interval; EDC, endocrine disrupting chemical; GCT, germ cell tumour; ICD-O, International Classification of Diseases for Oncology; PGC, primordial germ cell; US, United States.

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GCTs manifest at all ages, with incidence peaks during infancy and young adulthood. In Australia, GCTs comprise 4% of cancers in children aged 0–14 [3], and over 10% of cancers in people aged 15–29, in whom they are the second-most common cancer [4]. Testicular GCTs are the most common, and constitute almost all testicular tumours [5]. A sustained increase in testicular GCT incidence rates has been consistently observed in Western countries, including Australia, over the past several decades [6–8], although rates now appear to be reducing in some populations in what has been described as a global transition of incidence trends [8]. A strong birth cohort effect has also been repeatedly demonstrated [7,8]. In contrast, malignant ovarian GCTs comprise only a small proportion (4%) of total ovarian tumours [9]. Incidence rates do not appear to have increased to the extent seen for testicular GCTs [10–12].

GCT incidence studies have been typically presented in an organ-oriented approach. However, age- and sex-specific differences in GCT incidence by site and histology reflect important underlying differences in the biology of these tumours [2]. To-date, these have not been fully explored. Indeed, descriptive epidemiological studies of GCT incidence, other than of testicular GCT incidence, are few [10–13] and previous Australian studies have included only testicular GCTs [6]. Detailed analyses of paediatric GCTs – some of which are known to be biologically distinct from adult GCTs – are also limited [14–16]. Reporting GCT incidence patterns categorised according to known, underlying biological differences [2] may be more informative with respect to GCT aetiology and pathogenesis. We present a nationwide, population-based study of malignant GCTs registered in Australia during 1982–2011.

2. Materials and methods

2.1. Data sources

Nationwide data on all malignant GCT cases (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] [17] codes 9060–9105/3, excluding 9090/3 struma ovarii), as notified to each state and territory cancer registry of Australia, were obtained for the years 1982–2011. Cancer notification is mandatory in Australia; cases are reported to the cancer registries by multiple sources, including hospitals, pathology laboratories, radiotherapy centres, and registries of births, deaths and marriages. Data were aggregated by histology, site, sex, 5-year age-group (0–85+) and calendar year. Corresponding population counts were obtained from the Australian Bureau of Statistics [18]. All data were obtained with institutional ethics committee approval (HC15424).

Cases were stratified by histology into germinomas (9060–9064) and non-germinomas, which collectively included: GCT, non-germinomatous (9065); embryonal carcinoma (9070); yolk sac tumour (9071); polyembryoma (9072); teratoma (9080–9084); mixed germ cell tumour (9085); and trophoblastic neoplasms (9100–9105). Note, for ease of terminology, germinoma/non-germinoma refers to seminoma/non-seminoma in males, and to dysgerminoma/non-dysgerminoma in females.

Cases were further stratified by site, including: gonadal (C569, ovary; C620-C629, testis); extragonadal (C000-C779, excluding C569, C620-C629); and, unknown primary site (C809). The following specific extragonadal sites were also considered based on the published literature in paediatric and adult cases: central nervous system (CNS, C700-C729, C751-C753); mediastinum (C379, C380-C388); retroperitoneum (C480); pelvis (including the sacrococcygeal region; C495, C763); and all other specified sites combined.

A number of distinct subtypes were separately examined, based on known biological differences [2,19], including: yolk sac tumours and teratomas in paediatric patients; spermatocytic seminomas (9063); and, dermoid ovarian cysts with malignant transformation (9084 at site C569). Trophoblastic neoplasms arising from molar pregnancies are considered as GCTs in some classifications [2]. However, these cannot be adequately distinguished in Australian cancer registry data from tumours arising from non-molar pregnancies. Therefore, trophoblastic neoplasms of the placenta (C589; n = 200), uterus (C54-C55; n = 51) and other (non-ovarian) female reproductive organs (C51-C53, C57; n = 13) were excluded.

2.2. Statistical analysis

Age-specific and directly age-standardised (World 2000) incidence rates (ASRs) were calculated (per million person-years) for each calendar year from 1982 to 2011. Rates were calculated overall, and separately, for paediatric (0–14) and adult (15+) cases.

Segmented linear (Joinpoint) regression modelling was used to examine temporal trends in ASRs (Joinpoint Regression Program, Version 4.2.0.0, April 2015, Statistical Research and Applications Branch, National Cancer Institute). Joinpoint modelling selects points at which the trend changes significantly ($p < 0.05$), based on Monte Carlo permutation testing. The annual percent change (APC) in incidence is then estimated for each distinct segment or trend, with 95% confidence intervals (CIs) [20]. Up to five Joinpoints were permitted, with a minimum of four data points between two consecutive Joinpoints, and a minimum of three data points from the last Joinpoint to the end of the data.

Analyses were performed using STATA Version 13.0 (StataCorp LP, College Station, TX).

3. Results

3.1. Overall incidence

In total, 17,279 GCTs were diagnosed in Australia during 1982–2011, including 16,204 in males (ASR 57.8 per million person-years; 95% CI, 56.9-58.7) and 1075 in females (ASR 4.2; 95% CI, 4.0-4.5).

ASRs for paediatric and adult cases are shown in Table 1. There were 552 paediatric cases, including 282 in boys and 270 in girls; rates were identical for boys and girls (ASR 4.7; 95% CI, 4.2-5.3).

Table 1
Age-standardised incidence rates of paediatric and adult germ cell tumours by site and sex, Australia, 1982–2011.

		Paediatric (0–14)		Adult (15+)	
Site	Sex	No.	ASR (95% CI)[a]	No.	ASR (95% CI)[a]
All	Male	282	4.7 (4.2–5.3)	15922	76.5 (75.3–77.7)
	Female	270	4.7 (4.2–5.3)	805	4.1 (3.8–4.4)
Gonadal	Male	119	2.0 (1.7–2.4)	15315	73.6 (72.4–74.7)
	Female	129	2.2 (1.8–2.6)	717	3.6 (3.4–3.9)
Extragonadal	Male	157	2.6 (2.2–3.0)	482	2.4 (2.2–2.6)
	Female	139	2.5 (2.1–2.9)	71	0.3 (0.3–0.4)
CNS	Male	101	1.7 (1.3–2.0)	161	0.8 (0.7–1.0)
	Female	44	0.8 (0.5–1.0)	22	0.1 (0.1–0.2)
Mediastinum	Male	8	0.1 (0.0–0.2)	217	1.1 (0.9–1.2)
	Female	4	0.1 (0.0–0.1)	16	0.1 (0.0–0.1)
Retroperitoneum	Male	7	0.1 (0.0–0.2)	33	0.2 (0.1–0.2)
	Female	4	0.1 (0.0–0.1)	2	0.0 (0.0–0.0)
Pelvis	Male	20	0.3 (0.2–0.5)	4	0.0 (0.0–0.0)
	Female	63	1.1 (0.9–1.4)	4	0.0 (0.0–0.0)
Other specified site	Male	21	0.4 (0.2–0.5)	67	0.3 (0.2–0.4)
	Female	24	0.4 (0.3–0.6)	27	0.1 (0.1–0.2)
Unknown primary site	Male	6	0.1 (0.0–0.2)	125	0.6 (0.5–0.7)
	Female	2	0.0 (0.0–0.1)	17	0.1 (0.0–0.1)

Abbreviations: ASR, age-standardised rate; CI, confidence interval; CNS, central nervous system.
[a] Standardised to the World (2000) population, and expressed per million person-years.