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# Global incidence comparisons and trends in ovarian germ cell tumors by geographic region in girls, adolescents and young women: 1988–2012

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## HIGHLIGHTS

- Ovarian germ cell tumor incidence rates are highest in Central America and Eastern Asia.
- In the United States the highest rates were in Asian/Pacific Islander and Hispanic populations.
- The concordance of international rates with ethnicity suggests genetic etiology.
- There was greater variability in the international incidence rates of adolescents and young adults than in children.
- Significant increases in incidence were seen in countries with high and very high human development index.

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## ABSTRACT

*Objective.* Ovarian germ cell tumors (OGCT) are the primary ovarian malignancy affecting girls and young women. Globally, incidence rates and trends for OGCTs have not been compared in the literature and their etiology is not well described. Comparisons of incidence globally could inform etiologic hypotheses. The aim of this analysis was to evaluate geographic variation in OGCT incidence and to identify trends in incidence rates.

*Methods.* Data were extracted from *Cancer Incidence in 5 Continents* (*CI5*) from 1988 to 2012. Rates of OGCT in women and girls were calculated for ages 0–9, 10–19, and 20–39 years and standardized to the 2000–2025 average world population. Data were aggregated within subregions corresponding to the United Nations Statistics Division (UNSD) geoscheme. Incidence rates were compared in subregions and average annual percent change (AAPC) was estimated using Poisson regression.

*Results.* Overall, the highest incidence rates were observed in 10–19-year-olds. Incidence was generally the highest in Eastern Asia, Central America and North America. While incidence was variable by geographic region, less variation was observed in 0–9-year-olds as compared to adolescents and young adults. Significant increases in incidence were seen in some regions (Eastern Asia, Oceania, Western Europe, Southern Europe, and North America) and in countries with a high or very high human development index for one or more age groups.

*Conclusions.* Evaluating 25 years of OGCT incidence data, the highest incidence rates and largest increases in incidence were seen in Eastern Asia. Future studies should focus on etiologic features that may account for geographic variation and increases in incidence of OGCT.



## 1. Introduction

Germ cell tumors (GCT) are a heterogeneous group of neoplasms that are grouped together due to their shared origins in the primordial germ cell [1]. GCTs occur in the gonads of males and females and also in extragonadal locations. Incidence patterns and trends differ between gonadal and extragonadal GCT, suggesting the etiology may differ [2–4]. In contrast to testicular germ cell tumors (TGCT), analyses of ovarian germ cell tumors (OGCT) remain limited [5]. Thus, the etiology of OGCT is still poorly understood [6]. Explorations of variation in incidence and trends in incidence could lend some insight into the etiology of OGCTs.

OGCTs primarily affect adolescent girls and young women [1]. Generally the incidence is low in childhood, increases at age 8–9 and reaches its peak around age 18 years [6]. GCTs are the second largest

*Abbreviations:* OGCT, ovarian germ cell tumor; TGCT, testicular germ cell tumor; CI5, Cancer in 5 Continents; SEER, Surveillance, Epidemiology, and End Results; UNSD, United Nations Statistics Division; AAPC, Average Annual Percent Change; WHO, World Health Organization; API, Asian/Pacific Islander.

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group of ovarian neoplasms and constitute 15–20% of all ovarian neoplasms [7]. The frequency of GCTs relative to other histologic subtypes of ovarian cancer differs widely in children and adults, with GCTs representing approximately 75% of malignant ovarian tumors in children [8] and <5% of malignant ovarian tumors in adults [9]. In Asia and Africa where the prevalence of epithelial ovarian tumors is lower, germ cell tumors account for a larger proportion of ovarian neoplasms [10]. The incidence of OGCT has been characterized in some countries [2,3,11] and comparisons have been conducted in Europe [12], but incidence comparisons have not been conducted globally and generally group all ages together. This may mask differences in incidence trends or patterns by age that could lead to greater etiologic insight.

The trends in incidence over time have been reportedly stable in some publications [10–12], but may differ by age group according to others [2,13]. Additionally, the time-periods for both incidence rates and trend analyses in many countries are different and therefore difficult to compare. The primary aim of this analysis is to compare incidence rates by geographic region for OGCT in ages 0–39 years to capture the pediatric and adolescent and young adult (AYA) age range where these tumors typically occur. The secondary aim of this analysis is to examine temporal trends in OGCT incidence rates among girls and AYA women.

## 2. Materials and methods

This analysis was conducted utilizing data from the *Cancer Incidence in Five Continents* (*CI5*) series. The aim of this series is to make comparable data available in as many geographic locations as possible by providing peer-reviewed data from population-based cancer registries worldwide [14]. The adherence to strict quality criteria for registry inclusion makes *CI5* a rich, high-quality resource for incidence rate comparisons [15]. Starting with volume VII (1988–1992), the *CI5* data were expanded to include cancer by histology rather than just primary site, which facilitate the evaluation of OGCT specifically. Additionally, the *CI5* datasets provide population at risk for each registry and age group allowing the aggregation of data across regions. In this analysis, we compared incidence and incidence trends in OGCT by geographic region and human development index (HDI) from 1988 to 2012 [16]. We aggregated by HDI to compare incidence by human development. HDI is a measure of human development that is derived from the average of a nation's longevity, education and income [17]. The HDI is stratified into low, medium, high, and very high human development based on this average [17]. Cumulative incidence for the latest time-period (2008–2012) was calculated within HDI category in 2012.

We extracted incident cases of OGCT and population data from available registries from *CI5* volumes VIII, VIII, IX, X, XI, representing 1988–1992, 1993–1997, 1998–2002, 2003–2007, and 2008–2012, respectively. We aggregated data into subregions to overcome small numbers within individual countries. Subregions were determined using the United Nations Statistics Division (UNSD) geoscheme classification, devised to divide countries into macro-geographical and regional and subregional groups for statistical analysis [18]. We were unable to further divide Sub-Saharan Africa into its UNSD subregions due to lower sample size and heterogeneity of the registries available between volumes. Similarly, Oceania was primarily comprised of Australia and New Zealand in most time-periods and therefore, not broken down further. Central America was only represented by Costa Rica in all time-periods and Central Asia was excluded because it did not have registry data for two or more time-periods. There was variability in the countries and number of registries included in each region over time. Generally, more registries and countries were eligible for inclusion in later volumes (see Fig. 1 for countries with registries included in each time-period). To avoid dropping subregions or time-periods entirely from analysis, we did not impose a cutoff for the number of cases needed to include a disease or registry in the dataset and we assumed inclusion in the *CI5* volume met minimum quality standards. Inclusion criteria for *CI5* registries have been described in detail elsewhere [14]. While the International Agency for Research on Cancer (IARC) marks registries with inferior data quality with an asterisk in the *CI5* volumes, we included all registries as previous papers have done [19,20]. A sensitivity analysis was conducted among only registries without an asterisk for comparability.

Incidence rates were calculated for age groups 0–9, 10–19, and 20–39 years. The 5 year contributions to each category were adjusted to the World Health Organization (WHO) World Standard based on the average world population between 2000 and 2025 [21]. Data was not aggregated over the entire age range as previous reports show differences in incidence and incidence trends by age [13]. Incidence rates were not calculated when there were fewer than 5 cases. All rates are presented as incidence per million due to low incidence rates. For trends in incidence, the crude average annual percent change (AAPC) was estimated using Poisson regression to model counts as previously described [22]. A log population size offset term was used in the model to correct for population size heterogeneity and robust standard errors were used to correct for overdispersion in some regions and age groups. 95% Wald Confidence Intervals (CIs) and *p*-values were calculated and reported. All analyses were conducted using SAS software version 9.4 (Cary, North Carolina, USA).

In addition to *CI5* data, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database for comparisons of incidence rates in racial and ethnic groups in the United States. The purpose of our comparison was to understand whether genetic or environmental factors were more likely driving geographic differences in incidence. We used data from the SEER 13 registries, which represent approximately 14% of the U.S. population [23]. We included first cancer diagnoses starting in 1992 among individuals in the 0–9, 10–19 and 20–39 year old age groups and weighted the 5 year categories with the same methods as used for the *CI5* data for comparability. We calculated incidence rates in these age categories for Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Asian/Pacific Islander (API), and Hispanic females. We omitted females with American Indian/Alaskan Native ancestry due to very low numbers. SEER data analysis was conducted using SEER*Stat 8.3.5 [24].

## 3. Results

OGCT incidence rates were low overall in all age groups, with peak incidence in the 10–19-year age group for most subregions (Table 1, Fig. 2). Data were sparse in the Caribbean, Sub-Saharan Africa, and Northern Africa so we were not able to draw conclusions about incidence rates and trends in these regions. Rates were less variable across regions in young girls ages 0–9 than in adolescents and young adults (Fig. 2).Incidence rates using SEER data mirrored rates in geographic regions, with the highest rates in API and Hispanic females (Fig. 3). We observed evidence for increasing incidence rates in some but not all regions (Fig. 4). Finally, when we stratified by HDI category rather than geographic region, we found that increases in incidence occurred in the high and very high HDI categories (Table 2). More detailed results for each age group are provided below.

### 3.1. Ages 0–9 years

In girls ages 0–9 years, incidence rates ranged from 0.6 to 2.1 cases per million during 2008 to 2012 (Table 1). Incidence was lowest in the 0–9-year age group compared with the 10–19 and 20–39 year groups for all regions with available data (Fig. 2). The highest incidence in girls occurred in Eastern Asia and the lowest incidence was reported in Oceania (Fig. 2). In the United States, incidence was highest in API, followed by Hispanic, NHW and NHB girls respectively (Fig. 3). When compared with NHW girls, the incidence was statistically significantly higher in API girls while no differences were observed for other groups. When we evaluated trends over time, the only significant change in

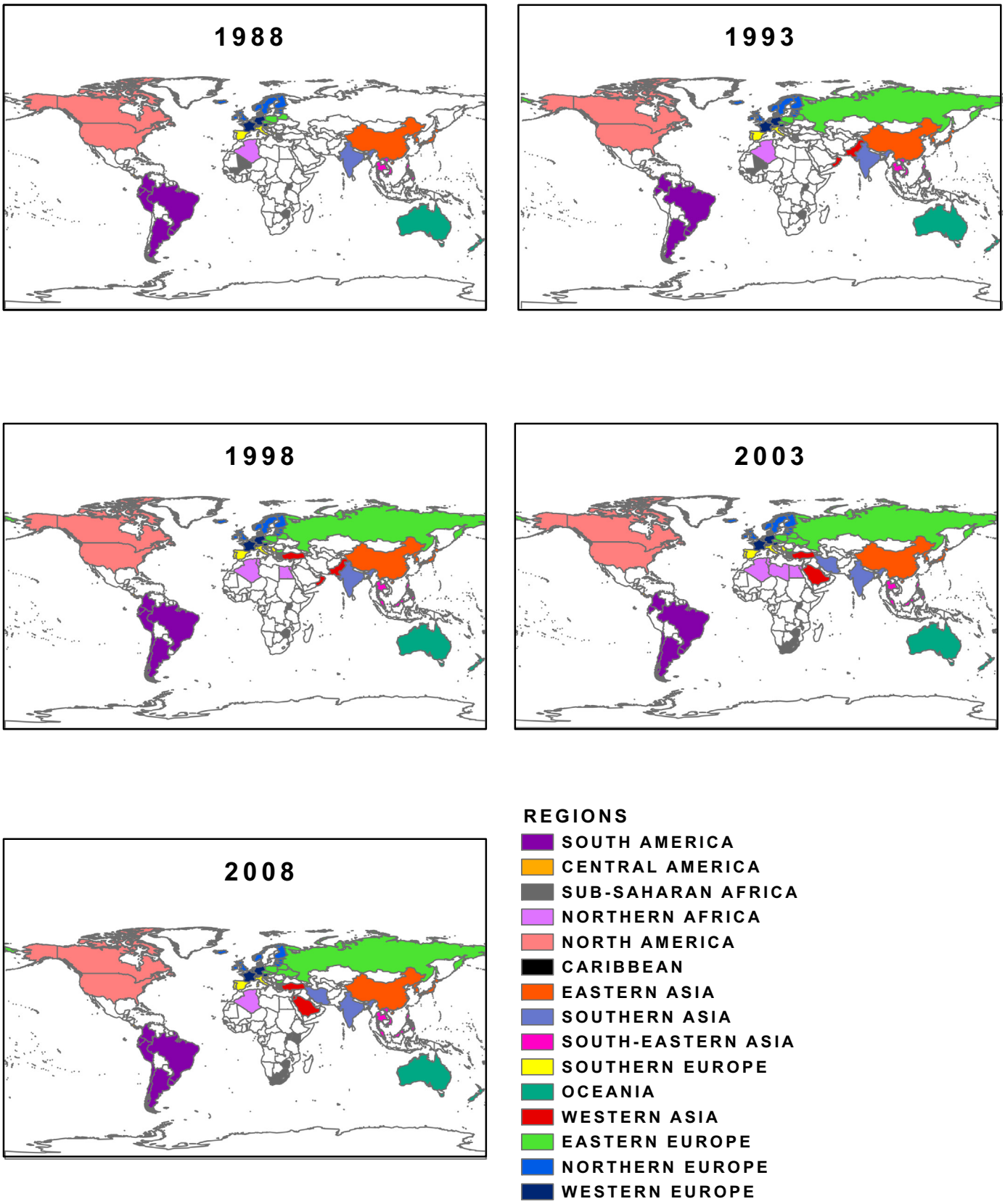


**Fig. 1.** Countries included in each time-period of the *CI5* data for each geographic subregion.

incidence from 1988 to 2012 occurred in Western Europe where a 2.44% increase (95% CI: 0.65, 4.26) was reported (Table 1, Fig. 4). Evaluating incidence by HDI category, the incidence ranged from 0.4 to 2.0 cases per million (Table 2). Data was too sparse in low HDI categories to calculate incidence rates, but generally little difference in incidence was seen between categories of HDI in this age group.

**Table 1**
Incidence per million (number of cases) and average annual percent change (AAPC) of ovarian germ cell tumors by region, age group, and year of diagnosis.

| Region | Age | Year of diagnosis | | | | | AAPC |
|---|---|---|---|---|---|---|---|
| | | 1988–1992 | 1993–1997 | 1998–2002 | 2003–2007 | 2008–2012 | (95% CI) |
| Northern Africa | 0–9 | * | * | * | * | * | 7.49 (−11.69, 30.84) |
| | 10–19 | * | * | 1.8 (5) | 3.9 (19) | * | 7.32 (−12.85, 32.17) |
| | 20–39 | * | * | 2.9 (11) | 3.6 (28) | * | 6.07 (−8.65, 23.15) |
| Sub-Saharan Africa | 0–9 | * | * | * | * | * | * |
| | 10-19 | * | * | 2.7 (6) | 3.7 (13) | 1.9 (8) | 2.44 (−3.82, 9.10) |
| | 20–39 | 3.0 (7) | 2.3 (7) | 4.6 (13) | 5.7 (25) | 1.2 (9) | −2.54 (−10.77, 6.46) |
| Caribbean | 0–9 | – | * | * | * | * | 3.07 (−2.89, 9.39) |
| | 10–19 | – | 5.1 (5) | * | 8.3 (18) | 8.5 (15) | 4.48 (−1.61, 10.94) |
| | 20–39 | – | 6.9 (13) | * | 6.2 (26) | 4.8 (16) | −1.18 (−0.43, 9.55) |
| Central America | 0–9 | * | * | * | * | * | * |
| | 10-19 | 8.8 (13) | 15.9 (11) | 10.4 (21) | 9.5 (20) | 9.1 (15) | −0.41 (−3.09, 2.35) |
| | 20–39 | 7.6 (19) | * | 6.1 (19) | 6.9 (24) | 7.5 (23) | 0.74 (−2.16, 3.72) |
| South America | 0–9 | 1.6 | * | 2.0 (15) | 2.5 (30) | 1.6 (20) | 1.39 (−4.40, 7.54) |
| | 10–19 | 4.2 (19) | 5.6 (17) | 6.9 (59) | 5.7 (75) | 7.4 (98) | 2.10 (−0.08, 4.31) |
| | 20–39 | 3.8 (31) | 3.2 (18) | 4.8 (80) | 4.0 (101) | 5.1 (126) | 1.34 (−0.66, 3.37) |
| North America | 0–9 | 1.2 (21) | 0.7 (13) | 1.4 (49) | 1.2 (46) | 1.4 (50) | 1.48 (−1.61, 4.66) |
| | 10–19 | 7.9 (131) | 8.5 (154) | 8.1 (274) | 7.8 (306) | 7.8 (296) | −0.22 (−0.59, 0.14) |
| | 20–39 | 5.8 (237) | 5.7 (237) | 5.7 (393) | 6.4 (496) | 7.2 (546) | **1.38 (0.40, 2.36)** |
| Eastern Asia | 0–9 | 1.5 (15) | 1.1 (18) | 2.3 (48) | 2.7 (68) | 2.1 (63) | 2.78 (−1.34, 7.07) |
| | 10–19 | 3.1 (34) | 4.9 (100) | 8.6 (211) | 9.3 (282) | 9.8 (374) | **4.37 (1.51, 7.30)** |
| | 20–39 | 1.9 (49) | 3.5 (169) | 5.8 (335) | 6.9 (522) | 7.1 (716) | **4.84 (1.94, 7.83)** |
| South-eastern Asia | 0–9 | 2.5 (13) | 2.3 (29) | 3.5 (24) | 2.2 (26) | 1.7 (23) | −1.70 (−4.69, 1.38) |
| | 10–19 | 3.6 (19) | 7.0 (92) | 8.3 (55) | 5.6 (72) | 6.4 (94) | 0.49 (−2.70, 3.79) |
| | 20–39 | 5.6 (60) | 5.7(157) | 7.6 (101) | 5.8 (158) | 4.7 (160) | −1.09 (−3.10, 0.95) |
| Southern Asia | 0–9 | 1.4 (14) | 1.7 (32) | 0.8 (12) | 1.0 (19) | 1.4 (26) | −1.29 (−5.90, 3.53) |
| | 10–19 | 4.4 (41) | 4.8 (81) | 3.3 (53) | 4.0 (87) | 3.8 (79) | −0.92 (−2.68, 0.88) |
| | 20–39 | 3.5 (55) | 3.1 (100) | 2.6 (80) | 2.7 (109) | 2.7 (118) | **−1.27 (−2.30, −0.23)** |
| Western Asia | 0–9 | * | 1.5 (8) | 0.8(7) | 1.4 (13) | 1.5 (23) | 2.53 (−1.16, 6.35) |
| | 10–19 | 3.9 (11) | 4.9 (23) | 6.8 (54) | 6.2 (55) | 6.1 (90) | 1.25 (−0.81, 3.36) |
| | 20–39 | 3.3 (15) | 4.5 (31) | 4.6 (63) | 4.7(78) | 4.1 (116) | −0.07 (−1.84, 1.73) |
| Eastern Europe | 0–9 | 0.9 (10) | 0.6 (7) | 1.7 (18) | 1.4 (29) | 1.4 (31) | 2.67 (−1.22, 6.72) |
| | 10–19 | 5.7 (70) | 3.3 (45) | 6.3 (94) | 6.2 (175) | 6.3 (166) | 1.50 (−1.25, 4.32) |
| | 20–39 | 3.8 (90) | 3.0 (75) | 4.0 (122) | 4.7 (242) | 3.7 (270) | 0.27 (−1.16, 1.71) |
| Northern Europe | 0–9 | 0.7 (13) | 1.0 (30) | 1.0 (28) | 1.1 (29) | 0.8 (20) | 0.68 (−1.95, 3.39) |
| | 10–19 | 3.2 (67) | 5.1 (141) | 5.6 (161) | 4.8 (144) | 6.1 (154) | 2.01 (−0.13, 4.19) |
| | 20–39 | 3.2 (150) | 3.8 (250) | 4.8 (303) | 4.1 (260) | 5.3 (296) | **2.02 (0.44, 3.62)** |
| Southern Europe | 0–9 | 1.5 (9) | 1.1 (7) | 1.8 (17) | 2.1 (21) | 1.6 (16) | 1.31 (−1.58, 4.28) |
| | 10–19 | 5.6 (42) | 5.5 (44) | 5.8 (67) | 5.6 (62) | 5.1 (51) | −0.30 (−0.99, 0.41) |
| | 20–39 | 3.6 (58) | 3.6 (71) | 4.2 (123) | 4.4 (135) | 5.1(134) | **1.62 (1.21, 2.03)** |
| Western Europe | 0–9 | 0.9 (8) | 1.0 (9) | 1.0 (15) | 1.0 (17) | 1.4 (36) | **2.44 (0.65, 4.26)** |
| | 10–19 | 4.0 (38) | 6.3 (56) | 4.7 (79) | 6.1 (117) | 7.2 (206) | **2.47 (0.48, 4.49)** |
| | 20–39 | 3.9 (90) | 4.5 (102) | 4.0 (156) | 4.0 (174) | 4.5 (283) | 0.36 (−0.59, 1.31) |
| Oceania | 0–9 | 1.0 (6) | 0.8 (6) | 1.4 (11) | 0.6 (5) | 0.6 (5) | −2.07 (−6.61, 2.69) |
| | 10–19 | 4.2 (28) | 5.9 (45) | 6.4 (51) | 7.3 (60) | 6.8 (58) | **2.02 (0.56, 3.50)** |
| | 20–39 | 4.4 (59) | 5.6 (93) | 6.4 (107) | 6.4 (107) | 6.8 (126) | **1.90 (0.97, 2.85)** |

* Rates were not calculated for time periods with less than five cases.
– Denotes time periods without data.
AAPCs in bold are statistically significant.

### 3.2. Ages 10–19 years

In adolescents ages 10–19 years, age-adjusted incidence rates ranged from 1.9 cases per million in Sub-Saharan Africa to 9.8 cases per million in Eastern Asia during 2008 to 2012 (Table 1). The incidence in the 10–19-year-old age category was higher than the other age ranges for all regions except Southern Europe and Oceania where the incidence was the same in the 10–19 and 20–39 year age groups (Fig. 2). Particularly high incidence rates were seen in the latest time-period for Eastern Asia, Central America and the Caribbean at 9.8, 9.1 and 8.5 cases per million, respectively. All European regions had lower incidence than North, South, and Central America (Fig. 2). In the United States, incidence rates were highest in females of Hispanic ethnicity, followed by API, NHW, and NHB females, respectively (Fig. 3). Significant increases in incidence were observed in Eastern Asia, Western Europe and Oceania with AAPC of 4.37, 2.44 and 2.06% from 1988 to 2012, respectively (Table 1, Fig. 4). Aggregation by HDI category yielded incidence rates ranging from 2.4 to 6.9 cases per million (Table 2). Significant increases in incidence within this age group were seen in both the high and very high HDI categories at 1.79 and 2.06% respectively (Table 2).

### 3.3. Ages 20–39 years

In women ages 20–39 years, the incidence rates ranged from 1.2 cases per million in Sub-Saharan Africa to 7.6 cases per million in Central America during the 2008 to 2012 time-period (Table 1, Fig. 2). Significant increases in incidence were seen in Oceania, Southern Europe, Northern Europe, Eastern Asia and North America (Fig. 4). Comparable to the 10–19-year age category, significant increases in incidence within this age group were observed in both the high and very high HDI categories at 2.27 and 1.87% respectively (\Table 2).

In the sensitivity analysis where we removed registries with an asterisk, rates did not change in most regions (Northern Africa, Caribbean, Central America, South America, North America, Eastern Asia, Western Asia, Eastern Europe, Northern Europe, Southern Europe, Western Europe, and Oceania) although estimates were less precise due to the reduced sample size (data not shown). We observed notable differences in three regions (Southern Asia, South-eastern Asia and Sub-Saharan Africa); however, these regions were reduced to one or two registries and therefore are likely not representative of the region as a whole.

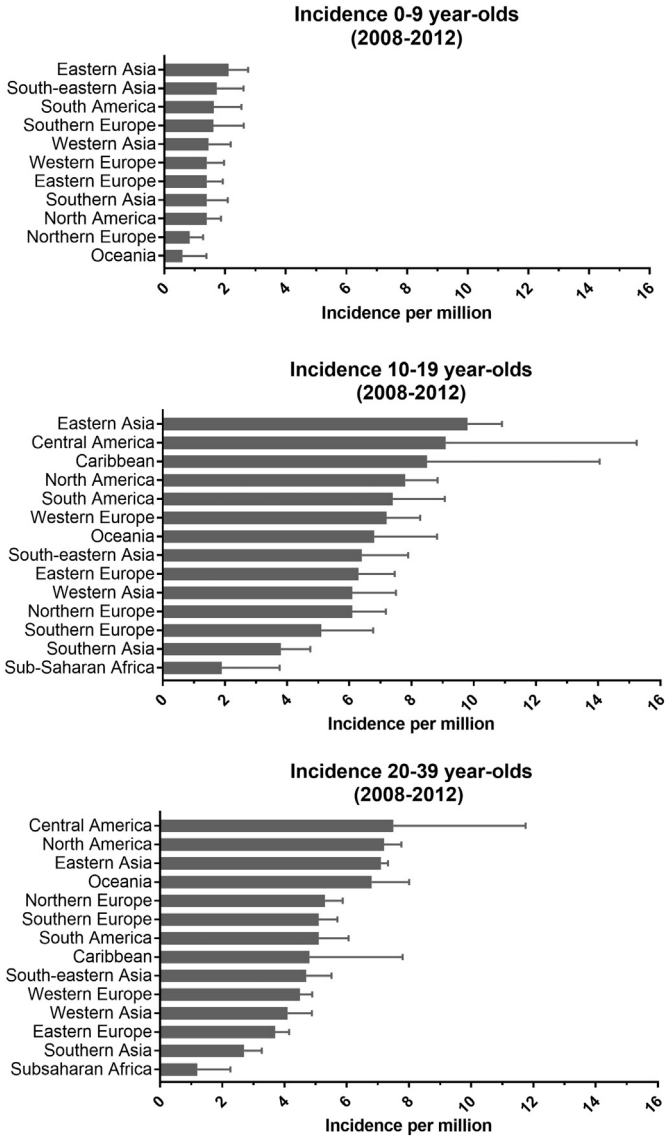


**Fig. 2.** Ovarian germ cell tumor incidence (per million) and 95% confidence intervals by geographic subregion for each age group during 2008–2012. *Incidence was not calculated or plotted for regions with <5 cases.

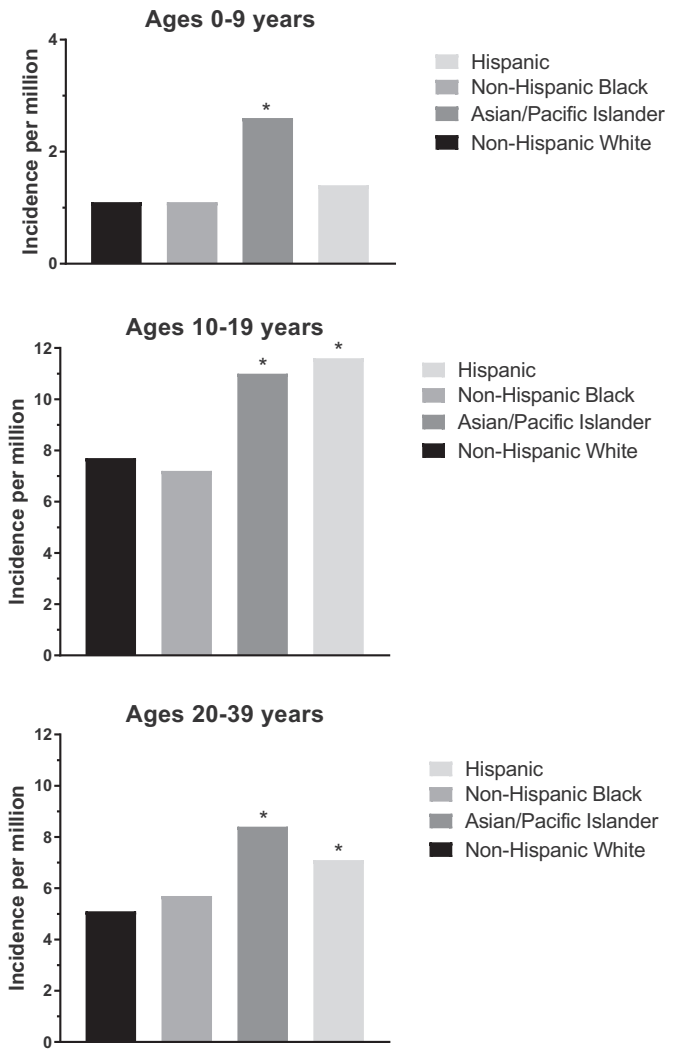


**Fig. 3.** Ovarian germ cell tumor incidence by race/ethnicity and age group in the United States (SEER 13: 1992–2014).

## 4. Discussion

This analysis uses high-quality and consistent registry data to compare OGCT incidence and incidence trends across geographic regions over a 25 year time period. To our knowledge, this is the first global comparison of OGCT incidence in children, adolescents and young adults. When we compared incidence rates by region, we found that geographic variation was less common in the 0–9-year age group when compared with adolescents and young adults. Differences in the incidence rates between age groups could represent differences in etiology of germ cell tumors in young children compared to adolescents and young adults.

The primary limitation of these findings is the lack of data in some regions. When we stratified by HDI, countries with high and very high HDI were overrepresented in our dataset. Therefore, these findings cannot be extrapolated to low or medium HDI countries where the incidence is often unreported. Furthermore, Sub-Saharan Africa is a large and ethnically diverse region; however, due to the limitations of the available data, we were unable break this region into smaller subregions and had limited ability to assess trends even within the larger region. There was also a great deal of heterogeneity in the registries included within each region in each time point and data was missing for some regions entirely, like Central Asia. Central America is represented solely by data from Costa Rica, so rates and trends from this subregion may not be representative.

Given the low incidence of malignant OGCTs, few studies have been conducted to identify risk factors for these tumors. OGCTs in girls have been evaluated in studies including GCTs at all locations; however, power has not been sufficient in these studies to evaluate risk of OGCT specifically [25–28]. For pediatric GCT overall, risk factors that have been evaluated include parental demographic characteristics, *in utero* exposure to hormones and pesticides, maternal reproductive history, and congenital abnormalities; however, none has emerged as a consistent risk factor [5]. The few risk factors that have been evaluated specifically in OGCT include inflammatory cytokines during pregnancy and maternal hormone exposure [5]. Parental smoking and alcohol consumption were also evaluated specifically for OGCT, but no association was found [29]. Given this uncertainty regarding risk factors for OGCT, it is not possible to speculate on what exposures are driving the differences in incidence rates by region.

Similar to TGCT [30], we found that Eastern Asia had the highest incidence of OGCT in young girls. The rates were highest in Eastern Asia and in API within the United States in most age groups, which may

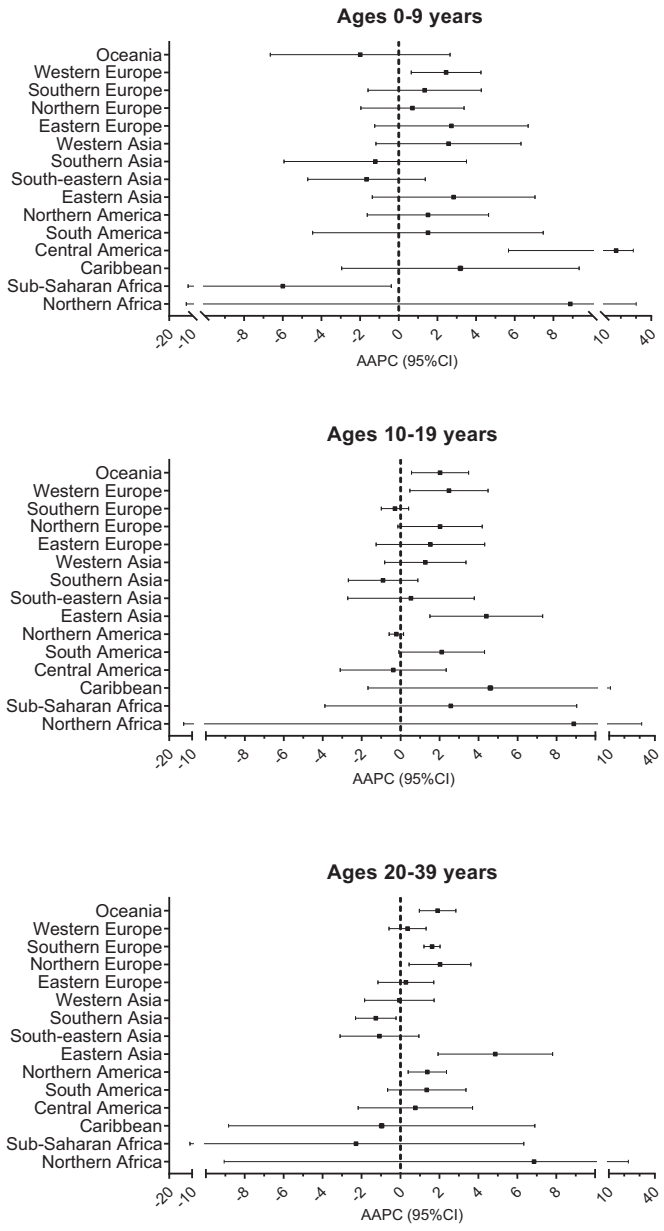


**Fig. 4.** Estimated average annual percent change (AAPC) and 95% confidence intervals (CI) by geographic subregion and age category.

suggest a genetic component. Similarly, OGCT incidence rates were high in Central America and in Hispanic children in the United States, which may also support a genetic risk. Many studies have evaluated the genetic etiology of adult TGCT [31], but genetic etiology has not been evaluated in OGCT specifically. TGCT studies have shown strong heritability and genome-wide associations studies (GWAS) have found susceptibility loci near many genes associated with survival and differentiation of primordial germ cells, sex differentiation, and transcription regulation [32,33]. Notably, many of the findings for TGCT have been predominantly in populations with European ancestry and thus do not account for the genetic susceptibility that maps to ancestry. The few studies of genetic susceptibility to pediatric GCTs, including OGCT, have identified variants in KITLG, SPRY4, BAK1 and GAB2 as susceptibility loci [32,34]. Future studies in diverse populations will be required to confirm a role of genetic susceptibility in OGCT.

Previous studies of OGCT incidence specifically have been sparse and are difficult to compare due to differences in age groups. Multiple studies have reported a similar peak in incidence in adolescence [2,4,5,10,13,35,36]. Also similar to our results, previous reports show Northern Europe generally has incidence rates lower than the United States [3,35,36]. Japan has previously reported that their incidence rates were higher than the US, but comparable to the US API population [37]. Trends in OGCT incidence have been previously evaluated in Finland, Germany, England, Japan and the United States. Finland and Japan reported no change in incidence [10,36], the United states reported no significant change or change in specific ages only [2,13], and Germany reported a small increase in incidence during 1987–2011 [38], but another analysis performed from 1998 to 2008 reported the incidence was stable [4]. Generally, the analyses that found increasing incidence included a longer time period in their evaluations.

In contrast to literature showing no significant increase in rates of OGCT [2,4,36], we did see small increases in incidence in some regions. When stratified by HDI category, these increases were mainly observed in the high and very high HDI categories with some precision. While development likely occurred during the time-period, most countries with a very high HDI were also high or very high HDI at the start of the time-period. This may suggest that development may be less of a factor for the increases seen in these countries. However, further investigation would be needed to determine if increases are real or an artifact of health system changes.

In addition to data availability, there are some limitations in our analysis. First, the model used to calculate the AAPC assumes the incidence rates are constant within the *CI5* volumes (five-year periods) and that cases follow a Poisson distribution. Second, OGCTs are rare in some age groups and regions and this can give rise to unstable incidence rates. Likewise, while robust standard errors were used to account for overdispersion, the 95% CIs serve to provide context for descriptive analysis only. Third, trends in incidence may reflect changes in reporting, surveillance, diagnostics, and health care delivery over time. Finally, caution should be applied to comparing incidence rates as the wide variation in incidence may be in part due to underdiagnosis, underreporting, care abandonment, or comorbid conditions, particularly in low income countries [39]. As stated previously, the data in low and medium income countries are sparse and do not permit us to draw definitive conclusions regarding trends in incidence rates.

In summary, evaluating the incidence rates and trends across geographic regions in OGCT over 25 years, we found evidence that OGCT may be increasing in some regions. We also found that incidence rates were generally higher in Eastern Asia, Central America and North America than other regions. Analyses stratified by HDI show precise, but small increases in incidence within the high and very high HDI categories. Further exploration should be devoted to determining which increases cannot be explained by changes in health systems over the time-period.

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## Author contribution

Conceptualization: JN Poynter
Methodology: AK Hubbard and JN Poynter
Data Analysis: AK Hubbard
Writing – original draft: AK Hubbard
Writing – review & editing: AK Hubbard and JN Poynter
Supervision: JN Poynter

## Declaration of Competing Interest

The authors have no conflict of interest relevant to this article to disclose.

**Table 2**
Average annual percent change (AAPC) and incidence (per million) of ovarian germ cell tumors by human development index (HDI) category and year of diagnosis.

| Age category | HDI level** | Year of diagnosis | | | | | AAPC |
|---|---|---|---|---|---|---|---|
| | | 1988–1992 | 1993–1997 | 1998–2002 | 2003–2007 | 2008–2012 | (95% CI) |
| 0–9 years | Low | * | * | * | * | * | – |
| | Medium | 1.6 | 2.0 | 1.2 | 1.2 | 1.3 | −2.22 (−4.79, 0.41) |
| | High | 1.0 | 0.4 | 1.4 | 1.7 | 1.5 | 3.34 (−1.48, 8.41) |
| | Very high | 1.1 | 1.0 | 1.5 | 1.5 | 1.5 | **1.85 (0.04, 3.70)** |
| 10–19 years | Low | * | * | 2.7 | 4.9 | 2.4 | 5.12 (−2.88, 13.80) |
| | Medium | 3.8 | 5.4 | 4.3 | 4.2 | 3.9 | −0.94 (−2.77, 0.92) |
| | High | 3.7 | 4.5 | 5.8 | 5.3 | 5.9 | **1.79 (0.53, 3.06)** |
| | Very high | 5.0 | 5.8 | 6.9 | 7.1 | 7.9 | **2.06 (1.44, 2.68)** |
| 20–39 years | Low | * | 2.0 | 4.6 | 6.1 | 1.7 | 0.94 (−7.49, 10.13) |
| | Medium | 3.7 | 3.7 | 3.2 | 3.3 | 2.9 | −1.26 (−1.88, −0.62) |
| | High | 2.9 | 2.9 | 4.1 | 4.1 | 4.4 | **2.27 (1.10, 3.46)** |
| | Very high | 4.1 | 4.4 | 5.2 | 5.5 | 6.0 | **1.87 (1.54, 2.20)** |

* Rates were not calculated for time periods with less than five cases.
** There were 5 countries with low HDI, 7 countries with medium HDI, 21 countries with high HDI and 53 countries with very high HDI.
– AAPCs were not calculated when >3 periods had less than five cases.
AAPCs in bold are statistically significant.

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