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The influence of birth cohort and calendar period on global trends in ovarian cancer incidence

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Abstract

Ovarian cancer is the eighth most common cancer in women worldwide and incidence rates vary markedly by world region. This study provides a comprehensive overview of ovarian cancer incidence trends globally, examining the influence of birth cohort and period of diagnosis on changing risk. We presented current patterns and trends of ovarian cancer incidence until 2012 using data from successive volumes of *Cancer Incidence in Five Contents*. The incidence of ovarian cancer is highest in northern and eastern European countries, and in northern America. Declining trends were observed in most countries with the exception of a few central and eastern Asian countries. Marked declines were seen in Europe and North America for women aged 50–74 where rates have declined up to 2.4% (95% CI: −3.9, −0.9) annually in Denmark over the last decade. Additionally, declines in the incidence rate ratio (IRR) were observed for generations born after the 1930s, with an additional strong period effect seen around 2000 in United States and Denmark. In contrast, IRRs increased among younger generations born after the 1950s in Japan and Belarus. Overall, the favourable trends in ovarian cancer incidence is likely due to the increase use of oral contraceptive pills, and changes in the prevalence of other reproductive risk and

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protective factors for ovarian cancer over the years studied. Changes in disease classifications and cancer registry practices may also partially contribute to the variation in ovarian cancer incidence rates. Thus, continuous cancer surveillance is essential to detect the shifting patterns of ovarian cancer.

Keywords

ovarian cancer; global incidence trends; age-period-cohort

Introduction

There were an estimated 300,000 new cases of ovarian cancer diagnosed worldwide in 2018[1], corresponding to 3.4% of all cancer cases among women. Although there is substantial geographic variation in the burden of ovarian cancer (rates varying from 5.0 per 100,000 person-years in Africa to 9.5 per 100,000 person-years in Europe[1]), gradual declines in incidence have been observed in most countries in Europe (e.g. Denmark, Norway, and France) and in North America (e.g. United States and Canada), where incidence has been historically higher compared to less developed regions[2]. Nevertheless, many countries in these regions, such as Belarus, Poland and Czech Republic, continue to have a high incidence of ovarian cancer compared to other regions of the world[3]. Recently, however, a steady increase in ovarian cancer has been observed in some Asian countries that previously had low rates, such as Japan or India[3].

The reasons for differences in ovarian cancer rates between countries is likely multifactorial. Family history and reproductive factors, including a lower number of children and the use of menopausal hormone therapy, increase a woman's risk of ovarian cancer[4]. In contrast, the use of oral contraceptives (OC), breastfeeding, and tubal ligation may be protective[4]. In particular, the widespread use of OC has played an important role in the decline of ovarian cancer incidence over the past few decades[5, 6].

The main purpose of this article is to provide an overview of the latest patterns and trends of ovarian cancer worldwide. We examined the incidence of ovarian cancer globally using national estimates and population-based cancer registry data recorded in 27 different countries. We also assessed the influence of birth cohort and period of diagnosis on the secular trends to better identify factors underlying the changing trends.

Materials and Methods

Data source

Incidence data on primary malignant ovarian cancer *(International Classification o f Disease for Oncology, 3rd edition* (ICD-O-3): C56) was obtained from *Cancer Incidence in Five Continents* (CI5) *plus* database *(*http://ci5.iarc.fr/CI5plus), which contains high-quality global cancer incidence data provided by national and subnational population-based cancer registries (PBCR) worldwide[7]. PBCRs with 25 or more consecutive years of incidence data were included, yielding a total of 53 PBCRs from 30 countries eligible for analysis. Multiple subnational cancer registries in the same countries were combined, and countries with

population coverage of less than 500,000 females were excluded in the analysis, namely, Austria (Tyrol), Germany (Saarland) and Iceland. Hong Kong, China was also excluded due to the inconsistency of the data from 1983–2000. In addition, a few high quality registries had to be excluded due to the unavailability of the data in the public CI5 database for the last 5-year period. After all the exclusions, a total of 27 countries remained in the analysis.

Statistical analysis

Truncated age-standardized incidence rates (ASR, per 100,000 person-years) for two broad age groups (25–49 and 50–74 years) were calculated per calendar year using the World Standard population[8, 9]. A separate analysis was performed to calculate the truncated age-standardized incidence rates for women 75+ years. Incidence rates were plotted on a log-scale, and trend lines were smoothed with a smoothing coefficient of 0.5. The estimated annual percent change (EAPC) and corresponding 95% confidence intervals were computed for the latest 15-year period (1998–2012) to summarize the change in incidence for the most recent years.

To examine the effects of birth cohorts and period by 5-year interval, age-period-cohort (APC) analysis was performed for five selected countries representing different world regions, namely, Australia, Belarus, Japan, Denmark and United States. Age-specific incidence rates were plotted against the estimated year of birth and year of diagnosis. Due to the linear dependency of age, period and cohort, the effects of these three factors cannot be analysed simultaneously. In this analysis, a method developed by Holford[10] was applied to calculate the incidence rate ratio (IRR) using the 1998–2002 period of diagnosis as the reference period and 1950 as the reference birth cohort. To examine the cohort effect, the period effect was constrained to zero on average with an assumption that the linear change in rates is due to the influence of birth cohort. A similar method was applied to examine the influence of period to the secular trend. The *apcfit* command in Stata was used, a restricted cubic splines model was fitted with age, period and cohort as continuous variables[11]. The goodness-of-fit of the models was assessed using the analysis of deviance of nested models as described by Clayton and Schifflers[12, 13], and the importance of non-linear cohort and period effects were examined using the likelihood ratio test. Findings were considered statistically significant at a p-value of <0.05. All analyses were performed using Stata/IC version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Incidence trends of ovarian cancer

Figure 1 illustrates the estimated ovarian cancer incidence rates by country worldwide from GLOBOCAN 2018. Highest rates in 2018 (ranging from 8.2 to 16.6 per 100,000 person-years) were estimated mostly in Eastern Europe (e.g. Serbia, Belarus, and Poland). Table 1 presents the total number of observed cases and ASRs in countries with long-term ovarian cancer data for the last 5-year period (2008–2012) for pre- and post-menopausal age groups: 25–49 years and 50–74 years. Overall, European countries had the highest incidence of ovarian cancer among women ages 50–74 years, ranging from 27.1 per 100,000 person-

years in Spain to 44.9 in Lithuania. In the more recent 5–year period, Belarus (ASR=14.8) had the highest incidence in the younger age group (25–49 years), followed by Lithuania (ASR=13.7). Switzerland (ASR=4.2) had the lowest incidence of ovarian cancer, followed by black women in the United States (ASR=4.5).

Assessing the long-term trends among women aged 25–49 years, a clear declining trend were observed in several high-income countries, such as Australia, New Zealand, United States (White), Canada, Scotland, Norway, Denmark and France (Figure 2A). On the other hand, over the last 15 years most changes are statistically insignificant (Figure 3A & Table S1). Meanwhile, among women aged 50–74 years, marked declines in ovarian cancer incidence were observed in almost all countries, particularly in Northern and Western Europe, North America, as well as, in Australia and New Zealand (Figure 2B). The highest decrease in this region was seen in Denmark with an estimated annual percent change of −2.4% (95% CI=−3.9, −0.9) (Figure 3B & Table S1). Incidence trends in countries in economic transition were not significantly different over time in the last 15 years, although rising incidence rates were observed among post-menopausal Japanese and Indian women. As for the oldest age group, women aged 75+, incidence trends were generally stable (Figure S1 & S2).

Birth cohort effects

APC analysis was performed on five selected countries in the study: Australia, Belarus, Denmark, Japan, and United States (White). The full APC model was the best fitting model for all five countries (Table S2). Figure 4 illustrates the age-specific incidence rate of ovarian cancer by 5-year age group plotted against the year of birth (period effect) and years of diagnosis (cohort effect). The figure shows declining incidence rates of ovarian cancer for the majority of age groups among birth cohorts born after 1930 in Australia, Denmark and United States. Additionally, the United States and Denmark exhibited decreasing trend in IRR among birth cohorts born after 1930 that continued to the youngest cohort (IRR=0.61 [95% CI=0.52, 0.71] and IRR=0.53 [95% CI=0.41, 0.68] vs the 1950 birth cohort) (Figure 5 & Table S3). In comparison, the descending trend of IRR in Australia slowly levelled-off among the younger birth cohorts starting with cohorts born around 1965 (IRR=0.83, 95% CI=0.78, 0.89). Meanwhile, a consistent increase of IRR was observed across birth cohorts in Belarus born after 1950. An IRR of 2.50 (95% CI=2.09, 3.00) was observed in the youngest cohort born around 1985 compared to the reference birth cohort (1950). A steady rise of IRR across successive birth cohorts was also detected in Japan starting with the 1920 birth cohorts.

Period effect to the secular trend

Denmark and the United States also exhibited declining IRRs across periods of diagnosis after the year 2000 indicating possible period effect (Figure 4, 5 & Table S4). In contrast, IRRs in Japan has been steadily increasing across all periods of diagnosis, however, the non-linear period effect was not significant (Table S2). The IRR in Belarus was relatively stable until 2010 when an upsurge (IRR=1.14, 95% CI=1.09, 1.19 vs the 1998–2002 period) was observed.

Prevalence of selected risk and protective factors for ovarian cancer

Figure S3 illustrates the fertility rates by calendar year using data from World Bank Open Data (https://data.worldbank.org/), as well as the estimated prevalence of OC use in 2015 among married or in-union women aged 15–49 (based on data published by the United Nations, Population Division14) for selected countries plotted with their ovarian cancer ASRs. Similarly, Figure S4 shows the prevalence of obesity from 1988 to 2012 among women aged 20 and above using data from the NCD Risk Factor Collaboration (http://ncdrisc.org/).

Discussion

The current study provides a comprehensive overview of recent global burden and long-term trends in ovarian cancer incidence across 27 countries. Ovarian cancer occurs largely in post-menopausal women with incidence levels higher in European and North American countries relative to countries in Asia, Central and South America in the 50–74 years age group. For the past few decades, in most countries where rates were traditionally high, overall declines in incidence rates were observed particularly in post-menopausal women aged 50–74 years. Among the five countries analysed for APC, cohort and period effects were observed in Denmark and the United States. In contrast, large increases in ovarian cancer incidence rates were distinctly observed in Japan and Belarus, which were linked to generational changes over the birth cohorts.

Marked decreases in ovarian cancer were seen in Europe, North America, Australia and New Zealand have been reported in other studies and are driven by the changing incidence in post-menopausal women, potentially linked to the widespread use of OC[5, 15, 16]. A previous study observed a decrease in ovarian cancer incidence starting in cohorts born around the 1920s in Australia and the United States, which was suggested to be driven by the use of OC starting around the 1960s[5]. Moreover, several epidemiological studies showed that the use of OC is associated with a significant decrease in ovarian cancer with an estimated reduction of approximately 30–50% for OC use of at least five years, and the protective effect persisting at least 10–15 years since last use[4, 17–19]. Over the last decades decline in OC use and a slight increase in use of other methods of contraceptives[14, 20, 21], as well as changes in OC formulations[16], may impact future patterns and trends of ovarian cancer. Nonetheless, recent findings from a Danish prospective study showed reduced risks of ovarian cancer in women using any contemporary hormonal contraception, including various type of OC, patch, vaginal ring, and implants[22] suggesting that the decrease in ovarian cancer may continue.

High-income countries in the current study generally exhibited declining incidence of ovarian cancer, except for Japan and Belarus where rates have markedly increased. A previous study has reported a steady increase of ovarian cancer in Niigata, Japan from 1983 to 2007[23]. The observed trend in Japan may partly be explained by the low level of OC use among Japanese women. In 2015, the prevalence of OC use among married or in-union women aged 15–49 years in Japan was only1.1%, which is dramatically lower compared to other high-income countries such as the United States (16.0%) and France (39.5%)[14]. Another potential explanation is lower parity, for instance, studies have shown that a history of one or more full-term pregnancies decreases the risk of ovarian cancer in women, and

with further reduction in risk for each additional pregnancy[4, 17, 18]. This might explain the increasing rates especially in the younger cohorts also in countries such as India and Thailand. We also observed that mucinous carcinoma, which is less closely linked to OC use[19], was more commonly seen in Asia and South American countries (Figure S5 shows the distribution of histological groups in the current study for periods 1988–1992 and 2008–2012 by country). Adoption of western lifestyle in these countries may thus partly contribute to the increasing incidence[24, 25]. Hence, continued surveillance remains relevant to detect early changes in the incidence trends, particularly in the younger generations.

The current study also showed a continuous decrease of incidence in Israel. Israel has high frequency of *BRCA1* and *BRCA2* mutations, specifically among the Ashkenazi Jewish population with an estimated prevalence of 1 in 40[26, 27]. The cumulative cancer risk for ovarian cancer up to age 70 years is estimated to be approximately 40% for *BRCA1* carriers and 18% for *BRCA2* carriers[27]. High rates of risk reducing surgery for ovarian cancer in Israeli women[28] with *BRCA* mutation may contribute to the decreasing trend observed in the country.

Other reproductive factors, such as age at menarche, age at menopause, tubal ligation, and use of menopausal hormone therapy[4, 17, 29, 30], may also contribute to observed patterns in ovarian cancer incidence. Asides from reproductive risk factors, body mass index (BMI) has also been associated with ovarian cancer risk[31, 32]. Particularly, findings from a pooled study showed an association between BMI and risk of non-serous and low-grade serous ovarian cancer[33]. Thus, the rise of obesity may potentially contribute to the increase of incidence observed in the study, particularly in the younger generations, however further study is warranted.

The period effect observed in the study may be partially explained by changes in disease classifications and cancer registry practices, which impact the incidence rates of ovarian cancer for the entire population. In the study, a noticeable increase in incidence rates across all age groups was observed between the last two consecutive periods in Belarus, indicating a possible period effect perhaps due to changes in registration practices over time. On the other hand, decreases in incidence rates across women ages 25–64 years were observed in Denmark and United States between the period 2000 and 2005. This decline may likely be due to changes in the disease classification. The ICD-O 2nd edition (ICD-O-2) was published by the World Health Organization in 1990, and the most recent version, ICD-O 3rd edition (ICD-O-3), was published in 2000. In ICD-O-3 ovarian tumors with borderline malignancy or low malignant potential were no longer considered as malignant tumors. Generally, the incidence of borderline tumors ranged from 14–15% out of the total incidence of primary ovarian cancer neoplasms[34]. Thus, the observed period effects in Denmark and United States may be a reflection of the transition of the cancer registries to ICD-O-3 in early 2000.

Ovarian cancer mortality has also been persistently decreasing over time[35], although the decline has been at a lower magnitude compared to the steep decrease in the incidence rates. The majority of women with ovarian cancer are diagnosed with advanced stage[36], and there are no effective early detection or screening methods[37, 38]. Overall, ovarian cancer has low

survival, and previous large population-based cancer survival studies have only shown slight improvements in ovarian cancer survival over the past decades[39–41]. Thus, decrease in mortality rates are likely due to the decreasing ovarian cancer incidence rather than improvements in survival.

The main strength of the study is the utilization of CI5 data. Only long established and reliable PBCRs with 25 consecutive years of data were included in the study to assess trends in incidence and to perform the APC analysis. The restrictive time inclusion, however, limits the number of countries represented in the study, and excluded most low- and middle-income countries, as well as limiting the number of PBCRs included in countries with sub-national cancer registries. Therefore, trends reported in this study from countries with sub-national cancer registries may not fully reflect the incidence trends experienced by these specific countries. In addition, women less than 25 years of age were excluded in the study due to very low number of cases leading to unstable ASRs. Ovarian cancer in this age group is uncommon, and are likely non-sporadic and linked to genetic factors. The study is also limited by the small number of cases in the younger age group resulting in wider IRR confidence intervals in the younger cohorts.

The study only had data for C56, malignant neoplasm of the ovary, while the more rare fallopian tubes and peritoneal primary carcinomas originating from the ovary were not accounted for in the current incidence estimate. Data from previous studies have suggested that many serous ovarian cancers likely originated from fallopian tubes[42]. Thus, the number of ovarian cancers coded as fallopian tubes may have increased recently, which may lead to the underestimation of the incidence in the most recent years of the study. Furthermore, previous studies showed that borderline ovarian cancer has been misclassified as carcinoma with misclassification ranging between 9–21%[43], which may result in an overestimation of the true incidence in some registries. Finally, the data presented in our study lacks individual records on the risk and protective factors for ovarian cancer, therefore a firm conclusion regarding the true causes of the observed trends could not be drawn. Despite these limitations, the data used in this study were very high quality from a reliable database that allowed for valid comparisons across countries.

In conclusion, the current study provided an overview of ovarian cancer trends worldwide and examined the influence of birth cohort and period on secular trends. In general, a marked decline of ovarian cancer incidence among post-menopausal women was observed for over three decades in the majority of the countries in the study, which is likely due to the widespread use of OC. Meanwhile, less geographic and temporal variability was observed on the incidence trends of pre-menopausal women. Differences in incidence trends can partly be explained by variations in the prevalence of several reproductive risk and protective factors, as well as, changes in classification and cancer registry practices. Hence, on-going cancer surveillance plays an essential role in detecting early shifts in the incidence trends of ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

A	age
Ad	age + drift
AP	age + period
AC	age + cohort
APC	age-period-cohort
ASR	age-standardized incidence rates
BMI	body mass index
BRCA1	breast cancer 1
BRCA2	breast cancer 2
CI	confidence interval
CI5	Cancer Incidence in Five Continents
df	degrees of freedom
EAPC	estimated annual percent change
ICD-O	International Classification of Disease for Oncology
IRR	incidence rate ratio
NCD	non-communicable disease
NL	non-linear
OC	oral contraceptive
PBCR	population-based cancer registry
SEER	Surveillance, Epidemiology, and End Result
UN	United Nations
AUS	Australia
BLR	Belarus
CAN	Canada
CHE	Switzerland

CHN	China
COL	Colombia
CRI	Costa Rica
CZE	Czech Republic
DNK	Denmark
ECU	Ecuador
ESP	Spain
EST	Estonia
FRA	France
HRV	Croatia
IND	India
ISR	Israel
ITA	Italy
JPN	Japan
LTU	Lithuania
NOR	Norway
NZL	New Zealand
PHL	Philippines
SCO	Scotland
SVK	Slovakia
SVN	Slovenia
THA	Thailand
USA (B/W)	United States (Black/White)

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Novelty and Impact

We provide an overview of international ovarian cancer patterns and trends in 27 countries using latest national estimates of incidence and recorded incidence from successive Volumes of *Cancer Incidence in Five Continents*. The influence of birth cohort and calendar period was examined in selected countries to better identify factors underlying the changing trends. We postulate on the reasons for the divergent trends in different populations, particularly the use of oral contraceptives and changing registration practice.

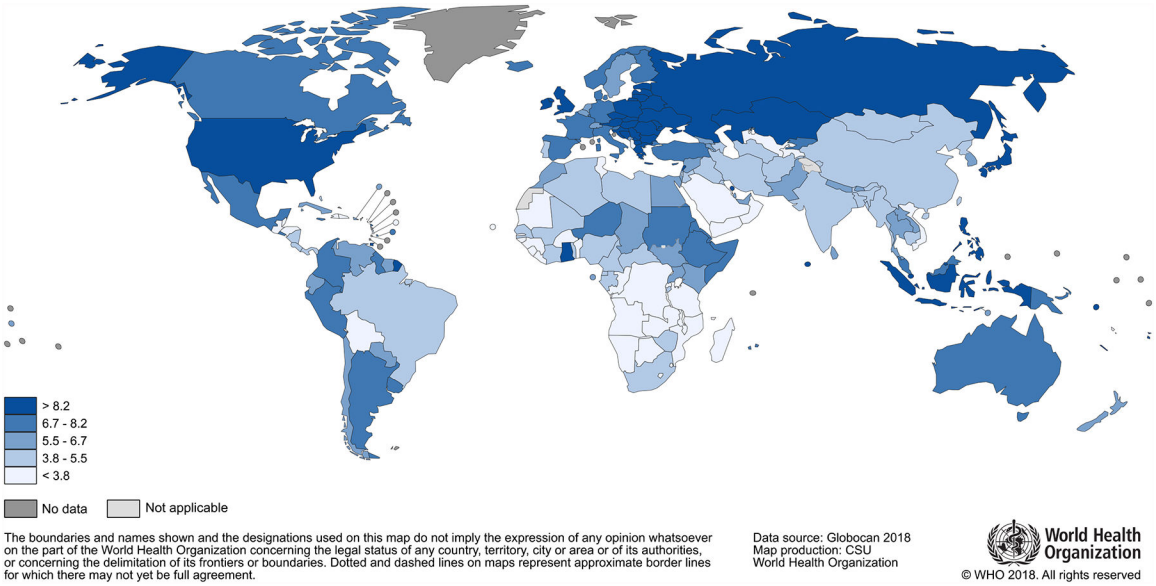

Figure 1.

Estimated age-standardized incidence rates (world standard, per 100,000 person-years) for ovarian cancer in 2018.

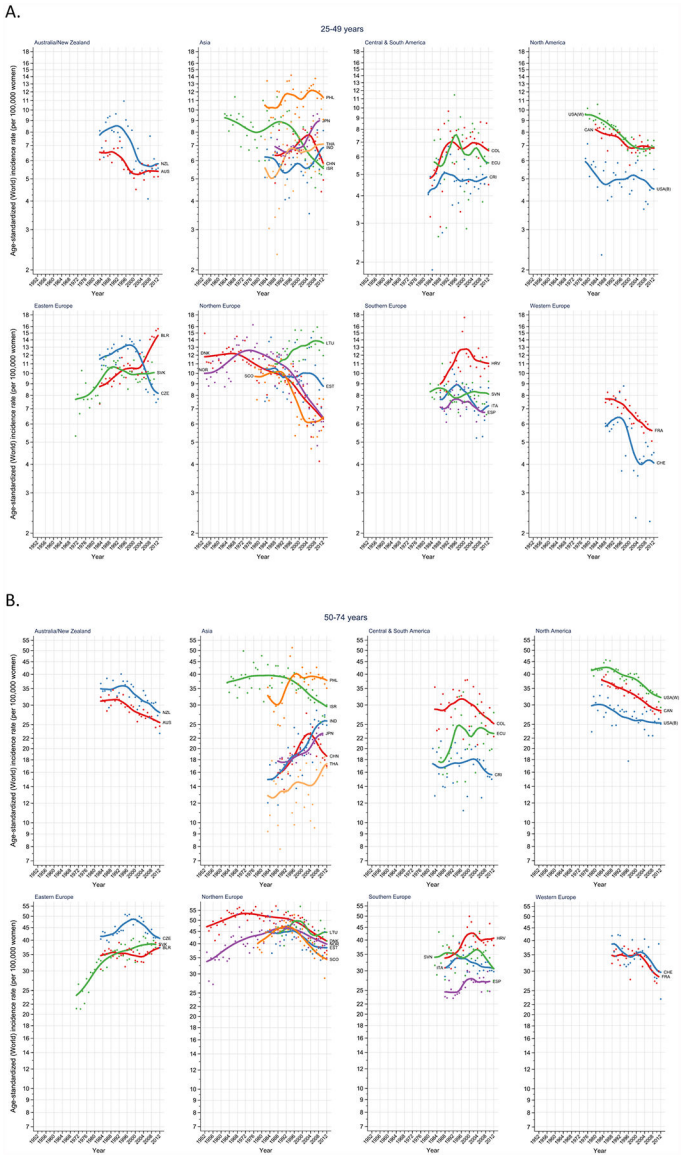

Figure 2.

Age-standardized incidence rates (ASR, per 100,000 person-years, log scale) of ovarian cancer by age groups. Two age groups: (A) 25–49 years and (B) 50–74 years. Countries included: (Asia) CHN=China, IND=India, ISR=Israel, JPN=Japan, PHL=Philippines, THA=Thailand; (Oceania) AUS=Australia, NZL=New Zealand; (North America) CAN=Canada, USA=United States; (Central & South America) COL=Colombia, CRI=Costa Rica, ECU=Ecuador; (Eastern Europe) BLR=Belarus, CZE=Czech Republic, SVK=Slovakia; (Northern Europe) DNK=Denmark, EST=Estonia, LTU=Lithuania, NOR=Norway, SCO=Scotland; (Southern Europe) ESP=Spain, HRV=Croatia, ITA=Italy, SVN=Slovenia; (Western Europe) CHE=Switzerland, FRA=France.

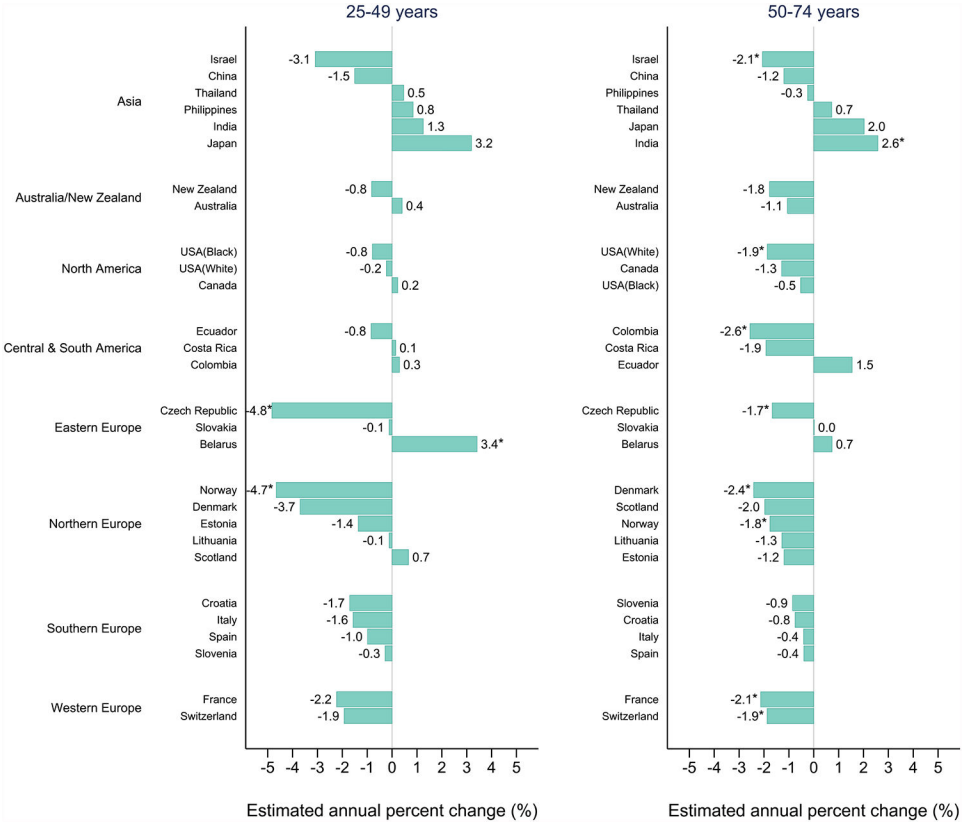

Figure 3.

Estimated annual percent change (EAPC, %) of ovarian cancer between 1998 and 2012 by age groups. Costa Rica and France only until 2011; Japan, Slovakia, and Spain only until 2010. Statistically significant EAPC, 95% confidence interval not including zero, indicated by (*).

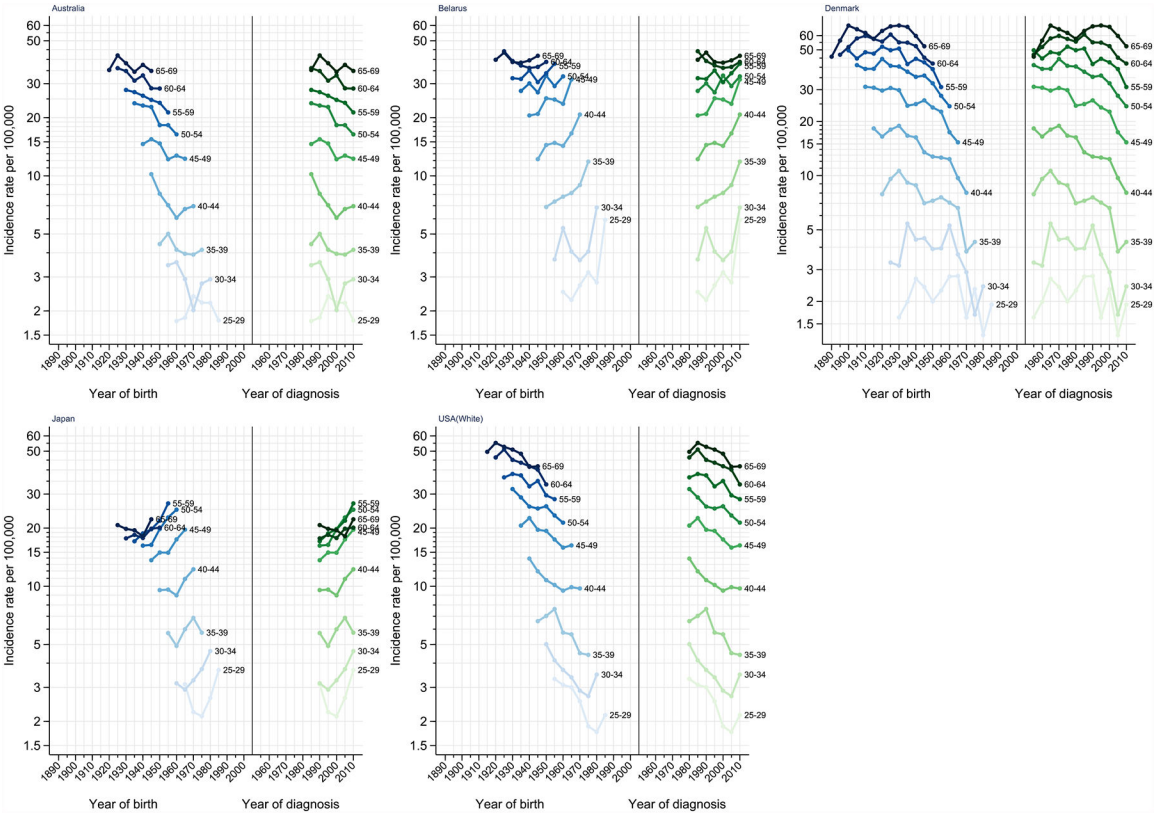

Figure 4.

Age-specific incidence rates for ovarian cancer by year of birth (cohort) and year of diagnosis (period). Australia includes New South Wales, Tasmania, Victoria, South Australia, and Western Australia. United States includes Georgia, Greater California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Utah, and Wisconsin (SEER-9).

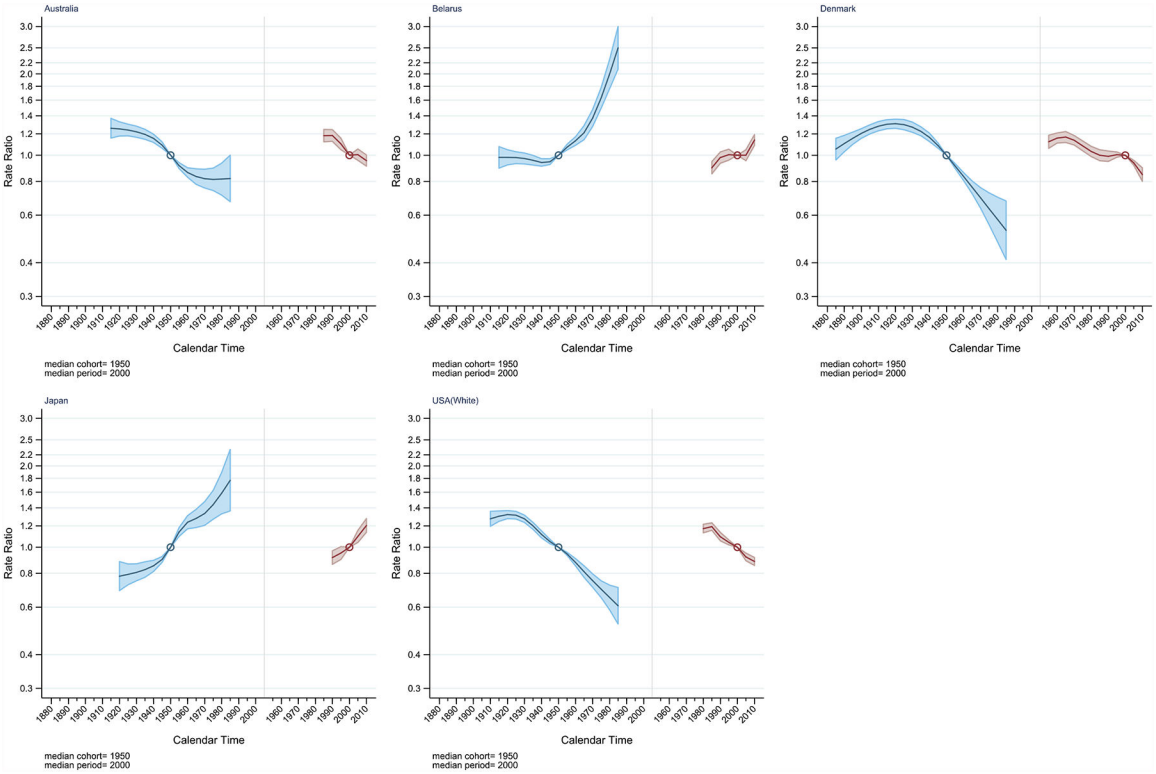

Figure 5.

Ovarian cancer incidence rate ratio for cohort (blue) and period (red) for selected countries. Australia includes New South Wales, Tasmania, Victoria, South Australia, and Western Australia. United States includes Georgia, Greater California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Utah, and Wisconsin (SEER-9).

Table 1.

Age-standardized incidence rates (per 100,000 person-years) of ovarian cancer for 2008–2012[¶], by age groups

Country	Population coverage (million)	Period		24–49 years		50–74 years	
		Start	End	Cases	ASR	Cases	ASR
Asia							
China (Shanghai)	3.1	1988	2012	353	6.2	1143	19.2
India (Chennai)	2.3	1983	2012	303	6.9	498	25.7
Israel[†]	3.9	1963	2012	313	5.4	1093	28.0
Japan[‡]	6.6	1978	2010	577	8.8	1454	23.2
Philippines (Manila)	3.3	1983	2012	631	11.4	838	37.6
Thailand (Chiang Mai)	0.8	1983	2012	111	6.9	180	17.6
Australia/ New Zealand							
Australia[‡]	8.6	1983	2012	865	5.4	2894	25.5
New Zealand[†]	2.2	1983	2012	249	6.1	799	28.3
Central and South America							
Colombia (Cali)	1.2	1983	2012	146	6.6	273	24.9
Costa Rica[†]	2.2	1982	2011	160	4.9	229	15.5
Ecuador (Quito)	0.8	1985	2012	79	5.5	153	23.4
North America							
Canada[‡]	13.1	1983	2012	1726	6.8	5111	28.3
United States[‡]: Black	2.0	1978	2012	163	4.5	504	25.1
United States[‡]: White	10.8			1341	6.9	4744	32.0
Eastern Europe							
Belarus[†]	5.1	1983	2012	1404	14.8	2775	37.2
Slovakia[†]	2.8	1971	2010	304	10.0	899	38.5
Northern Europe							
Denmark[†]	2.8	1953	2012	311	6.1	1670	38.9
Estonia[†]	0.7	1983	2012	111	9.1	440	38.2
Lithuania[†]	1.7	1988	2012	436	13.7	1171	44.9
Norway[†]	2.4	1953	2012	255	5.8	1259	38.5
United Kingdom (Scotland)	2.7	1978	2012	336	6.6	1400	34.3
Southern Europe							
Croatia[†]	2.3	1988	2012	437	10.9	1442	40.4
Italy[‡]	1.5	1988	2012	190	7.2	645	30.9
Slovenia[†]	1.0	1983	2012	164	8.4	473	30.5
Spain[‡]	3.0	1988	2010	241	6.7	648	27.1

Country	Population coverage (million)	Period		24–49 years		50–74 years	
		Start	End	Cases	ASR	Cases	ASR
Western Europe							
France[‡]	3.0	1983	2011	243	5.7	958	28.6
Switzerland[‡]	1.0	1988	2012	79	4.2	400	29.7

[¶]Costa Rica (2008–2011); France (2008–2011); Japan (2008–2010); Slovakia (2008–2010); Spam (2008–2010)

[†]National cancer registry

[‡]**Australia** - New South Wales, Tasmania, South Australia, Victoria, and Western Australia; **Canada** excludes Nunavut, Quebec and Yukon; **France** - Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, and Somme; **Italy** - Modena, Parma, Ragusa, and Romagna; **Japan** - Miyagi, Nagasaki, and Osaka; **Spain** - Basque Country, Granada, Murcia, Navarra and Tarragona; **Swi tzerland** - Geneva, Neuchatel, St. Gall-Appenzell, and Vaud; **United States** - Georgia, Greater California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Utah and Wisconsin (SEER-9)