Trends in hormone use and ovarian cancer incidence in US white and Australian women: implications for the future

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ABSTRACT

Purpose: To compare trends in ovarian cancer incidence in the USA and Australia in relation to changes in oral contraceptive pill (OCP) and menopausal hormone therapy (MHT) use.

Methods: US cancer incidence data (1973-2013) were accessed via SEER*Stat; Australian data (1982-2012) were accessed from the Australian Institute of Health and Welfare Cancer Incidence and Mortality books. Age-period-cohort models were constructed to assess trends in ovarian cancer incidence by birth cohort and year of diagnosis.

Results: Ovarian cancer rates were increasing until the cohorts born around 1918 in the USA and 1923 in Australia who were the first to use the OCP. They then declined dramatically across subsequent cohorts such that rates for the 1968 cohort were about half those of women born 45 years earlier; however, there are early suggestions this decline may not continue in more recent cohorts. In contrast, despite the large reduction in MHT use, there was no convincing evidence that ovarian cancer incidence rates in either country were lower after 2002 than would have been expected based on the declining trend from 1985.

Conclusions: The major driver of ovarian cancer incidence rates appears to be the OCP. This means that when those women born since the late 1960s (who have used the OCP at high rates from an early age) reach their 60s and 70s, incidence rates are likely to stop falling and may even increase with changes in the prevalence of other factors such as tubal ligation and obesity. Forward predictions based on past trends may thus under-estimate future rates and numbers of women likely to be affected.

Keywords: Ovarian cancer, incidence rates, trends, oral contraceptive pill, menopausal hormone therapy

INTRODUCTION

Globally, ovarian cancer was the seventh most common cancer in women in 2012 with approximately 240,000 new cases [1] although, in most high-income countries, age-standardized incidence rates have been falling over the last two to three decades [2]. Factors that influence risk of ovarian cancer include use of exogenous hormones. The oral contraceptive pill (OCP) has consistently been shown to reduce a woman's risk of developing ovarian cancer by approximately 20% for every five years of use. Benefits persist for several decades after last use and although OCP formulations have changed over time, particularly with the introduction of lower estrogen doses in the early 1970s, the reduction in risk of ovarian cancer associated with use does not appear to have changed [3]. In contrast, use of menopausal hormone therapy (MHT) appears to increase risk of ovarian cancer, particularly the serous and endometrioid subtypes, by about 40% [4].

The OCP was first approved for contraception in the USA in 1960 closely followed by Australia in 1961, although use in Australia was initially restricted to married women. Uptake was rapid (Figure 1a). In the USA, 19% of women of reproductive age were using the OCP by 1965 increasing to a peak of 27% in 1975 [5]. Levels then dropped and stabilised at 15-18% as tubal sterilisation, which is also associated with a 20-30% reduced risk of ovarian cancer [6], became more common as a form of contraception [5]. Similarly, OCP use among Australian women increased from 6% in 1961 to 28% by 1976 however, unlike the USA, use has remained high [5, 7]. Trends in MHT use are similar in the USA and Australia (Figure 1b). Use increased dramatically from 1980 until 2002 when the Women's Health Initiative (WHI) Trial results were published showing increased risks of breast cancer among women using combined estrogen plus progestogen hormone therapy [8]. This led to more than a 50% reduction in use of both combined and estrogen-only MHT over the next few years [4, 9-11].

Given the known associations between hormone use and ovarian cancer risk it is likely the dramatic changes in hormone use over the preceding decades will have influenced ovarian cancer rates. The observed decline in ovarian cancer incidence is most likely due, at least in part, to the introduction of the OCP. There are also suggestions that the reductions in MHT use after 2002 may have led to lower incidence of ovarian cancer [12] as has been previously reported for breast cancer [11, 13]. A recent report used joinpoint regression models to predict future global trends in ovarian cancer [14] however this focused only on mortality and also assumed that recent trends would continue. We are now at a point where women in their 50s and 60s, the ages when ovarian cancer becomes more common, have had access to the OCP for the whole of their reproductive lives. It remains unclear what the final impact of the changes in MHT use on ovarian cancer rates might be. The aims of this study were therefore to evaluate and compare trends in ovarian cancer incidence in the USA and Australia, two countries with early uptake and high rates of hormone use, in relation to changes in the prevalence of OCP and MHT use to inform predictions of future incidence rates.

METHODS

We used publically available data to construct age-period-cohort models using the NIH Age Period Cohort Web Tool (available at http://analysistools.nci.nih.gov/apc/) to assess trends in ovarian cancer incidence by birth cohort and year of diagnosis. Joinpoint analysis was conducted using the Joinpoint Regression Program (version 4.3.1.0, April 2016) from the Statistical Research and Applications Branch, National Cancer Institute, USA.

We have restricted our analyses to women aged 30 years and over as most is known about the epidemiology of epithelial ovarian cancers which comprise the vast majority of ovarian cancers diagnosed in women over the age of 30 but are rare among younger women. US

cancer incidence data for the years 1973 to 2013 were accessed via SEER*Stat using the April 2016 release of the US SEER 9 Registries Research Data [15]. Australian cancer incidence data for the years 1982 to 2012 were accessed from the Australian Institute of Health and Welfare Australian Incidence Cancer Incidence and Mortality book for Ovarian cancer [16]. For the USA we restricted our analysis to white women as they are the largest subgroup and are genetically comparable to the Australian population. In Australia, detailed data are not available by race but, among the age-groups most affected by ovarian cancer, more than 90% of the population is Caucasian. Age-standardized rates for both the USA and Australia are standardized to the US 2000 population.

For age-period-cohort analyses, age at diagnosis was categorised into 5-year groups from 30-34 up to 85 and older, and year of diagnosis into 5-year bands. For analyses of trends in relation to OCP use we included women aged 30 and older and used the 1923 birth cohort as the reference group for calculation of rate ratios (RR, adjusted for age and period effects) and 95% confidence intervals (CI) as this was the first cohort to be exposed to the OCP. For analyses of trends in relation to MHT we included women aged 50 and older and used 1983-1987 as the reference as this was the earliest period with data for both Australia and the USA.

RESULTS

Figure 2 shows trends in ovarian cancer incidence rates from the early 1970s in the USA (whites) and from the 1980s in Australia, by 10-year age group. Historically, rates were much higher in the US than Australia, but greater declines in the USA have reduced this difference in more recent years. Join-point analysis showed that, overall, age-standardized rates among women aged 30 and over in the US fell by 0.9% (95%CI 0.8%-1.1%) per year between 1985 and 2010, increasing to a decline of 4.2% (0.2-8.0%) per year between 2010-2013. Much of

this decline, particularly in the most recent years, occurred among women aged 50 and over in whom rates fell by 1.8% per year (95%CI 1.3%-2.2%) from 1999. In contrast, while rates among younger women fell by an average of 1.4% (95%CI 1.2-1.5%) per year, there are suggestions they may have stabilised in more recent years (Figure 2, Supplementary Table 1). The pattern was similar in Australia where age-standardized rates among women aged 50 and over fell by 0.9% (95%CI 0.7%-1.2%) per year from 1994 with little change among younger women after 1998. Looking more closely at the older age-groups, Figure 2 and Supplementary Table 1 show that while rates among women aged 50-59 declined across the whole period, rates among those over aged 60 only started to fall from the mid-1980s for the 60-69 year age-group and from the mid-1990s for the 70-79 year age-group and, in the USA, the 80+ group.

Consistent with these patterns, age-period-cohort models show that the declines in incidence began with the cohort born around 1918 in the USA and around 1923 in Australia (Figure 3, Supplementary Table 2); these are the women who were in their 60s in the 1980s and their 70s in the 1990s. Rates then declined across successive birth cohorts such that the rate among women born in the 1960s is only around half that among those born in the early 1920s (1968 vs. 1923: USA RR=0.56, 95%CI 0.45-0.68; Australia RR=0.55, 95%CI 0.42-0.71). However, the limited data for the more recent birth cohorts suggest the decline may not continue for more recent cohorts in Australia or for cohorts born from the mid-1970s in the USA.

Figure 4 shows period rate ratios for women aged 50 years and over. The rate ratio compares incidence at different periods to that from1983-87, adjusted for age- and birth cohort effects. Although rates in the USA have generally declined over time, the trend is not smooth. As previously reported, rates fell dramatically between 1998-2002 and 2003-2007 [12]; however, this does not appear to be due to a lower than expected rate in 2003-2007, but because the 1998-2002 rate was higher than would have been expected based on the previous trend

(Figure 4). It is unlikely the slight up-turn in incidence around 2000 was due to MHT as ovarian cancer rates had been declining since the mid-1980s when the dramatic increase in MHT use began [4]. Overall, age-period-cohort models showed no evidence for deviation from a constant log-linear decrease across the whole time period (Wald test, p=0.5). In contrast, rates in Australia declined steadily from the early 1990s with no evidence for deviation from a log-linear trend (p=0.99) and no suggestion that rates declined more quickly after 2002. A very similar pattern was seen when the analysis was restricted to women aged 50 to 79 years when MHT use is most common (results not shown).

DISCUSSION

Ovarian cancer incidence rates began to decline from the cohort born around 1920; this cohort was aged about 40 in 1960 and so was the first to have any access to the OCP. Rates then declined dramatically over the successive birth cohorts when women could not only access the OCP at progressively younger ages, but both ease of access and the prevalence of use also increased, especially in Australia. These changes are consistent with the known strong protective effect of the OCP against ovarian cancer [3] with estimates from Australia suggesting that among women born in the late 1960s who have had maximum opportunity to use the OCP, prior OCP use reduced the number of ovarian cancers that would otherwise have occurred in 2010 by as much as 33% [17].

In contrast, the previously reported acceleration of the decline in ovarian cancer incidence among women aged 50 and over in the USA after the WHI publication in 2002 appears less dramatic when considered in the context of the trends before and after the relatively narrow time period (1995-2008) considered in that analysis [12]. There was also no suggestion that rates increased (or declined less rapidly) in the USA after 1985 when MHT use was

increasing, or that rates in Australia declined more rapidly after 2002 despite the fact that large numbers of Australian women also stopped using MHT at that time [11]. This is consistent with estimates that, in contrast to the large proportion of ovarian cancers prevented by the OCP, only a relatively small proportion are likely to be attributable to MHT use. In Australia it was estimated that about 2% of ovarian cancers among women over the age of 50 could be attributed to MHT based on the prevalence of use in 2004-5 [18]. Even assuming use prior to 2002 was two or three times higher, the attributable fraction would still have been only 4-6%. Any potential effect of changing MHT use on ovarian cancer incidence rates would thus be expected to be much smaller than that seen for the OCP. Similarly, although MHT use may have been slightly more common in the USA than Australia, the overall declining trend is likely a consequence of the increasing OCP use two decades earlier.

There have also been changes in the prevalence of other factors that influence a woman's risk of developing ovarian cancer. The increasing fertility rates after World War II [19] may have contributed to some of the decline in ovarian cancer incidence between about 1970 and 1990 as the mothers of the baby boom generation reached the ages when ovarian cancer becomes more common. Although fertility rates then fell again between 1960 and 1980 [19, 20], the potential adverse effects of this on ovarian cancer rates may have been counteracted by increasing rates of tubal ligation, which reduces a woman's risk of ovarian cancer, between 1970 and 1985 [21]. Increasing obesity rates since the 1980s may also have led to increased incidence of the less common histotypes of ovarian cancer [22, 23]. However, as obesity only accounts for a small proportion of ovarian cancers overall, 3-4% in Australia in 2010 [24], any effect is likely to have been small in comparison to that seen for the OCP. Reductions in the average age of menarche are unlikely to have had much effect as the absolute changes are small (~6 months between cohorts born from 1910-1949 and little change in more recent cohorts [25]) and age at menarche has not been established as a strong risk factor for ovarian

cancer. Likewise, although hysterectomy rates have fallen [26], recent studies have not shown an association with ovarian cancer risk [27]. Trends in oophorectomy rates are less clear, however they would have had to have increased dramatically over a period of several decades to explain the overall downward trend in ovarian cancer incidence.

OCP use is most common among women aged 20-35 whereas the highest incidence rates of ovarian cancer are not seen until ages 60-79 years so there will be a lag of two to three decades between changes in the prevalence of OCP use and any resulting changes in ovarian cancer incidence. Thus although OCP use started to become prevalent in the 1960s, age-standardized ovarian cancer rates did not start to fall until the mid-1980s in the USA and the early 1990s in Australia. However, by the 1960s birth cohort, women had ready access to the OCP from a young age thus it is less likely that this and the subsequent cohorts will have lower ovarian cancer rates than the cohorts that preceded them and, in Australia at least, there are suggestions that ovarian cancer rates may no longer be falling in these younger women. In 15 years when the women born in the 1960s reach their 70s it is likely that rates among the older age groups will also stabilise. Meanwhile, changes in the prevalence of other factors noted above may start to drive ovarian cancer rates up in the future. After peaking in 1985, rates of tubal sterilisation in the USA and Australia have since stabilised or even declined [5, 21] while, as in most high income countries, obesity rates continue to increase in both the USA and Australia [28, 29].

In conclusion, considering 30-40 years of cancer data from the USA and Australia, the trends in ovarian cancer incidence can largely be explained by changes in OCP use two to three decades earlier while more recent changes in MHT use seem less likely to have had a major impact. The implications of this and the rises in other risk factors like obesity are that the current declines in incidence are unlikely to continue. If forward predictions are based on

past trends of declining rates it is likely they may under-estimate future incidence rates and the numbers of aging women likely to be affected.

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Figure 1.

Trends in (a) the proportions of women using the oral contraceptive pill (OCP) and (b) estimated prescriptions for menopausal hormone therapy (MHT) per 1000 women aged ≥50 in the USA and Australia

a. Sources of data: USA OCP (age 15-44 years) [5], Australia OCP use (age 15-44 years) prior to 1986 [7], Australia OCP use (estimated for age 15-44 years) from 1986 [5]

b. Note: USA [9, 10] and Australian data [11] come from different sources so the absolute values may not be directly comparable. Australian data are only available for those eligible for subsidised medications; total numbers are estimated assuming these account for 50% of all prescriptions (based on data from 2013-14 when full data are available).

Figure 2. Ovarian cancer incidence rates in (a) USA whites and (b) Australia, by age group

Rates are rolling 3-year averages.

Figure 3. Ovarian cancer incidence age 30+ years in (a) USA whites and (b) Australia, by birth cohort

The cohort rate ratio (RR) compares incidence among women born in a given birth cohort to the 1923 cohort, adjusting for age and period effects. Shaded areas show the 95% confidence intervals.

Figure 4. Ovarian cancer incidence age 50+ years in (a) USA whites and (b) Australia, by year of diagnosis

Period rate ratios in (a) USA Whites and (b) Australia. The period rate ratio compares incidence in a given time period to the incidence in 1983-1987, adjusting for age and cohort effects. Shaded areas show the 95% confidence intervals.