Why have ovarian cancer mortality rates declined? Part I. Incidence

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ABSTRACT

The age-adjusted mortality rate from ovarian cancer in the United States has declined over the past several decades. The decline in mortality might be the consequence of a reduced number of cases (incidence) or a reduction in the proportion of patients who die from their cancer (case-fatality). In part I of this three-part series, we examine rates of ovarian cancer incidence and mortality from the Surveillance Epidemiology and End Results (SEER) registry database and we explore to what extent the observed decline in mortality can be explained by a downward shift in the stage distribution of ovarian cancer (i.e. due to early detection) or by fewer cases of ovarian cancer (i.e. due to a change in risk factors). The proportion of localized ovarian cancers did not increase, suggesting that a stage-shift did not contribute to the decline in mortality. The observed decline in mortality paralleled a decline in incidence. The trends in ovarian cancer incidence coincided with temporal changes in the exposure of women from different birth cohorts to various reproductive risk factors, in particular, to changes in the use of the oral contraceptive pill and to declining parity. Based on recent changes in risk factor propensity, we predict that the trend of the declining age-adjusted incidence rate of ovarian cancer in the United States will reverse and rates will increase in coming years.

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1. Introduction

Ovarian cancer accounts for 3% of all cancers in women, but is over-represented in terms of cancer deaths (5%). In 2014, in the United States, 21,980 women were diagnosed with ovarian cancer and 14,270 women died of it [1]. Ovarian cancer is primarily a disease of post-menopausal women; approximately 70% of cases and 85% of ovarian cancer deaths occur after age 55 [2]. A woman who is diagnosed with breast cancer at age 70 is likely to die of another cause [3]—in contrast, if a woman is diagnosed with ovarian cancer at age 70, there is an 80% chance that the cancer will cause her death [4]. This is because the fatality rate is high (70%) and because 80% of deaths occur within five years of diagnosis [4]. As the American population ages and expands [5], the annual number of ovarian cancer cases is expected to rise. In order to reduce the burden of ovarian cancer in the population, it is necessary to prevent deaths across the age spectrum, and in particular, deaths in older women.

The modern era of ovarian cancer therapy began in 1977 with the introduction of cis-platinum. Nowadays, over 60% of women with invasive ovarian cancer are treated with debulking surgery and with a combination of a platinum agent and a taxane [6]. Since 1975, the mortality rate for ovarian cancer in the USA has declined by 23% [7]; it is tempting to conclude that the decline was the consequence of chemotherapy, but before doing so, it is prudent to explore alternative explanations. In the first two parts of the three-part series, we examine SEER rates of ovarian cancer incidence, case-fatality and mortality, with reference to calendar year, age and tumour stage, and we consider possible reasons for the observed decline in mortality. In Part I, we consider if the decline was due to a reduced number of cases (through changing trends in elective oophorectomy and/or in reproductive risk factors) or was due to a downward stage shift at presentation (through screening or better awareness). In part II, we consider if the decline in mortality was due to new and better treatments [8]. In part III, we discuss potential approaches for reducing ovarian cancer mortality in the future, through prevention, early detection and treatment [9].

Mortality rates describe the number of deaths from ovarian cancer in a given year, relative to the size of the population. A decline in mortality may reflect a reduction in the number of women diagnosed with ovarian cancer (incidence) or a reduction in the proportion of ovarian cancer patients who die from their disease (case-fatality). After a decline in incidence or in case-fatality, there will be a corresponding decline in mortality following a lag period of several years.

The Surveillance, Epidemiology, and End Results (SEER) registry has reported incidence, case-fatality and mortality data for 26% of the United States population since 1975 [7]. The use of standardized (versus crude) rates removes the effect of any changes in the age distribution of the underlying population in order to facilitate comparisons over time. All age-adjusted incidence and mortality rates are standardized to the year 2000 United States population (the standard population) and are expressed in terms of cases per 100,000 women per year. We complement the SEER data analysis by cross-referencing other data sources which compile information on reproductive risk factors and oophorectomies. Information on the use of oral contraceptives, parity, breast-feeding and tubal ligations was abstracted from questionnaires that were completed by 2000 North American women without ovarian cancer who attended a clinic appointment for BRCA genetic testing at our research laboratory and were found to be negative for mutations in BRCA1/2. Oophorectomy data were obtained from the National Health Discharge Survey database maintained by the Centers for Disease Control and the National Center for Health Statistics.

2. Trends in mortality

From 1975 to 2011, in the United States, the age-adjusted mortality rate from ovarian cancer declined by 23%, from 9.8 per 100,000 per year to 7.5 per 100,000 per year. The rate declined by 8% from 1975 to 2001 and by 17% from 2002 to 2011 (Fig. 1).

The 23% decline in the age-adjusted mortality rate is an indication that progress has been made; however, it does not reflect the actual burden of the disease in the United States. The total number of ovarian cancer deaths in a given year is influenced by the age-specific mortality rates, as well as by the age-distribution and the size of the population at risk. The unadjusted (i.e. crude) mortality rate is calculated by dividing the total number of ovarian cancer deaths in a given year by the total number of women in the population. From 1975 to 2011, the crude mortality rate fell by only 2% (from 9.3 per 100,000 per year to 9.1 per 100,000 per year) (Fig. S1). That is, the aging of the female population between 1975 and 2011 has offset the decline in age-specific mortality rates. From 1975 to 2011, the total number of ovarian cancer deaths in the United States increased by 38%, from 10,367 deaths to 14,323 deaths, despite the 23% reduction in the age-adjusted mortality rate.

The trends in age-adjusted mortality differed for women in different age groups (Fig. S2). From 1975 to 2011, for women from ages 50 to 64, the mortality rate declined continuously (by 44.7%). For women between ages 65 to 74, the mortality rate first increased (by 9.2% from 1975 to 1991) and then declined (by 22.8% from 1991 to 2011). For women ages 75 and older, the rate increased by 43% from 1975 to 2002 and then declined (by 12.3% from 2002 to 2011).

Trends in age-specific rates may be attributable to period and/or cohort effects. A period effect results from the introduction of a change that affects the risk of an entire population simultaneously, irrespective of age. A cohort effect compares the lifetime experiences of individuals grouped by year of birth. For example, women who were 50 years of age in 1975, 65 years of age in 1990 and 75 years of age in 2000 all belong to the same birth cohort—the first women exposed to the oral contraceptive pill, which was introduced in 1960 [10].

3. Trends in incidence

Incidence rates describe the number of women who are diagnosed with ovarian cancer in a given year, relative to the size of the population. Incidence rates are calculated by dividing the number of cases by the population at risk. Only people with ovaries are at risk for developing ovarian cancer (i.e. males are not included in the denominator of ovarian cancer rate calculations). Women who have had their ovaries removed are also, by definition, not at risk for ovarian cancer, but these women are not excluded from the population at risk in SEER incidence and mortality rates. Changes in the proportion of women in the population with intact ovaries may therefore influence trends in ovarian cancer incidence and mortality. Incidence rates differ from mortality rates because not all women who are diagnosed with ovarian cancer will die from it. If a particular factor affects the incidence of ovarian cancer, the impact on the number of ovarian cancer deaths will not be seen until several years later. The lag period between a change in incidence and a change in mortality reflects the survival times of the patients (i.e. from diagnosis to death).

The observed trends in ovarian cancer incidence parallel the trends in ovarian cancer mortality. From 1975 to 2011, the age-adjusted ovarian cancer incidence rate fell by 26%, from 16.3 per 100,000 women per year to 12.1 per 100,000 women per year (Fig. 2). Ovarian cancer incidence declined by 3.4% from 1975 to 1991 and by a further 23% from 1991 to 2011. The decline, which began in 1991, was followed by a decline in mortality about 10 years later. The trends in incidence varied for women from different age groups (Fig. S3). From 1975 to 2011, ovarian cancer incidence in women ages 50 to 64 years fell by 13.5 per 100,000 per year, and by 17% from 2002 to 2011. Incidence in women ages 75 and older rose by 14.8 per 100,000 per year from 1975 to 1993 (a relative increase of 31%) and fell by...
13.3 per 100,000 per year from 1993 to 2011 (a relative decline of 21%). The decline in incidence in women ages 65 and older suggests that the reduction in ovarian cancer deaths is the result of a reduction in cases of ovarian cancer (surprisingly, in 1984 and 1985, the age-specific incidence rates were higher in women ages 65 to 74 than in women ages 75 and older. This is unexpected, given that incidence rates for ovarian cancer typically increase monotonically with age (Fig. 3). This transient reversal in 1984 and 1985 may be an artifact of sampling error or small sample size rather than a true increase in incidence. It might also reflect changing constellations in risk factor propensity for ovarian cancer).

In 2011, the incidence rate of ovarian cancer in the United States peaked among women ages 80 and older (Fig. 3), whereas the incidence count of ovarian cancer (i.e. the actual number of new ovarian cancer diagnoses) peaked among women ages 60 to 64, and then declined (Fig. 5). Women who were 60 to 64 years old in 2011 were born between 1946 and 1950, and represent the first born of the baby boom generation. After age 80, women tend to die of other causes and the at risk population becomes smaller.

4. Early detection

If the decline in ovarian cancer mortality were attributable to improvements in early detection (i.e. through screening or better awareness) we would expect to see a stage-shift in disease at presentation. Ovarian cancer may be diagnosed because of symptoms (e.g. abdominal pain) or signs of disease (e.g. distended abdomen), or as a consequence of a positive screening test in an asymptomatic woman (i.e. abnormal pelvic examination, serum CA125 concentration or trans-vaginal
The definitive diagnosis of ovarian cancer requires historical confirmation; the conventional date of diagnosis is the date of surgery.

In the SEER database, between 1975 and 2011, ovarian cancers were classified as either localized, regional or distant, based on the extent of cancer present at the time of surgery (i.e. stage at diagnosis). Localized disease (stage I) refers to ovarian cancer that is confined to the ovary, regional (stage II) refers to ovarian cancer that is confined to the pelvic tissues (uterus, fallopian tubes, ovaries or other intra-peritoneal tissues), and distant (stage III/IV) refers to ovarian cancer that has spread beyond the pelvic tissues (i.e. retroperitoneal lymph nodes, peritoneal cavity, liver, spleen or pleural effusion). The goals of staging are to aggregate patients into groups who have a similar prognosis and who require a similar approach to treatment, and to facilitate comparisons over time.

Statistical cure is defined as the point in time following diagnosis when the mortality rate from ovarian cancer is the same as the mortality rate of women in the general population. Ovarian cancer patients who survive for 12 years may be considered cured [11]. In the following pages, the term “cure rate” refers to the proportion of patients who are alive 12 years after diagnosis. The cure rate for patients with localized ovarian cancer is 88%; however, most patients (65%) present with distant-stage ovarian cancer, and for them the cure rate is 18% (SEER database).

It is hoped that the proportion of women who are diagnosed with early-stage ovarian cancer (and who are ultimately cured) might be increased through screening (i.e. by identifying pre-symptomatic ovarian cancer), through increased awareness (i.e. by reducing the time from first symptoms to doctor visit) or through better diagnostic methods (i.e. by reducing the time from first doctor visit to pathologic confirmation of ovarian cancer). If ovarian cancer screening has contributed to the observed decline in mortality, we would expect to see an increase in the incidence of localized ovarian cancer and a decrease in the incidence of distant ovarian cancer (i.e. a stage-shift). From 1975 to 2011, the incidence of localized ovarian cancer fell by 1.5 per 100,000 per year (a relative decline of 35%), the incidence of regional ovarian cancer fell by 0.1 per 100,000 per year (a relative decline of 8%), and the incidence of distant ovarian cancer fell by 2.1 per 100,000 per year (a relative decline of 22%) (Fig. 4). The incidence of ovarian cancer has declined at all stages; therefore it is unlikely that screening has had a significant impact on ovarian cancer rates.

An increase in the incidence of early-stage ovarian cancer without a proportionate decline in late-stage ovarian cancers is an indicator of overdiagnosis, i.e. the detection of low-risk cancers that might never become clinically apparent in the absence of screening (and rarely lead to death). For ovarian cancer, the detection of borderline tumours through screening may be considered examples of overdiagnosis; in general, these cancers do not progress into high-grade or advanced-stage tumours [12]. The absence of a significant increase in the incidence of localized ovarian cancer through screening precludes overdiagnosis. Further, there is no evidence that invasive ovarian cancers, however small, regress spontaneously.

Several randomized control trials have shown that screening asymptomatic women using trans-vaginal ultrasound and CA125 can detect a significant proportion of ovarian cancers in pre-clinical and early stages [11,12]; however, no screening protocol has yet been shown to reduce the number of advanced stage diagnoses or the number of ovarian cancer deaths [13]. Other approaches to ovarian cancer screening that are being evaluated include the use of serial CA125 measurements (e.g. the Risk of Ovarian Cancer Algorithm) [14] and the addition of other biomarkers (e.g. Human Epididymis Protein 4) in combination with CA125 [15]. The United States Preventive Services Task Force currently recommends against screening for ovarian cancer in asymptomatic women at average risk [16].

The symptoms of ovarian cancer are non-specific (e.g. bloating, pelvic pain or bowel irregularities) and patients and doctors may overlook their potential significance. Retrospective studies have reported delays of four to six months from symptom onset to a diagnosis of ovarian cancer [17–19]. Delays attributable to the patient and the doctor are roughly equal; about 70% of patients present with symptoms to their doctor within two months of first symptom onset, and about 65% of patients are diagnosed with ovarian cancer within two months after presenting with symptoms to their doctor. There has recently been an impetus to increase awareness of ovarian cancer symptoms in an attempt to reduce the time from first symptoms to diagnosis with the hope of improving ovarian cancer survival rates [20].

If formal efforts to increase awareness are successful, there should be an increase in the proportion of cancers diagnosed at an early stage.
over time may therefore impact on mortality rates. (Table S1). A shift in the histological distribution of ovarian carcinomas superior to that of patients with serous ovarian carcinoma (27%) endometrioid (57%), clear cell (64%) or mucinous carcinoma (58%) are carcinous (6%). The 12-year survival rates (all stages) of patients with histologic types: serous (68%), endometrioid (20%), clear cell (8%) and mucinous (6%). It has recently been proposed that the category of serous carcinomas be subdivided into two subcategories, which are distinguishable from each other (primarily) by grade. The largest category, high-grade serous carcinomas, comprises 90% of the total. It is proposed that the majority of high-grade serous carcinomas arise from the epithelium of the fallopian tube [25]. SEER does not distinguish between high-grade and low-grade serous carcinomas. The distinction has important implications for treatment; the smaller group (low-grade serous carcinomas) does not respond to chemotherapy. The distinction is also potentially important for screening and prevention. In principal, the greatest impact of any prevention program will be realized by reducing the number of high-grade serous cancers (discussed in part III). Also, screening must go beyond detecting non-serous and low-grade serous carcinomas if it is to be used to reduce ovarian cancer mortality.

6. Ethnic group

The incidence of ovarian cancer is higher in white women than in women from other racial or ethnic groups (Table S2). Ovarian cancer survival rates at 12 years are superior in white women (38%) compared with African-American women (32%) but they are inferior compared with Hispanic women (43%) and Asian women (52%). If the relative frequencies of the various racial and ethnic groups in the United States population change appreciably over time, this might impact on ovarian cancer incidence and mortality rates. From 1970 to 2011, the proportion of females that were white dropped from 87% to 80% [26]. At the same time, the proportion of Asian women increased from 1% to 5%. From 1992 to 2011, ovarian cancer incidence fell by 19% in white women, by 8% in African-American and by 8% in Asian women.

7. Bilateral oophorectomy

Bilateral oophorectomy refers to the surgical removal of the ovaries. Elective bilateral oophorectomy may be undertaken for the prevention of ovarian cancer or for the treatment of benign conditions such as pelvic pain, ovarian cysts or endometriosis [27]. Approximately 90% of all elective oophorectomies in the United States are performed as an adjunct operation in women who undergo hysterectomy for a benign

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condition [28]. At the time of hysterectomy, about 45% of pre-menopausal women and 75% of post-menopausal women undergo a concomitant bilateral (salpingo-) oophorectomy [29]. Women who have had their ovaries (and tubes) removed have a 95% reduction in their risk of developing ovarian cancer [30,31]. The probability that a woman will have both ovaries intact (i.e. have not undergone an elective bilateral oophorectomy) at a given age can be calculated based on the age-specific rates of bilateral oophorectomy for each year since birth.

Between 1965 and 2005, the rates of elective bilateral oophorectomy fluctuated between 1.5 and 3.0 per 1000 women per year [32,33]. Following the Women's Health Initiative report on the adverse health effects associated with the use of hormone replacement therapy in 2002 [34], rates of oophorectomy in premenopausal women began to decline [35]. In 2008, the American Congress of Obstetricians and Gynecologists released a statement recommending against prophylactic bilateral oophorectomy in women below age 45 [36].

From 1975 to 2005, there was a steady decline in the proportion of women in the population without ovaries. Women from recent birth cohorts (i.e. born after 1950) have had fewer oophorectomies than older women (Fig. S6). In 2005, an estimated 19% of women ages 70 and older have previously undergone an elective bilateral oophorectomy (Fig. S7). We estimate that, in the absence of these oophorectomies, there might have been 25,155 cases of ovarian cancer in 2005 versus 21,557 observed (i.e. about 14% of ovarian cancers were prevented in 2005 as a result of elective bilateral oophorectomies).

8. Risk factors for ovarian cancer

The principal risk factors for ovarian cancer are oral contraceptives, pregnancy, breast-feeding and tubal ligation [37]. These factors are of particular importance as they are protective, ubiquitous, and they have significant and long-lasting effects. Temporal changes in exposure to these four risk factors are expected to impact upon ovarian cancer incidence and mortality rates. Few risk factors that increase the risk of ovarian cancer have been confirmed; these include hormone replacement therapy [38], talcum powder [39], high body mass index [40] and endometriosis [41] and are not considered here. The role of genetic predisposition in ovarian cancer is discussed in part III [9].

We plotted the age-specific incidence rates for ovarian cancer by birth cohort (Fig. S8). The cumulative risk of ovarian cancer to age 70 was 1.1% for women born in 1920 and was 0.98% for women born in 1940 (a relative decline of 10.9%). The cumulative risk to age 50 was 0.29% for women born in 1940 and was 0.25% for women born in 1960 (a relative decline of 13.8%). (Because age-specific incidence data are only available beginning in 1975, cumulative risk estimates for earlier birth cohorts are partially based on incidence rates from later birth cohorts, and will underestimate any difference in risk between birth cohorts.)

Using data abstracted from questionnaires that were completed by 2000 women from North America, we estimated the probability that women born in various birth cohorts (from 1920 to 1969) were exposed to each risk factor at some time (Table S3), and based on the estimates for each risk factor we generated relative risks for developing ovarian cancer at or above age 60 compared with a theoretical reference group with no exposure (Fig. 5).

8.1. Oral contraceptives

Oral contraceptives were introduced in the United States in 1960 by G.D. Searle and Company [10]. Women of reproductive age in 1960 (ages 15 to 44) were born between 1920 and 1945. The proportion of women who have ever taken an oral contraceptive increased from 18% for women born in 1920 to 84% for women born in 1945, and has remained stable at 83% to 86% thereafter (Table S3).

On average, women who have ever used oral contraceptives have a 25% reduced risk of ovarian cancer compared with women that have never used oral contraceptives [42]. The level of protection increases with the duration of use and attenuates with time since last use. Thirty years after discontinuation of an oral contraceptive, the relative risk for ovarian cancer is approximately 0.8 for less than five years of use, 0.7 for five to ten years of use and 0.6 for more than 10 years of use. Because most women with ovarian cancer are diagnosed after age 60, the full impact of exposure to oral contraceptives on ovarian cancer incidence and mortality has only recently been observed.

In the United States population in 2014, about 85% of women below age 70 have previously taken an oral contraceptive, whereas only 18% of women age 90 to 95 have previously taken an oral contraceptive (Fig. 5). This indicates that between 1990 and 2015, the proportion of 70-year old women who had ever taken an oral contraceptive increased from about 20% to 85%.

![Fig. 5. Proportion of women in 2014 who have ever taken an oral contraceptive, by age.](http://dx.doi.org/10.1016/j.ygyno.2015.06.017)
8.2. Parity

On a population basis, parity is the second most important risk factor for ovarian cancer. The relative risk for ovarian cancer is estimated to be approximately 0.81 per child born (for practical purposes, we limit the protective effect of parity at five births, which corresponds to a 65% reduction in risk, compared with nulliparous women) [37]. In the United States, the average number of children per woman (mean parity) peaked at 3.8 children between 1946 and 1964 (during the post-World War II baby boom), and declined thereafter [43]. The mean parity of women born between 1920 and 1935 fell from 3.9 to 3.0 children (Table S3). This declined further to 1.8 children for women born in 1945 and to 1.5 children for women born in 1965.

8.3. Breast-feeding

Women who breast-feed their infants have a lower risk of ovarian cancer, compared with mothers who do not breast-feed. The relative risk for ovarian cancer among parous women that have ever breast-fed is approximately 0.85 (independent of parity) [44]. The extent of protection increases with duration of breast-feeding (i.e. the total number of months). 51% of mothers born between 1920 and 1924 breast-fed at some point. This fraction dropped to 44% of mothers born between 1935 and 1939, because of increasing numbers of women entering the workforce and because of the introduction and promotion of infant formula around 1970 [45]. In 1975, the proportion of mothers who breast-fed began to increase, stabilizing at 70% to 75% of mothers born in 1960 or later. The resurgence of breast-feeding has been attributed to increased knowledge about the benefits of breast-feeding and successful efforts to increase breast-feeding awareness, initiation and duration [45].

Breast-feeding is unique among risk factors in that the prevalence of ever-exposure is currently increasing (Table S3). However, the extent of protection is dependent on the total duration of breast-feeding (number of months), which in turn, depends on the number of children born (parity). Although the proportion of mothers who breast-feed their infants has increased in the United States, the mean parity of women in the population has decreased; in consequence, the average number of months of breast-feeding in the population has declined.

8.4. Tubal ligation

Tubal ligation is associated with a 15% to 25% reduction in the risk of ovarian cancer [46]. The magnitude of risk reduction is greater for endometrioid and clear cell carcinomas (50%) than for mucinous (30%) and serous carcinomas (20%). The protective effect appears to persist for 20 or more years; however, long-term studies are required to confirm the duration of protection. From 1975 to 1990, there was a shift in contraceptive use among women ages 30 to 44 from the oral contraceptive pill to tubal ligation [47]. The prevalence of tubal ligation increased from 4% of women born in 1920 to about 35% of women born between 1940 and 1949, and has declined thereafter (Table S3).

8.5. Relative risk of ovarian cancer from exposure to the four risk factors

Compared with a theoretical cohort of women who have never taken an oral contraceptive, the estimated proportion of cases prevented by the use of oral contraceptives was 3% for women born between 1920 and 1924 and increased to 25% for women born between 1945 and later (Fig. 6). Compared with nulliparous women, parity conferred a 56% reduction in ovarian cancer risk for women born between 1920 and 1924, after which the extent of protection from parity began to decline, with a 32% reduced risk for women born between 1945 and 1949, and a 27% reduced risk for women born between 1965 and 1969. Women born between 1920 and 1945 experienced a 22% reduction in ovarian cancer risk due to oral contraceptives, and a 24% increase in ovarian cancer risk due to declining parity.

The impacts of breast-feeding and tubal ligation on ovarian cancer incidence rates in the United States are modest in comparison with the effects of oral contraceptives and parity. Compared with women who have never breast-fed, the percent of ovarian cancers prevented by breast-feeding is estimated to be 7% for women born in 1920, decreasing to 6% for women born between 1945 and 1954, and then increasing to 9% for women born in 1960 or later (Fig. 6). Compared with women who have not had a tubal ligation, the greatest protection against ovarian cancer from tubal ligations was for women born between 1940 and 1949 (5% risk reduction).

8.6. Cumulative effects

The probability that a woman will develop ovarian cancer in her lifetime depends to a large extent on her cumulative exposure to all risk factors. In the absence of any exposure to the protective factors described above, the lifetime risk of ovarian cancer is estimated to be approximately 2.7% (as opposed to the observed population risk of 1.4%). Fig. S9 shows the overall propensity for women in different birth cohorts to develop ovarian cancer, as a result of exposure to all risk factors. Compared with a theoretical cohort of women with exposure to none of the four risk factors, the percentage of ovarian cancers prevented rises from 66% for women born between 1920 and 1924 to 71% for women born between 1940 and 1944 (a 5% reduction in ovarian cancer risk), and subsequently declines to 63% for women born between 1965 and 1969 (an 8% increase in ovarian cancer risk).

Examination of the trends in reproductive risk factors can be used to predict future ovarian cancer incidence rates. Women born between 1920 and 1945 were below age 65 between 1975 and 2010, corresponding to the continuous decline in ovarian cancer incidence in the 20 to 49 and 50 to 64 age groups since 1975 (Fig. S3). Women born between 1920 and 1945 were between the ages of 65 to 74 years beginning in 1985 (and ending in 2019), coinciding with the decline in incidence in women ages 65 to 74 that also began in 1985. Women born between 1920 and 1945 were 75 years of age and older beginning in 1995. In 2025, these women will be 75 to 100 years of age, at which point the decline in incidence due to risk factors is expected to reverse. (We assume that the relative risk for ever-exposure to a given risk factor is constant with time. We did not account for differences in the duration of exposure or recency of risk factor exposure between birth cohorts. We assume that the relative risks attributable to each factor are independent and cumulative.)

9. Synopsis

From 1975 to 2011, ovarian cancer mortality fell by 23%. The greatest period of decline (18%) was between 2001 and 2011, when mortality fell from 9.0 per 100,000 per year to 7.5 per 100,000 per year. The decline in ovarian cancer mortality is a consequence of a decline in ovarian cancer incidence. The decline in incidence is largely due to the introduction of oral contraceptives in 1960, and the subsequent expansion in their use (from 0% to 85%) from 1960 to 1990. The introduction of oral contraceptives has previously been implicated in declining incidence and mortality rates among women younger than age 60 [48,49], but the impact in older women and on overall mortality is only now being captured.

The SEER database is a very useful resource due to its large size and long period of record; however, there are some intrinsic limitations of using SEER data which should be acknowledged. SEER does not have a centralized review. There may be some misclassification of the ovarian cancer diagnoses in terms of both primary site and histology. The staging classification of ovarian cancer has changed over time. We do not have information on stage for all women and it is possible that some women were classified incorrectly. Our risk factor analysis is based on
prevalence data from 2000 North American women and this may not be representative of the entire United States female population.

10. Future trends

In 2025, it is estimated that 85% of younger women than age 80 will have taken an oral contraceptive at some time, and the mean parity will fall below two. The total duration of breastfeeding in the population and the proportion of women with a tubal ligation are also declining. As a result, after 2025 age-standardized ovarian cancer incidence rates will increase. Due to the aging of the baby boom generation (i.e. women born between 1946 and 1965), the mean age of the United States population is increasing. The population is also expanding in size. As a result, we estimate that from 2010 to 2030 the annual number of ovarian cancer cases diagnosed in the USA will increase by 37%, from 20,921 cases to 28,591 cases. The number of cases will increase by 18% (3698 cases) due to a shift in the age-distribution and by 19% (3972 cases) due to population growth. Based on changing risk factor propensity and changing population demographics, we expect to see an increase in the number of ovarian cancer cases over the next 15 to 30 years.

In part II, we examine SEER rates of ovarian cancer case-fatality, and we explore to what extent advances in ovarian cancer treatment contribute to the decline in ovarian cancer mortality [8]. In part III, we discuss future prospects for reducing ovarian cancer mortality, which incorporate genetic testing, preventive surgery, screening and treatment [9].

Conflict of interest

The authors have nothing to disclose.

Transparency document

The Transparency document associated with this article can be found, in the online version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.06.017.

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