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ORIGINAL REPORT

Ovarian Cancer Incidence Trends in Relation to Changing Patterns of Menopausal Hormone Therapy Use in the United States

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ABSTRACT

Purpose
After a report from the Women's Health Initiative (WHI) in 2002, a precipitous decline in menopausal hormonal therapy (MHT) use in the United States was linked to a decline in breast cancer incidence rates. Given that MHT use is also associated with increased ovarian cancer risk, we tested whether ovarian cancer incidence rates changed after 2002.

Methods
Using the North American Association of Central Cancer Registries database (1995 to 2008; N = 171,142 incident ovarian cancers), we applied standard analytic approaches and age-period-cohort (APC) models to estimate ovarian cancer incidence rate changes before (1995 to 2002) and after (2003 to 2008) the WHI report.

Results
Among women age ≥ 50 years, age-standardized ovarian cancer incidence declined by 0.8% per year (95% CI, −1.8% to −0.5% per year) before the WHI announcement; after the WHI report, the rate declined by 2.4% per year (95% CI, −2.5% to −2.2% per year). APC models confirmed an accelerated decline in ovarian cancer incidence after the WHI report, adjusted for age and birth cohort effects. This sudden change was notable among women most likely to have used MHT (ie, women age 50 to 69 years, white women, and residents of regions with highest MHT prescription frequency). The largest changes were found for the endometrioid histologic subtype.

Conclusion
After a marked reduction in MHT use around 2002, ovarian cancer incidence rates demonstrated an accelerated decline, with the largest changes for endometrioid carcinomas. This strong temporal association, although not proving a causal role of hormones in ovarian carcinogenesis, suggests that future analytic research supporting cancer control efforts should clarify the role of hormonal exposures on the development and behavior of subtypes of ovarian cancer.

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INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy in the United States, accounting for a projected 22,280 cases and 15,500 related deaths in 2012.[1] Most women with ovarian cancer present with advanced-stage disease, which is often fatal despite aggressive treatment. Accordingly, developing improved methods of early detection or prevention of these tumors based on a deeper understanding of their pathogenesis is a research priority.

Historical examples have shown that links between sudden temporal changes in the prevalence of specific hormonal exposures and rapid changes in cancer incidence may provide insights into carcinogenesis. In the 1970s, the correlation between increased use of exogenous unopposed estrogens and increasing endometrial cancer rates provided evidence for an etiologic relationship.[2] In 2002, results from the Women's Health Initiative (WHI) linked combined estrogen plus progestin menopausal hormone therapy (MHT) to adverse health effects,[3] which was followed by a sharp decrease in MHT use, irrespective of formulation or geographic region in the United States,[4-6] along with a decrease in breast cancer rates,[7] supporting a link between these agents and breast cancer. However, a comparable analysis of ovarian cancer incidence rates has not been performed.

A meta-analysis of population-based case-control and prospective studies found that use of estrogen-only MHT increased ovarian cancer risk

by 22% (risk ratio, 1.22; 95% CI, 1.18 to 1.27) and that combined estrogen plus progestin therapy increased risk by 10% (risk ratio, 1.10; 95% CI, 1.04 to 1.16).[8] Three additional cohort studies have been published since the meta-analysis[9-11]; the largest demonstrated a statistically significant link between combined MHT use and ovarian cancer risk, whereas the smaller studies reported increased but nonsignificant risks. Before 2002, ovarian cancer incidence rates were declining slowly, but it is unknown whether this trend changed after the WHI announcement. Given the epidemiologic evidence that unopposed estrogens increase ovarian cancer risk and more recent evidence suggesting a similar, albeit weaker, association for combined MHT, we hypothesized that the WHI announcement in 2002 would be followed by a subsequent accelerated decline in ovarian cancer incidence rates.

To test our hypothesis, we analyzed temporal trends in ovarian cancer incidence before and after the WHI announcement in mid-2002. Given that rates of ovarian cancer incidence have been declining for decades,[12] we applied joinpoint regression models[13] and also used age-period-cohort (APC) models to analyze temporal changes, adjusted for the interrelated effects of age and birth cohort.[14,15] Specifically, we tested whether rates of decline suddenly accelerated after 2002. In addition, we performed stratified analyses by age, race, histologic subtype, and US regions categorized by the frequency of MHT prescriptions. To achieve the statistical power required for this analysis, we used data from the large-scale North American Association of Central Cancer Registries (NAACCR), which covers greater than 80% of the US population.[16]

METHODS

Data Source

We used the Cancer Incidence in North America (CINA) Analytic File for Expanded Races provided by NAACCR (www.naaccr.org) for this analysis. Cancer incidence data that are provided by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program or the Centers for Disease Control and Prevention's National Program of Cancer Registries and that meet high-quality standards are included in the CINA analytic data set.[17] Ovarian cancer incidence data were available for 42 consenting population-based cancer registries of the 56 included in CINA (1995 to 2008; Appendix Table A1, online only).

Study Population

The analytic file included 240,912 malignant ovarian tumors, which we further restricted to 211,534 carcinomas, based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes, as follows: serous (ICD-O-3 codes 8441, 8442, 8460, 8461, 8462, and 9014), endometrioid (8380, 8381, 8560, and 8570), clear cell (8310 and 8313), mucinous (8470, 8471, 8472, 8480, 8481, 8482, 8490, and 9015), and other/unspecified. For analyses restricted to women age 50 years and older, a reasonable population-based surrogate for postmenopausal status[18] and a relevant age range for MHT use, the analytic file included 192,075 malignant ovarian tumors, which we further restricted based on ICD-O-3 codes to 171,142 carcinomas (Appendix Table A2, online only).

Population counts used for estimation of age-standardized incidence were derived from the 2000 US Census in 1-year age intervals. The 2005 incidence data and underlying population data for Louisiana, Alabama, Mississippi, and Texas were adjusted to account for displacement related to Hurricanes Katrina and Rita.

Subgroup Variables

We computed ovarian cancer incidence by age ($< v \geq 50$ years [50 to 69 *v* 70 to 84 years]), race (white, black, or other/unknown), and histologic subtypes (serous, mucinous, endometrioid, or clear cell; other/unspecified carcinomas were not separately analyzed). We also computed rates in regions previously identified as having comparatively low MHT use (Middle Atlantic: New Jersey, New York, and Pennsylvania) and comparatively high MHT use (West South Central: Arkansas, Louisiana, and Texas) during the study period.[6]

Statistical Analysis

Age-standardized ovarian carcinoma incidence rates per 100,000 women-years with 95% CIs were generated using SEER*Stat Software (version 7.0.9; http://www.seer.cancer.gov/seerstat)[19] and plotted on a linear scale. Trends in cancer incidence were analyzed by fitting a linear regression to the natural log of the incidence rate, with the slope representing the annual percent change for a specified time period,[13] and we compared the annual percent change between the before (1995 to 2002) and after WHI (2003 to 2008) time periods. To further test for significance of temporal trends in ovarian cancer rates and to identify the point at which the trends changed, we performed a joinpoint analysis (Joinpoint Regression Program version 3.5.1 software; http://www.srab.cancer.gov/joinpoint),[13] which fits a series of joined straight lines to the log of the annual age-standardized rates.

Although SEER*Stat and joinpoint regression can identify significant temporal trends in age-standardized incidence and estimate the years of transition, they do not distinguish between influences that occurred in specific time periods for all age groups (ie, period effects) versus effects associated with year of birth (ie, generational or birth cohort effects). Accordingly, to develop more refined estimates of period changes adjusted for both age and birth cohort effects, we analyzed period effects using APC models.[14,15]

For the APC analysis, we used 32 2-year age groups (21 through 22, 23 through 24, and so on to 83 through 84 years) and seven 2-year time periods (1995 through 1996, 1997 through 1998, 1999 through 2000, 2001 through 2002, 2003 through 2004, 2005 through 2006, and 2007 through 2008), spanning 38 partially overlapping 4-year birth cohorts referred to by midyear of birth (1912, 1914, and so on to 1986). APC models were fitted to the entire data set and in substrata according to age (50 to 69 *v* 70 to 84 years old), race (white, black, or other/unknown), histologic subtypes (serous, mucinous, endometrioid, or clear cell), or low- and high-MHT region.

To explore changes in the APC period deviations circa 2002, we used the Tarone-Chu method.[20,21] Specifically, we contrasted the three 2-year time periods (1995 through 1996, 1997 through 1998, and 1999 through 2000) before the 2-year interval 2001 through 2002 with the three 2-year time periods (2003 through 2004, 2005 through 2006, and 2007 through 2008) after 2001 through 2002. In addition, using a method similar to one recently developed by one of the authors (P.S.R.) for cohort relative risks,[22] we estimated the corresponding period relative risks compared with the referent 2002 time period.

As sensitivity analyses, we restricted analysis to 30 registries that achieved gold/silver NAACCR certification status for 10 or more years between 1995 and 2008[23] and restricted analysis to 31 registries included in the NAACCR 2011 annual report on the status of cancer.[16] To account for the expected reporting delays and data corrections that most frequently occur in the most recent 1 to 3 years of incidence data, we additionally examined the delay-adjusted rates in 13 SEER registries from 1992 to 2009.[24]

RESULTS

Trends in Ovarian Cancer Incidence

Figure 1 compares the age-standardized incidence rates between women younger than age 50 years and women age 50 years and older. Joinpoint regression models identified a single joinpoint at the year 2001 (range, 1999 to 2002) among women age 50 years and older and no joinpoint among women younger than age 50 years. That is, ovarian cancer incidence rates decreased significantly from 1995 to 2001 in the older age group by −0.8% per year, and by 1.6% per year more

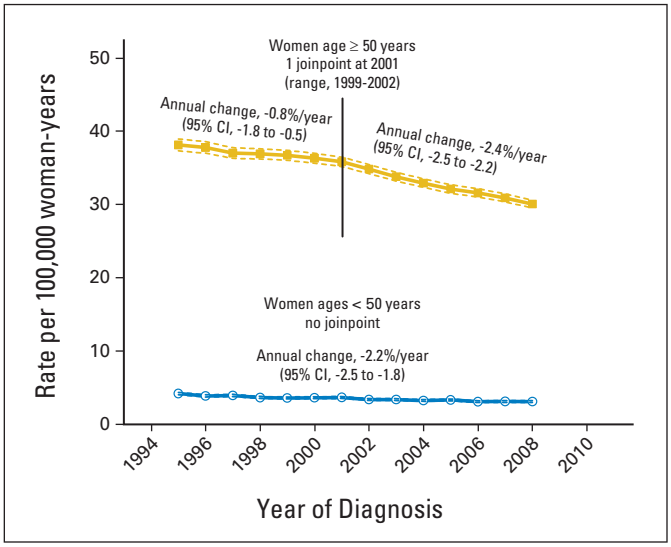

Fig 1. Age-standardized ovarian cancer incidence rates in the United States (North American Association of Central Cancer Registries Incidence, 1995 to 2008). Age standardized to the 2000 US population.

rapidly thereafter (ie, by −2.4% per year from 2001 to 2008). However, ovarian cancer incidence decreased steadily for the entire time period among the younger age group, (ie, −2.2% per year; 95% CI, −2.5% to −1.8% per year). Accordingly, we further analyzed data for women age 50 years and older.

Among the older women (Table 1), SEER*Stat analyses confirmed that ovarian cancer incidence rates decreased by 21.1% from 1995 to 2008, with an annual percent change of −1.87% per year (95% CI, −2.09% to −1.64% per year). Before the WHI announcement (1995 to 2002), rates declined by 1.17%, whereas afterward (2003 to 2008), rates decreased by 2.19% per year. Sensitivity analyses restricted to various subsets of registries and accounting for reporting delays (see Methods) showed similar trends (data available on request), and therefore, we present results for the entire data set.

APC Model

The observed rates from SEER*Stat and fitted rates from the APC model were similar, confirming a greater deceleration in the incidence of ovarian cancer after 2002 compared with earlier years, adjusted for both age and cohort effects. The period deviations declined with a slope difference of −1.2% after 2002 (P for change adjusted for age and cohort effects = .001; Fig 2A). Additionally, the period relative risk for ovarian cancer overall was 7% higher (period relative risk, 1.07; 95% CI, 1.05 to 1.09) in 1995 compared with the 2002 referent time period and 14% lower (period relative risk, 0.86; 95% CI, 0.84 to 0.88) in 2008 compared with 2002 (Fig 2B).

Ovarian Cancer Stratified by Key Factors

We estimated the period relative risk by age at ovarian cancer diagnosis (Fig 3A), race (Fig 3B), histologic subtype (Fig 3C), and US geographic regions associated with low (Middle Atlantic) and high (West South Central) MHT use (Fig 3D). Period relative risks generally declined over the entire study period. The most notable sudden declines circa 2002 occurred among women most likely to have used MHT (women age 50 to 69 years, white women, and residents of regions with the highest MHT prescription frequency;

Table 1. Ovarian Carcinomas Among US Women Age ≥ 50 Years (NAACCR Incidence, 1995 to 2008)

Year	Age-Standardized Rate per 100,000*	No. of Ovarian Carcinomas†	Population (No.)	Ovarian Cancer Incidence Rates (%)		
				Percent Change‡	Annual Percent Change	95% CI
Total	34.32	171,142	495,041,648			
1995	38.22	9,336	23,591,415			
1996	38.06	9,675	24,545,508			
1997	37.11	11,061	29,051,668			
1998	37.00	11,504	30,495,803			
1999	36.65	12,047	32,422,731			
2000	36.36	12,198	33,146,759			
2001	35.98	12,948	35,671,176			
2002	34.94	13,202	37,529,315			
2003	33.85	13,011	38,375,429			
2004	32.95	13,392	40,676,844			
2005	32.36	12,639	39,152,508			
2006	31.80	13,531	42,642,491			
2007	31.03	13,350	43,341,843			
2008	30.15	13,248	44,398,158			
1995-2002				−8.57	−1.17§	−1.44 to −0.89
2003-2008				−10.92	−2.19§‖	−2.45 to −1.93
1995-2008				−21.10	−1.87§	−2.09 to −1.64

NOTE. Data from the SEER*Stat Database ("NAACCR Incidence, CINA Analytic File, 1995-2008, for Expanded Races, Standard File").
Abbreviation: NAACCR, North American Association of Central Cancer Registries.
*Rates are per 100,000 population and age standardized to the 2000 US population (single ages to 84 years; Census P25-1130).
†Ovarian cancer (International Classification of Diseases code 56.9); included only malignant carcinomas and excluded noncarcinomas (n = 20,821).
‡Percent changes were calculated using 1 year for each end point; annual percent changes were calculated using the weighted least squares method.
§The annual percent change is significantly different from zero ($P < .05$).
‖The annual percent changes is significantly different from the annual percent changes for 1995 to 2002 ($P < .05$).

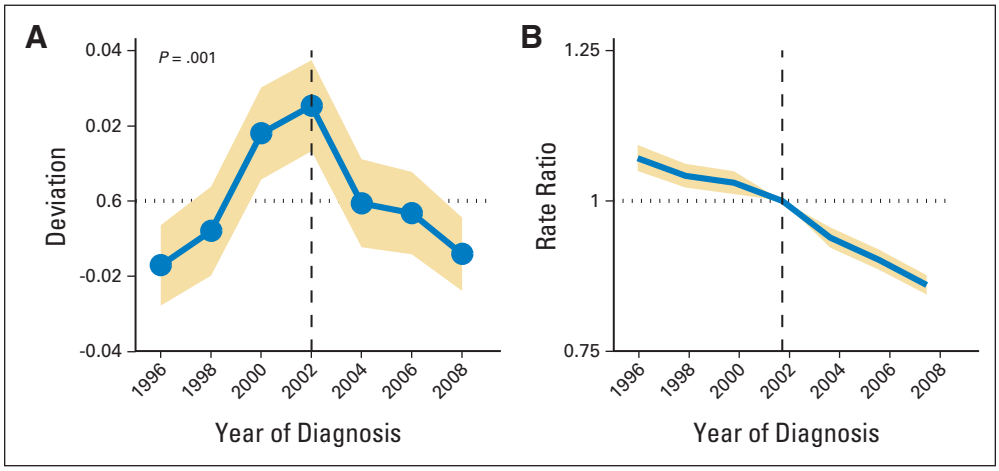

Fig 2. Age-period-cohort effects among US women age ≥ 50 years (North American Association of Central Cancer Registries Incidence, 1995 to 2008). Point estimates are shown in blue, with 95% CIs shaded in gold. (A) The significance of period deviations was assessed by contrasting the three time periods before the Women's Health Initiative (WHI; 1995 to 1996, 1997 to 1998, and 1999 to 2000) with the three time periods after WHI (2003 to 2004, 2005 to 2006, and 2007 to 2008). *P* value is for change in the slopes of the period deviations, adjusted for age and cohort effects. (B) Period relative risks were calculated as rate ratios adjusted for age and birth cohort effects, comparing the ovarian cancer incidence rates for a given time period with the rate of a referent period (the 2002 time period in this analysis). The period relative risks declined from more than 1.0 before the 2002 referent period, after which the period relative risks were significantly less than 1.0.

P for change adjusted for age and cohort effects < .02). The largest change points circa 2002 were found for endometrioid histologic subtype. Clear cell subtype showed no decline or change point. Mucinous tumors decreased steadily without a change point circa 2002. In contrast, serous carcinomas showed a unique pattern, in which the incidence increased then decreased slightly but significantly around 2002. The change in the period relative risks was also statistically significant for both low- and high-grade serous carcinomas (data not shown). However, for low-grade serous carcinomas, the relative risks decreased slowly before 2002, after which the rate of decline accelerated; whereas for high-grade serous carcinomas, the relative risks increased before 2002, after which the rate of increase slowed significantly.

Finally, we analyzed ovarian cancer trends by stage at diagnosis (using the SEER summary and historic stage variables). We found decreasing trends for local, regional, and distant stages (data not shown), albeit results were only statistically significant for regional cancers.

DISCUSSION

Our analysis shows that the decline in ovarian cancer rates, which has been occurring for many years, accelerated around 2002 among women age 50 years and older, coinciding with health warnings emanating from the WHI study related to use of MHT.[25] Furthermore, using APC modeling to refine results of joinpoint regression, we demonstrate that the more rapid decline among women age 50 years and older is independent of both age and cohort influences. The decline in ovarian cancer rates after the WHI announcement parallels previously reported observations linking a reduction in MHT prescriptions in 2002 to decreasing breast cancer rates.[7] The sudden changes in rates for these two hormonally sensitive cancers during the same time period strengthens the evidence linking MHT use to the declining incidence of both tumors and is consistent with the view that hormones have a promoter effect for both breast and ovarian carcinogenesis.[26]

The APC period relative risks showed the most significant declines among groups of women most likely to have used MHT (ie, women age 50 to 69 years, white women, and residents in regions with the highest frequency of MHT prescriptions). We also observed statistically significant period changes circa 2002 for both endometrioid and serous histologic subtypes, with the largest changes in incidence rates for endometrioid ovarian tumors. For serous tumors overall, the period relative risks showed a unique pattern, with a slight increase before the decline after 2002. However, the relative risks varied by histologic subtype, which might be related to etiologic heterogeneity, with hormonal exposures impacting some types of ovarian cancers more than others.

We considered alternatives to reduced MHT use as an explanation for the ovarian cancer rate declines after 2002, but view these as less likely. For an exposure to account for the abrupt accelerated decline in ovarian cancer incidence rates after 2002, the prevalence of the exposure would have to shift rapidly around that time period. To the best of our knowledge, we do not know of any other calendar-period changes (eg, screening) with a temporal relationship that is similar to MHT use. Furthermore, we used APC models to adjust for potentially confounding age and birth cohort influences, such as those related to oral contraceptive use.[27] The decline is unlikely an artifact of oophorectomy prevalence in the United States because performance of oophorectomy in the United States decreased from 2002 to 2006, placing more women rather than fewer women at risk.[28] Indeed, although oophorectomy is effective in reducing ovarian cancer risk and its benefit is well documented among high-risk women such as *BRCA1/2* mutation carriers, there has been a general lack of awareness of the potential prophylactic effect of oophorectomy for ovarian cancer risk reduction in past years.[29] Increased recognition of metastases to the ovary[30,31] and better recognition of fallopian tube primary tumors[32] also could affect rates modestly, but the effects would likely have been small during the years of analysis and would not have shown

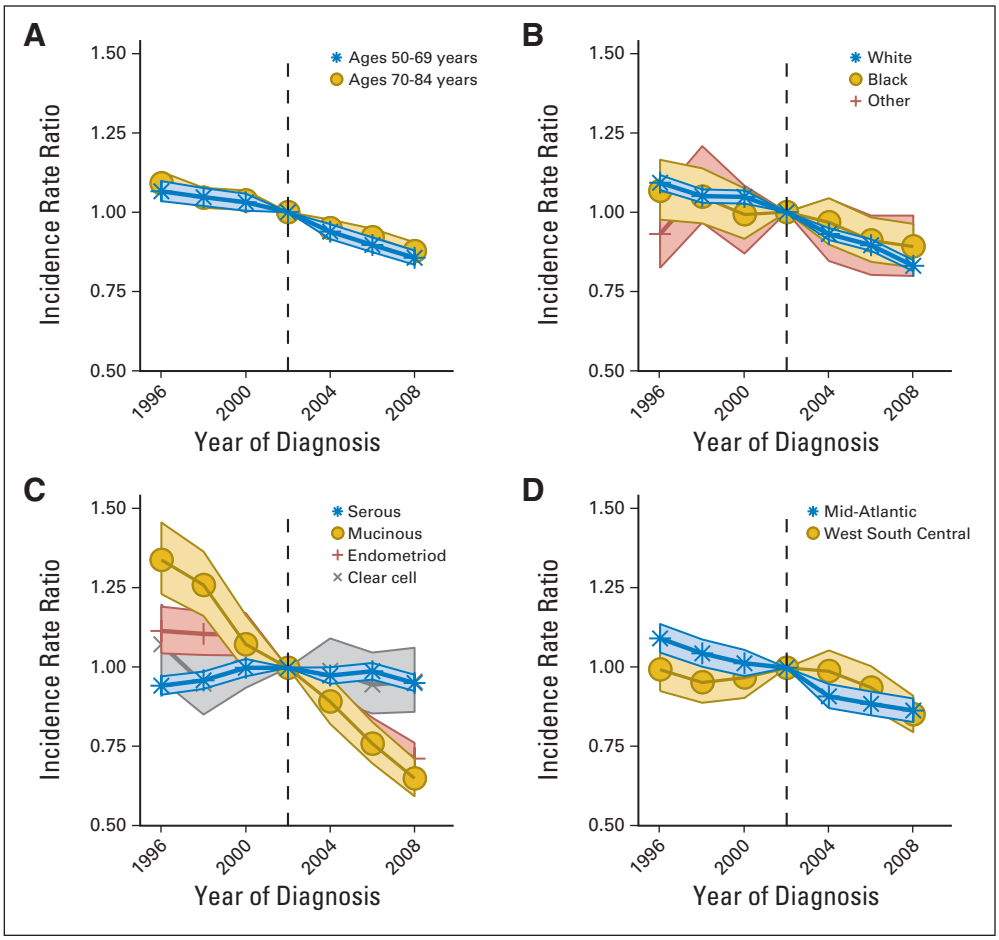

Fig 3. Age-period-cohort period relative risks among US women age ≥ 50 years (North American Association of Central Cancer Registries Incidence, 1995 to 2008). The period relative risks by (A) age at ovarian cancer diagnosis, (B) race, (C) histologic subtype, and (D) US geographic regions associated with high (West South Central) and low (Mid-Atlantic) menopausal hormone therapy frequency. For most strata, the period relative risks declined from more than 1.0 before the 2002 referent period, after which the period relative risks were less than 1.0 (see text for further details).

the temporal, demographic, and regional specificity that we identified. This concern is most relevant for mucinous carcinomas, which have decreased at least in part secondary to better recognition of GI metastases to the ovary. Lastly, use of selective estrogen receptor modulator agents for chemoprevention, such as tamoxifen or raloxifene, is unlikely to account for the observed data because these agents have not been shown to lower ovarian cancer risk[33,34] and use of aromatase inhibitors is a more recent practice that would not impact the ovarian cancer incidence during the time period we evaluated.[35]

The main strengths of this analysis include the availability of a large number of data points from a representative, regionally diverse population in the United States and use of APC modeling to specifically estimate period effects adjusted for both age and cohort effects. A major limitation of ours and any other descriptive analysis is that it can only be used to generate a hypothesis about carcinogenesis and cannot determine the causes of incidence trends observed. Other limitations include our inability to link an individual's MHT use to cancer development and the potential for pathologic misclassification. Another limitation is that we used modeled results (joinpoint and APC analyses), but our findings for the observed and modeled data were consistent and provided complementary evidence.

Our data suggest a possible link between the decline in MHT use after the WHI announcement in 2002 and the accelerated decline in ovarian cancer incidence that is parallel to the declining breast cancer incidence rates.[36] It is unclear whether ovarian cancer rates will continue to decrease beyond our study period, and our descriptive study cannot establish a direct causal relationship between exogenous hormone exposure and ovarian cancer. Nonetheless, our results provide compelling temporal evidence that hormonal exposures contribute to ovarian carcinogenesis with the clearest suggestion for endometrioid carcinomas. In fact, changes in rates for serous carcinomas (the numerically predominant cause of ovarian cancer deaths) were significant but of considerably smaller magnitude than for endometrioid tumors. Although there are some large studies linking MHT use to an increased risk for serous carcinomas, this association does not seem to be established at this time. Therefore, our findings for serous carcinomas should not be overinterpreted.

In summary, analytic studies show that oral contraceptive use at early ages is highly protective for ovarian cancer and that MHT use increases ovarian cancer risk, and limited data suggest that aromatase inhibitors may have value in treating ovarian cancers, all of which support the concept that hormonal mechanisms are important to the etiology of some ovarian cancers. Our descriptive findings based on 171,000 incident cases are not intended to inform an individual woman's decision about MHT use. Rather, they are presented to clarify the national patterns and also highlight the need to increase our knowledge of hormonal mechanisms in ovarian cancer development, which ultimately may allow women to

make evidence-based personal decisions as well as guide policies that have implications for cancer control.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Hannah P. Yang, William F. Anderson, Mark E. Sherman
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. North American Association of Central Cancer Registries Included in Analysis

Registry
Alabama
Alaska
Arizona
Arkansas
California (including Greater Bay and Los Angeles)
Colorado
Connecticut
Delaware
Florida
Georgia (including Atlanta)
Hawaii
Iowa
Kentucky
Louisiana
Maine
Massachusetts
Michigan
Mississippi
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New York
North Carolina
North Dakota
Ohio
Oregon
Pennsylvania
Rhode Island
South Carolina
South Dakota
Tennessee
Texas
Utah
Virginia
Washington
West Virginia
Wyoming

Table A2. Demographics and Clinical Characteristics Among US Women Age ≥ 50 Years With Ovarian Carcinoma (NAACCR Incidence, 1995 to 2008)

	Women With Malignant Cancer* (N = 171,142)	
Demographic or Clinical Characteristic	No.	%
Age, years		
50-59	45,701	27
60-69	48,250	28
70-79	47,312	28
≥ 80	29,879	17
Race		
White	153,178	90
Black	11,390	7
Other	6,574	4
Histologic subtype		
Serous	75,495	44
Endometrioid	16,518	10
Clear cell	6,960	4
Mucinous	10,503	6
Other carcinoma	61,666	36
MHT use by US region		
High use (West South Central)	15,319	9
Low use (Mid-Atlantic)	35,250	21

Abbreviations: MHT, menopausal hormone therapy; NAACCR, North American Association of Central Cancer Registries.
*Excluded women with borderline malignant cancer.