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Recent Changes in Endometrial Cancer Trends Among Menopausal-Age US Women

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Abstract

Background—Changes in endometrial cancer incidence rates after the precipitous decline in menopausal hormone therapy (MHT) use in 2002 have not been evaluated.

Methods—Using data from the Surveillance, Epidemiology, and End Results Program from 1992–2009 (SEER 13), we identified 63,428 incident endometrial cancer cases among women ages 20–74. We compared Annual Percent Change (APC) in endometrial cancer incidence rates from 1992–2002 to rates from 2003–2009.

Results—In contrast to the constant endometrial cancer rate pattern observed from 1992–2002 (APC 0.0%), rates increased after 2002 in women 50–74 years old (2.5%; $P_{\text{APC comparison}} < 0.01$). Endometrial cancer incidence increased over the entire time period among women ages 20–49 (1992–2002: 1.1%; 2003–2009: 2.1%; $P_{\text{APC comparison}} = 0.21$). Post-2002 increases in incidence among women ages 50–74 were specific to Type I endometrial tumors (1992–2002: –0.6%; 2003–2009: 1.6%; $P_{\text{APC comparison}} < 0.01$).

Discussion—The increase in endometrial cancer incidence rates after 2002 may be related to the widespread decrease in estrogen plus progestin MHT use, which has been reported to lower endometrial cancer risk in overweight and obese women.

Keywords

Endometrial cancer; incidence; trends; menopausal-age women; menopausal hormone therapy

Introduction

Endometrial cancer is the fourth most common cancer among women and the most common gynecological cancer in the U.S. [1]. Multiple lines of evidence suggest that endometrial cancer is related to excess exposure to estrogens relative to progesterone, especially for the most common type of endometrial cancers (termed Type I) [2]. Specifically, elevated endogenous estrogen levels may mediate the increased endometrial cancer risk associated with postmenopausal obesity [3], and use of estrogen-only menopausal hormone therapy (MHT) is contraindicated among women with intact uteri because of its link to marked

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increases in endometrial cancer incidence [3]. In contrast, continuous regimen estrogen plus progestin MHT (26 days or more of progestin per month) is associated with a decreased endometrial cancer risk relative to non-hormone use [4].

In 2002, the Women's Health Initiative (WHI) randomized trial was stopped early due to an increased risk of breast cancer and other adverse events [5]. As a result of extensive media coverage there was a subsequent precipitous decline in usage of estrogen plus progestin MHT [5]. Following the decrease in estrogen plus progestin MHT use, breast cancer incidence fell rapidly [6]. Endometrial cancer incidence rates after the decline in MHT use have not been comparably analyzed. Using data from the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) we evaluated trends in endometrial cancer incidence before and after the early termination of the WHI trial and the resultant decrease in MHT use.

Materials and Methods

Data on endometrial cancer incidence was obtained from the National Cancer Institute's SEER 13 registries for the years 1992–2009 [7]. SEER 13 data is estimated to cover 13.8% of the US population and includes the following cancer registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, rural Georgia and the Alaska Native Tumor Registry. We identified endometrial cancer cases as primary tumors that demonstrated malignant behavior with site codes uterine corpus (C540–C549) or uterus, NOS (C559).

We further restricted our case definition to tumors with International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes that fell into one of three mutually exclusive categories: Type I (adenocarcinoma, NOS (8140), adenocarcinoma tubular (8210, 8211), papillary adenocarcinoma (8260, 8262, 8263), endometrioid (8380, 8381, 8382, 8383), mucinous adenocarcinoma (8480, 8481, 8482), adenocarcinoma with squamous metaplasia/adenosquamous (8560, 8570)); Type II (serous/papillary serous (8441, 8460, 8461), clear cell (8310)); and Other (small cell carcinoma (8041), squamous cell (8050, 8070, 8071, 8072, 8076), mixed cell adenocarcinoma (8323), malignant mixed müllerian tumors (8950, 8951, 8980, 8981, 8982)). A total of 63,428 endometrial cancer cases were reported among women ages 20–74 years.

Statistical Analysis

Using SEER*Stat 8.0.10 software (National Cancer Institute, Bethesda, MD), incidence rates of endometrial cancer per 100 000 woman-years were age-standardized to the US population in 2000. The Annual Percent Change (APC) was calculated for two time periods: before (1992–2002) and after (2003–2009) the early termination of the WHI trial. Rates were estimated for women ages 20–49 (n=10 936) and 50–74 (n=52 492), approximating pre- and postmenopausal groups.

For women 50–74 years old, we evaluated incidence rate trends by histologic type (as defined above) and race (white, black, American Indian/Alaska Native, Asian/Pacific Islander). Additionally, we conducted lag analyses excluding data 1, 2 and 3 years after the termination of the WHI trial and used the Joinpoint Regression Program 3.5.4 (National Cancer Institute, Bethesda, MD) to further evaluate change points in incidence trends.

Results

In contrast to the constant endometrial cancer incidence rate pattern observed from 1992–2002 in women ages 50–74 (APC, 0.0%; 95% CI, –0.5%, 0.5%), rates increased after 2002

among this age group (APC, 2.5%; 95% CI, 1.4%, 3.6%; $P_{\text{APC comparison}} < 0.01$) (Figure 1). A different pattern was observed among women ages 20–49, with rates increasing over the entire time period (1992–2002: APC, 1.1%; 95% CI, 0.3%, 2.0%; 2003–2009: APC, 2.1%; 95% CI, 0.7%, 3.5%; $P_{\text{APC comparison}} = 0.21$). In lag analyses, the increase in incidence among women ages 50–74 strengthened (APC 2004–2009: 2.8%, 2005–2009: 3.3%, 2006–2009: 4.2%).

Among white women ages 50–74, endometrial cancer incidence rates followed the same pattern as in all races; incidence rates were constant between 1992 and 2002 (APC, 0.0%; 95% CI, –0.6%, 0.5%), followed by an increase after 2002 (APC, 1.8%; 95% CI, 1.0%, 2.6%; $P_{\text{APC comparison}} < 0.01$) (Table 1). Among black women and Asian/Pacific Islanders, increases were seen over the entire time period; however, the increase accelerated after 2002 ($P_{\text{APC comparison}} = 0.03$ and 0.01, respectively). The endometrial cancer incidence rates for American Indians/Alaska Natives were suggestive of a constant pattern from 1992–2002 (APC, 0.0%; 95% CI –5.3%, 5.7%) followed by an increase in incidence after 2002 (APC, 8.4%; 95% CI, –4.5%, 23.0%); however, the APC comparison did not achieve statistical significance likely because of small numbers ($P_{\text{APC comparison}} = 0.13$).

For Type I endometrial cancers in women 50–74 years old, the incidence rate pattern changed from decreasing between 1992 and 2002 (APC, –0.6%; 95% CI, –1.2%, –0.1%), to increasing after 2002 (APC, 1.6%; 95% CI, 1.0%, 2.3%); $P_{\text{APC comparison}} < 0.01$). In Joinpoint analyses, endometrial cancer incidence rates showed a marked increase circa 2006 for women ages 50–74 and circa 2004 for type I tumors in this age group (results not shown).

Discussion

We observed increases in endometrial cancer incidence rates following the early termination of the WHI trial in 2002. This pattern was strongest among women in the age group most likely to use MHT, women 50–74 years old. Recently an evaluation of nationwide incidence rate trends among women of all ages between 1999 and 2006 reported a relatively stable rate of invasive uterine cancers [8]. While not directly comparable, the increasing incidence rate patterns in our study that were not observed by Duong and colleagues are likely due to the recent increases in uterine cancer that occurred between 2006 and 2009, particularly among menopausal-age women.

While an increase in the prevalence of overweight and obesity, the strongest risk factor for endometrial cancer [3], could theoretically explain the rising incidence, we have not seen a precipitous increase in BMI among women 50–74 years old that would independently explain the increase in endometrial cancer rates in recent years, nor have we seen an increase among women age 20–49 that would explain the 1–2% increase in incidence over the entire time period for that age group. Between 1999 and 2008, the prevalence of obesity increased slightly among women ages 20–39 and 40–59 and decreased slightly among women age 60 or older, however, there were no statistically significant trends in prevalence of obese BMI by survey cycle within any subgroup of women [9].

We suggest that the increased incidence of endometrial cancer reflects the interplay between BMI and decreased MHT use. Specifically, studies demonstrate that obese BMI is most strongly related to elevated endometrial cancer risk among non-users of combined MHT, suggesting that exogenous progestins may attenuate risk related to increased endogenous estrogen levels associated with elevated BMI [10]. Our finding that the post-2002 increase in endometrial cancer incidence was specific to Type I tumors also supports the progestin-withdrawal theory, as risk of Type I tumors is increased with decreased progestin [2].

Changes in the prevalence of other endometrial cancer risk factors seem less likely to explain the recent increase in endometrial cancer incidence. Use of tamoxifen is associated with increased endometrial cancer risk [11]; however, tamoxifen use is uncommon and has decreased since 2000 [12]. Cigarette smoking, which is related to decreased endometrial cancer risk, has changed only modestly in recent years [13]. Similarly, combination oral contraceptive use, another factor associated with decreased endometrial cancer risk, has not fallen sharply since 2002 [14]. Our data suggesting a link between increasing endometrial cancer incidence and a decline in MHT use since 2002 was motivated by and is consistent with the declining breast cancer incidence pattern observed at least through 2005 [6, 15]. Breast cancer rates declined by 8.6% from 2001 to 2004 [15], whereas our data suggest that endometrial cancer incidence increased by 2.5% over a comparable time period.

A major strength of our analysis is the use of an extensive cancer database, the SEER 13 registries. The standard methods used are suitable to identify significant temporal trends in age-standardized incidence rates and to estimate years of transition. They do not distinguish, however, between effects associated with birth year (generational or birth cohort effect) and those related to a specific time period for all ages combined (period effect) which could account, in part, for the increase in incidence. Although our analysis was based on SEER 13 registries that are generally representative of women in the United States, our findings may not necessarily apply to populations that are not proportionally represented in SEER. Our descriptive analysis is also limited by a lack of individual-level endometrial cancer risk factor data such as MHT use, BMI or other reproductive factors; instead we considered trends in MHT use [6] and BMI data [9] from published sources. An additional limitation is the inability to adequately account for hysterectomy prevalence. Without correction for hysterectomy prevalence the rates reported here are underestimates of the true incidence of endometrial cancer; however, given that the prevalence of hysterectomy has not changed substantially between 1992 and 2009 [16], the APCs are adequate estimates of temporal trends.

In summary, we hypothesize that the increase in endometrial cancer incidence rates from 2003 to 2009 is likely explained, in part, by a decrease in estrogen plus progestin MHT use in the setting of highly prevalent postmenopausal obesity. Contributions of other endometrial cancer risk factors seem less likely to have played a major role. Accordingly, continued monitoring of endometrial cancer incidence rates is warranted. Further evaluation, such as age-period-cohort analysis, may provide more insight into the observed increases.

Acknowledgments

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Abbreviations

APC	annual percent change
BMI	body mass index
MHT	menopausal hormone therapy
SEER	Surveillance, Epidemiology and End Results Program
WHI	Women's Health Initiative

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Figure 1.

Age-adjusted endometrial cancer incidence and annual percent change (APC) among U.S. women, 1992–2009, SEER 13.

APC = Annual Percent Change

* APC is significantly different from zero ($P < 0.05$)

† APC for 2003–2009 is significantly different from APC for 1992–2002 ($P < 0.05$)

Table 1

Age-adjusted incidence and average annual percent change (APC) in endometrial cancer by race among U.S. women ages 50 to 74, 1992-2009, SEER 13.

Race	Pre-WHI (1992–2002)			Post-WHI (2003–2009)			<i>P</i> ^c
	n	Rate ^a	APC (95% CI) ^b	n	Rate ^a	APC (95% CI) ^b	
White	24,995	73.8	0.0 (–0.6, 0.5)	18,764	74.5	1.8(1.0, 2.6)	<0.01
Black	1,943	49.4	1.9(0.3, 3.5)	2,019	62.7	5.3(1.7, 9.1)	0.03
American Indian/ Alaska Native	126	30.3	0.0 (–5.3, 5.7)	165	40.2	8.4 (–4.5, 23.0)	0.13
Asian/Pacific Islander	1,964	43.9	1.6(0.0, 3.3)	2,174	53.2	5.3 (3.4, 7.4)	0.01

^aRates are per 100,000 women and age-adjusted to the 2000 US standard population.

^b Annual percent change (APC) calculated using weighted least squares method, 95% confidence interval (CI) calculated using Tiwari modification.

^cThe p-value comparing the APC for 2003-2009 with the APC for 1992-2002.