Menopausal Hormone Therapy and Risk of Epithelial Ovarian Cancer

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Abstract

Substantial increase in the use of menopausal hormone therapy (HT) throughout the 1990s, followed by widespread discontinuation after the 2002 publication of the Women's Health Initiative findings, has resulted in large numbers of former HT users among U.S. women. However, few studies have examined whether ovarian cancer risk varies according to recency and duration of specific HT regimens. We assessed risk of epithelial ovarian cancer among users of unopposed estrogen (ET) and combined estrogen/progestogen (EPT). In a population-based study in Washington state, 812 women with ovarian cancer diagnosed in 2002 to 2005 and 1,313 controls were interviewed in person about the use of HT and other characteristics. Women who used a single form of therapy (ET or EPT) were compared with women who never used HT using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CIs). Risk was increased among current or recent (within the last 3 years) users of ET with ≥5 years of use (ORs, 95% CIs: 1.6, 1.1-2.5 and 1.8, 0.8-3.7, respectively). Little increase in risk was noted among long-term ET users who discontinued use in the more distant past (OR, 1.2; 95% CI, 0.6-2.6). No increase in risk was noted among women who used only EPT, regardless of duration. Compared with women who never used HT, current users of EPT had an OR of 1.1 (95% CI, 0.8-1.5), and risk declined with increasing time since stopping; the OR was 0.7 (95% CI, 0.4-1.0) among women who had discontinued EPT within the last 3 years and 0.5 (95% CI, 0.3-0.7) among women who stopped at an earlier point. Long-term ET may be associated with an increased ovarian cancer risk that wanes after use ceases. We did not observe an increased risk with EPT, and with increasing time after stopping, a reduction in risk became increasingly evident. The progestogen component of HT may confer a risk reduction that is masked by an opposing effect of estrogen until, among former users, estrogenic influences have diminished. These findings, if replicated, may have implications both for public health and development of chemoprevention strategies. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2548–56)

Introduction

Although the results of epidemiologic studies of epithelial ovarian cancer suggest a moderate increase in risk among women with a long duration of use of unopposed menopausal estrogen therapy (ET), the relation of risk to use of hormone preparations in which estrogen is combined with a progestogen (EPT) is much less well characterized. Fewer studies have examined EPT regimens, and with the exception of the recent Million Women Study (1), those that have are limited by small numbers of cancers or by a low proportion of women who used these products (2-15).

The formulation of the hormone therapy (HT), the duration that it is used, and the recency of use may bear on ovarian cancer risk. In the United States, prescriptions for oral and transdermal menopausal estrogens nearly tripled from 1982 to 1992, with an even more rapid (5-fold) increase in oral progestogens (16). From 1995 to 2001, oral EPT accounted for more than 70% of the growth in HT prescriptions (17). Use peaked in 2001, when an estimated 42% of U.S. women 50 to 74 years of age used HT, and declined dramatically after the publication in July 2002 of the Women's Health Initiative (WHI) findings of increased risks of cardiovascular disease and breast cancer among women randomized to EPT (17-19).

We conducted a population-based case-control study of women diagnosed with epithelial ovarian cancer from 2002 to 2005, in a setting in which a relatively high proportion of women used HT, and many women discontinued use during the years the study was conducted. Consistent with current recommendations, the use of ET occurred mostly among women who had undergone hysterectomy, whereas women with an intact uterus generally used EPT. The increasing use of EPT in the 1990s, followed by widespread discontinuation of HT since 2002, enhanced our ability to separately examine the risk among current and former users of specific HT regimens.

Materials and Methods

Cases. Female residents of a 13-county area of western Washington state, 35 to 74 years of age, who were

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diagnosed with a primary invasive or borderline epithelial ovarian tumor between January 1, 2002 and December 31, 2005, were eligible for the study. These women were identified through the Cancer Surveillance System (CSS), a population-based registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program of the U.S. National Cancer Institute, by October 31, 2006. We restricted our study to English-speaking women who had residential telephones at the time of cancer diagnosis because random digit dialing (RDD) was the method used to select control subjects.

Of 1,058 women identified, 812 (76.7%) were interviewed. Reasons for not obtaining an interview included physician refusal (n = 23); inability to locate the patient (n = 10); patient refusal (n = 110); and death (n = 103). Of the interviewed cases, 595 had invasive disease. Histologic type was collected and coded by the CSS using the third edition of the *International Classification of Diseases for Oncology* (ICD-O) morphology codes (20), and these codes were grouped according to guidelines of the WHO (21) as follows: serous (n = 452), 8441, 8442, 8450, 8451, 8460, 8461, 8462, 8463, and 9014; mucinous (n = 112), 8470, 8472, 8473, 8480, 8482; endometrioid (n = 104), 8380, 8381, 8570, 8950; clear cell (n = 35), 8310; and other epithelial tumors (n = 109), the most common of which were 8140 [adenocarcinoma, not otherwise specified (NOS), n = 34], 8323 (mixed cell adenocarcinoma, n = 33), and 8010 (carcinoma, NOS, n = 16). Among interviewed women, the large majority (73%) of those with borderline tumors had localized disease, whereas 85% of women with invasive tumors had regional or distant disease, according to the SEER staging system; these proportions were quite similar to the distribution among all eligible women (74% and 86%, respectively).

Controls. Controls were selected by RDD using the two-stage Waksberg-Mitofsky method with a clustering factor of 5 residences per sampling unit (22, 23). We used a stratified sampling design that apportioned controls into 5-year age categories, 1-year calendar intervals, and two county strata (consisting of the urban three counties encompassing Seattle and the more rural 10 surrounding counties), according to the anticipated distribution of these characteristics among women with invasive epithelial ovarian cancer. We aimed to enroll twice as many controls as women with invasive disease.

We were able to determine the residential status of all but 4,733 (8.3%) of the 57,066 numbers called; <20% of these telephone numbers would have been expected to be associated with residential addresses (24). For 14,561 (82.0%) of the 17,768 telephone numbers belonging to a residence, we determined whether an eligible (i.e., age and county eligible and able to communicate in English, and if so, with at least one ovary and no prior history of ovarian cancer) woman resided there (Table 1). Of the 1,561 eligible women identified, 1,313 were interviewed (84.1%); the remaining women refused (n = 240) or were lost to follow-up (n = 8). The overall control response proportion (screening response × interview response) was 69.0%.

Interviews. Case and control interviews were conducted from 2002 to 2006 and pertained to the time before diagnosis (for cases) or before an assigned, comparable reference date (for controls). The study

Table 1. Outcomes of telephone screening for control recruitment

Total telephone numbers called	57,066
Ineligible telephone number	34,565
Business	7,955
Non-working	23,217
Non-business (institutions, group quarters, data-lines, cell phones)	3,393
Unknown if residential telephone number	4,733
Known residential telephone number	17,768
Unknown if individual eligible	3,207
Answering machine on all attempts	1,070
Refused age/county questions	1,382
Age/county eligible, ovarian status unknown*	380
Other (language/communication barrier)	375
Respondent screened	14,561
Not eligible	13,000
Did not fit age/county eligibility or frequency matching criteria	12,511
No ovaries	470
Prior ovarian cancer	5
Selected woman had communication barrier	14
Eligible	1,561
Not interviewed	248
Interviewed	1,313

*We estimate 77% of these women may have had at least one ovary.

was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating. The interview covered demographic and lifestyle characteristics; medical history; family and personal cancer history; and reproductive history, including menstrual, pregnancy, and contraceptive history, as well as the use of noncontraceptive hormones. To aid recall, interviewers used a calendar to record life events and provided photographs of commonly used oral contraceptive and menopausal hormone preparations. To identify the latter, women were asked if, before the diagnosis/reference date, they had ever used hormones to treat or prevent menopausal symptoms or after a hysterectomy; and, in a separate question, if they had used hormones just before the onset of menopause, around the time of menopause, or after menopause.

Statistical Analysis. Our primary goal was to assess the independent effects of ET and EPT and, among EPT users, the risks associated with regimens with ≥25 days per month of progestogen [continuous combined EPT (CC-EPT)] and regimens with <25 days of progestogen per month (other EPT). Thus, we chose to include only women who had either never used HT (n = 1,054) or had used only one of either ET (n = 288) or EPT (n = 476; 309 used only CC-EPT), including oral and transdermal formulations. Excluded from analysis, in hierarchical order, were women who used both ET and EPT (62 controls, 20 cases); women who used unopposed progestogen as HT (31 controls, 19 cases); women who used HT in formulations other than pills or patches (90 controls, 43 cases); and 42 women (27 controls and 15 cases) who either used a hormone other than estrogen or progestogen as HT or were unable to report whether or not they had used an estrogen or combined estrogen/progestogen type of HT.

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Odds ratios (OR) and 95% confidence intervals (95% CI) for the risk of epithelial ovarian cancer associated with various aspects of HT were calculated using unconditional logistic regression. The reference group for all analyses was women who had never used any type of HT. Current HT was defined as use within the 6 months preceding the reference date, whereas former users were women who discontinued use before that time; among former users, we examined risk according to time since last use in categories of >6 months to 3 years, or ≥3 years before the reference date. All results shown are adjusted for the frequency matching variables of age (5-year intervals), county of residence (two strata, as described above), and calendar year of diagnosis/reference date (1-year strata), as well as number of full-term births (categorical variables for 0, 1, 2, 3, and 4 or more) and duration of hormonal contraception (categorical variables of never users and users of <6, 6-59, 60-119, and ≥120 months). Adjustment for other potential confounding variables [race/ethnicity, education, body mass index (BMI), age at menarche, age at last birth, history of breast cancer, family history of breast and/or ovarian cancer, smoking, tubal ligation, hysterectomy, menopausal status (assessed according to last menstrual period {LMP} or presence of vasomotor symptoms, as described below), age at menopause, and age at vasomotor symptoms] produced no important change in ORs. The probability (two-sided *P* value) of interaction between HT and BMI was assessed using the likelihood ratio statistic, comparing models with and without the interaction term. All analyses were conducted using STATA (version 9.2, STATA Corporation).

To allow more direct comparison of our results with analytic approaches used in some prior studies, we conducted additional analyses examining HT regimens among women with no prior history of cancer (other than nonmelanoma skin cancer) and women who had (for ET) or had not (for EPT) undergone a hysterectomy. Because some studies have been limited to women considered menopausal, we conducted similar analyses; in addition, we assessed the risk among women who began HT before or after age 50. We also assessed risk associated with HT regimens in women of normal weight (BMI <25) and overweight/obese (BMI ≥25) women, based on their reported weight 5 years before the reference date. Using polytomous logistic regression, we conducted analyses that separated case groups according to the degree of invasiveness or histologic type of the tumor. Invasive epithelial ovarian cancer has a considerably less favorable prognosis and tends to occur at older ages (when HT might be more prevalent) than does borderline disease; thus, for selected analyses, we present both the overall risk of epithelial ovarian cancer as well as risk of developing invasive disease.

We used a previously developed algorithm (25) to categorize menopausal status. Briefly, menopausal women were categorized as having known natural menopause; known induced menopause (via chemotherapy or radiation); or assumed natural menopause, defined as age 55 or older and either on HT and still menstruating or with periods ended by hysterectomy. Premenopausal women had had at least one menstrual period in the year before the reference date while not taking HT. Menopausal status was considered unclear among women <55 years of age whose periods were stopped by hysterectomy or who were <55 and having periods while taking HT. Because the occurrence and timing of menopause was not certain among some prevalent subgroups, e.g., women who were premenopausal when they had a hysterectomy, or who initiated HT before menopause (among whom menstrual bleeding patterns may be obscured by HT), we used the occurrence of vasomotor symptoms, and the age at which these symptoms first occurred, as a second means of identifying women undergoing the menopausal transition.

Results

Relative to controls, cases were more likely to be nulliparous and to report fewer full-term pregnancies, and they were less likely to have taken hormonal contraceptives. Also, cases tended to have a higher body mass than controls. Although prior hysterectomy was reported among a similar proportion of cases and controls, fewer cases than controls had had a tubal ligation. A personal history of breast cancer was more commonly reported by cases, and a larger proportion of cases than controls reported a family history of ovarian cancer (Table 2). Among women in whom age at menopause (natural or induced) could be determined, the median age at LMP was 50 years among both cases and controls. Vasomotor symptoms were reported by about two-thirds of women, with a median age at onset of 48 years in controls and 47 years in cases. Symptoms were reported by 79% of menopausal and 40% of premenopausal women.

In analyses adjusted for the frequency matching variables, duration of hormonal contraception, and number of full-term births, women who had used only ET had a slightly increased risk (OR, 1.3; 95% CI, 0.9-1.7) and women who had used only EPT had a slightly reduced risk (OR, 0.8; 95% CI 0.6-1.0) of epithelial ovarian cancer (Table 3). Overall, risk increased with increasing duration of ET (e.g., OR among users of ≥10 years, 1.6; 95% CI, 1.1-2.5). Among current users, the increased risk among women who had used ET for 5 years or more remained evident (OR, 1.6; 95% CI, 1.1-2.5), whereas among former users, this duration of use was associated with increased risk primarily among women who had last used ET relatively recently. The OR was 1.8 (95% CI, 0.8-3.7) among women with ≥5 years of use who had stopped <3 years before the reference date and 1.2 (95% CI, 0.6-2.7) among women who had used for a similar duration but had stopped ≥3 years before that date. In analyses restricted to invasive cancers, we observed similar patterns of increasing risk with longer duration of ET and a waning of the increased risk among former ET users with longer time since last use (Table 4).

In contrast, among women who had only used EPT, we observed no evidence that risk increased with longer duration. Also, whereas no clear alteration in risk was noted among current users (OR, 1.1, 95% CI, 0.8-1.5), former users were at a reduced risk, and the reduction was most evident among women who had stopped in the more distant past (OR for last EPT ≥3 years before the reference date, 0.5; 95% CI, 0.3-0.7). Among women who had only used EPT, CC-EPT was the only regimen used by 67% of controls and 61% of cases, and the pattern of risk was quite similar, with slightly lower ORs, to that

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Table 2. Characteristics of cases and controls among HT never users and exclusive users of ET or EPT

	Controls (n = 1,103),* n (%)	Cases (n = 715),* n (%)	Invasive cases (n = 520),* n (%)	OR† (95% CI)
Age at diagnosis/reference date (y)				
35-44	154 (14.0)	120 (16.8)	66 (12.7)	
45-54	338 (30.6)	247 (34.5)	162 (31.2)	
55-64	348 (31.6)	210 (29.4)	174 (33.5)	
65-74	263 (23.8)	138 (19.3)	118 (22.7)	
Race/ethnicity				
White, non-Hispanic	979 (88.8)	633 (88.5)	463 (89.0)	1.0
Nonwhite, non-Hispanic	81 (7.3)	52 (7.3)	39 (7.5)	1.0 (0.7-1.5)
Hispanic	43 (3.9)	30 (4.2)	18 (3.5)	0.9 (0.5-1.6)
Duration of use of hormonal contraceptives				
Never used	210 (19.0)	209 (29.2)	171 (32.9)	1.0
<6 mo	77 (7.0)	66 (9.2)	51 (9.8)	0.7 (0.5-1.1)
6 mo to <5 y	404 (36.6)	219 (30.6)	147 (28.3)	0.4 (0.3-0.5)
5 to <10 y	222 (20.1)	127 (17.8)	94 (18.1)	0.4 (0.3-0.6)
10+ y	190 (17.2)	94 (13.1)	57 (11.0)	0.3 (0.2-0.5)
Full-term pregnancies				
0	161 (14.6)	181 (25.3)	119 (22.9)	1.0
1	140 (12.7)	113 (15.8)	87 (16.7)	0.8 (0.6-1.2)
2	364 (33.0)	198 (27.7)	136 (26.2)	0.5 (0.3-0.6)
3	245 (22.2)	132 (18.5)	102 (19.6)	0.5 (0.4-0.7)
4+	193 (17.5)	91 (12.7)	76 (14.6)	0.5 (0.3-0.7)
Tubal ligation				
No	863 (78.2)	589 (82.4)	435 (83.7)	1.0
Yes	240 (21.8)	126 (17.6)	85 (16.3)	0.7 (0.5-0.9)
Hysterectomy				
No	891 (80.8)	566 (79.2)	409 (78.7)	1.0
Yes	212 (19.2)	149 (20.8)	111 (21.3)	1.1 (0.9-1.5)
Family history of breast and ovarian cancer				
None	671 (61.5)	416 (58.8)	295 (57.5)	1.0
Breast cancer only	341 (31.3)	210 (29.7)	151 (29.4)	1.0 (0.8-1.3)
Ovarian cancer only	47 (4.3)	52 (7.4)	42 (8.2)	2.1 (1.3-3.3)
Breast and ovarian cancer	32 (2.9)	29 (4.1)	25 (4.9)	1.8 (1.0-3.1)
Prior breast cancer				
No	1,045 (94.7)	667 (93.3)	476 (91.5)	1.0
Yes	58 (5.3)	48 (6.7)	44 (8.5)	1.7 (1.1-2.5)
Body mass index at age 30				
<18.5	75 (6.9)	37 (5.2)	30 (5.8)	0.9 (0.6-1.3)
18.5-24.9	826 (75.7)	520 (73.4)	386 (74.7)	1.0
25-29.9	127 (11.6)	91 (12.9)	58 (11.2)	1.0 (0.7-1.4)
30+	63 (5.8)	60 (8.5)	43 (8.3)	1.5 (1.0-2.3)
Age at last full-term pregnancy				
No full-term pregnancies	161 (14.6)	181 (25.3)	119 (22.9)	1.0
<25 y	172 (15.6)	147 (20.6)	114 (21.9)	0.8 (0.6-1.2)
25-29 y	308 (27.9)	173 (24.2)	138 (26.5)	0.6 (0.4-0.8)
30-34 y	295 (26.8)	145 (20.3)	99 (19.0)	0.4 (0.3-0.6)
35+ y	166 (15.1)	69 (9.7)	50 (9.6)	0.4 (0.3-0.6)
Menopausal status (see text for definition)				
Premenopausal	355 (32.2)	267 (37.3)	167 (32.1)	1.0
Natural menopause	420 (38.1)	226 (31.6)	179 (34.4)	1.0 (0.6-1.5)
Induced menopause	12 (1.1)	10 (1.4)	10 (1.9)	1.8 (0.8-4.5)
Assumed natural menopause	239 (21.7)	162 (22.7)	137 (26.3)	1.3 (0.8-2.1)
Unclear	77 (7.0)	50 (7.0)	27 (5.2)	0.7 (0.4-1.1)
Vasomotor symptoms				
No	367 (33.3)	269 (37.6)	180 (34.6)	1.0
Yes	736 (66.7)	446 (62.4)	340 (65.4)	0.9 (0.7-1.1)

*n of individual variables may not sum to total due to missing values.
†Odds ratios for invasive epithelial ovarian cancer, adjusted for age, reference year, and county of residence.

observed among EPT users overall (Table 3). Only 16% of controls and 18% of cases exclusively used an EPT regimen other than CC-EPT; among these women, any use and former use of EPT were also associated with reductions in risk, albeit with limited precision (OR, 0.8; 95% CI, 0.5-1.4, and OR, 0.6; 95% CI, 0.3-1.3, respectively). For invasive cancers, risk reductions among users of EPT and CC-EPT were again most evident among former users who had stopped in the more distant past and slightly stronger among women who only used CC-EPT (Table 4).

Results were similar in analyses restricted to women with no prior history of cancer (data not shown). In analyses of menopausal women, results for EPT were unchanged, although the smaller sample size reduced precision. For ET, point estimates for ever- and long-term use were slightly reduced when menopause was defined based on LMP and slightly increased when menopausal

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Table 3. Risk of epithelial ovarian cancer associated with exclusive use of ET, EPT, and CC-EPT hormone therapy

	ET			EPT			CC-EPT		
	Controls, *n*	Cases, *n*	OR* (95% CI)	Controls, *n*	Cases, *n*	OR* (95% CI)	Controls, *n*	Cases, *n*	OR* (95% CI)
Never used	614	440	1.0	614	440	1.0	614	440	1.0
Ever	167	121	1.3 (0.9-1.7)	322	154	0.8 (0.6-1.0)	215	94	0.7 (0.5-1.0)
Duration of use									
<60 mo	67	38	0.9 (0.6-1.5)	131	51	0.6 (0.4-0.8)	88	33	0.6 (0.4-0.9)
60-119 mo	26	21	1.3 (0.7-2.5)	83	50	1.0 (0.6-1.5)	61	35	0.9 (0.6-1.4)
120+ mo	74	62	1.6 (1.1-2.5)	108	53	0.9 (0.6-1.3)	66	26	0.7 (0.4-1.2)
Recency									
Current users	84	64	1.3 (0.9-2.0)	123	84	1.1 (0.8-1.5)	82	54	1.0 (0.7-1.5)
Former users	83	57	1.2 (0.8-1.8)	199	70	0.6 (0.4-0.8)	133	40	0.5 (0.3-0.7)
Recently quit (6-35 mo ago)	27	21	1.5 (0.8-2.8)	95	40	0.7 (0.4-1.0)	69	26	0.6 (0.4-1.0)
Quit ≥3 y ago (36+ mo)	56	36	1.1 (0.7-1.7)	104	30	0.5 (0.3-0.7)	64	14	0.4 (0.2-0.7)
Duration of use									
Among current users									
<60 mo	19	9	0.7 (0.3-1.5)	38	24	0.9 (0.5-1.6)	26	18	1.0 (0.5-1.9)
60+ mo	65	55	1.6 (1.1-2.5)	85	60	1.1 (0.8-1.7)	56	36	1.0 (0.6-1.7)
Among recently quit									
<60 mo	10	6	1.2 (0.4-3.4)	24	11	0.7 (0.3-1.5)	18	8	0.7 (0.3-1.6)
60+ mo	17	15	1.8 (0.8-3.7)	71	29	0.7 (0.4-1.1)	51	18	0.6 (0.3-1.0)
Among quit ≥3 y ago									
<60 mo	38	23	1.1 (0.6-1.9)	69	16	0.3 (0.2-0.6)	44	7	0.2 (0.1-0.6)
60+ mo	18	13	1.2 (0.6-2.7)	35	14	0.7 (0.4-1.4)	20	7	0.7 (0.3-1.6)

*Odds ratios adjusted for age, county of residence, year of diagnosis/reference date, number of full-term pregnancies, and duration of hormonal contraception.

transition was identified by vasomotor symptoms. Age at menopause could be determined only for women with a natural or induced menopause; adjustment for this characteristic proved difficult for ET, as most users were women who had had a hysterectomy. Adjustment for age at first vasomotor symptoms had little effect.

Nearly all (98% of cases and controls) women who used only EPT had an intact uterus, and results were identical in analyses restricted to these women. Among women who had used only ET, 83% and 81% of cases and controls, respectively, had undergone hysterectomy; however, owing to the small number of women with hysterectomy among never users of HT (10% of cases and 11% of controls), analyses of ET in this subgroup were imprecise (e.g., OR for 5 years duration, 1.5; 95% CI, 0.8-2.7).

Table 4. Risk of invasive epithelial ovarian cancer associated with exclusive use of ET, EPT, CC-EPT hormone therapy

	ET			EPT			CC-EPT		
	Controls, *n*	Invasive cases, *n*	OR* (95% CI)	Controls, *n*	Invasive cases, *n*	OR* (95% CI)	Controls, *n*	Invasive cases, *n*	OR* (95% CI)
Never used	614	299	1.0	614	299	1.0	614	299	1.0
Ever	167	94	1.3 (0.9-1.8)	322	127	0.8 (0.6-1.0)	215	75	0.7 (0.5-1.0)
Duration of use									
<60 mo	67	25	0.8 (0.5-1.4)	131	39	0.6 (0.4-0.8)	88	24	0.5 (0.3-0.8)
60-119 mo	26	17	1.4 (0.7-2.6)	83	41	1.0 (0.6-1.5)	61	28	0.9 (0.5-1.5)
120+ mo	74	52	1.7 (1.1-2.7)	108	47	0.9 (0.6-1.4)	66	23	0.8 (0.4-1.3)
Recency of use									
Current	84	49	1.3 (0.9-2.0)	123	66	1.0 (0.7-1.5)	82	41	1.0 (0.6-1.5)
Former	83	45	1.2 (0.8-1.9)	199	61	0.6 (0.4-0.9)	133	34	0.5 (0.3-0.8)
Recently quit (6-35 mo ago)	27	18	1.7 (0.9-3.2)	95	34	0.7 (0.4-1.1)	69	22	0.6 (0.4-1.0)
Quit ≥3 y ago (36+ mo)	56	27	1.0 (0.6-1.7)	104	27	0.5 (0.3-0.8)	64	12	0.4 (0.2-0.7)
Duration of use									
Among current users									
<60 mo	19	6	0.6 (0.2-1.6)	38	17	0.9 (0.5-1.6)	26	12	0.9 (0.4-1.8)
60+ mo	65	43	1.6 (1.0-2.5)	85	49	1.1 (0.7-1.7)	56	29	1.0 (0.6-1.7)
Among former users									
<60 mo	48	19	0.9 (0.5-1.6)	93	22	0.4 (0.3-0.7)	62	12	0.4 (0.2-0.7)
60+ mo	35	26	1.7 (1.0-3.1)	106	39	0.8 (0.5-1.2)	71	22	0.6 (0.4-1.1)

*Odds ratios adjusted for age, county of residence, year of diagnosis/reference date, number of full-term pregnancies, and duration of hormonal contraception.

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Table 5. Risk of epithelial ovarian cancer associated with exclusive use of ET and EPT hormone therapy by BMI

	ET*						EPT*					
	BMI <25			BMI ≥ 25			BMI <25			BMI ≥ 25		
	Controls, *n*	Cases, *n*	OR† (95% CI)	Controls, *n*	Cases, *n*	OR† (95% CI)	Controls, *n*	Cases, *n*	OR† (95% CI)	Controls, *n*	Cases, *n*	OR† (95% CI)
Never used	321	191	1.0	289	246	1.0	321	191	1.0	289	246	1.0
Ever	67	59	1.9 (1.2-2.9)	100	62	1.0 (0.6-1.4)	168	81	0.9 (0.7-1.4)	153	72	0.6 (0.4-0.9)
Duration of use												
<60 mo	24	15	1.3 (0.6-2.6)	43	23	0.8 (0.4-1.4)	59	28	0.9 (0.5-1.5)	71	23	0.4 (0.2-0.7)
60-119 mo	13	9	1.4 (0.6-3.5)	13	12	1.3 (0.5-2.9)	48	28	1.2 (0.7-2.1)	35	21	0.8 (0.4-1.4)
120+ mo	30	35	2.7 (1.5-4.8)	44	27	1.1 (0.6-1.9)	61	25	0.9 (0.5-1.5)	47	28	1.0 (0.6-1.7)
Recency of use												
Current	37	36	2.0 (1.2-3.5)	47	28	0.9 (0.5-1.6)	68	41	1.1 (0.7-1.8)	54	42	1.0 (0.6-1.6)
Former	30	23	1.7 (0.9-3.1)	53	34	1.0 (0.6-1.6)	100	40	0.8 (0.5-1.2)	99	30	0.4 (0.3-0.7)

*P interaction for HT use with BMI (assessed 5 y before reference date) = 0.02, 0.09, and 0.05 for ever, duration, and recency of ET use; and 0.09, 0.14, and 0.11 for ever, duration, and recency of EPT use.

† Odds ratios adjusted for age, county, year of diagnosis/reference date, number of full-term pregnancies, and duration of hormonal contraception.

A large proportion of ET users (67%) initiated use before age 50; the risk associated with ≥5 years duration was 1.7 (95% CI, 1.2-2.6) among these women, but 1.0 (95% CI, 0.5-1.9) among women who first used ET after that age. For EPT, 45% of users initiated use before age 50; current use was not associated with risk in women who began HT before or after reaching that age (ORs, 1.1 and 1.0, respectively) whereas former EPT was associated with a reduced risk among women who began use before (OR, 0.7; 95% CI, 0.4-1.1) or after (OR, 0.5; 95% CI, 0.3-0.7) 50 years of age. Roughly three quarters of HT users who reported vasomotor symptoms initiated HT within 3 years after the symptoms began.

In analyses that included invasive and borderline tumors, we observed no increase in risk of mucinous tumors associated with ever use or with long-term duration of ET. Increased risk associated with ET was most apparent for serous tumors (e.g., OR for ≥10 years of use, 1.8; 95% CI, 1.1-2.9), whereas this risk estimate was imprecise for the combined group of endometrioid/clear cell tumors (OR, 1.4; 95% CI, 0.5-3.6). For serous and mucinous subtypes, patterns of risk associated with EPT were similar to the overall results, whereas associations were less clear in other groups. For invasive cancers, risks for serous tumors were similar to those observed for invasive and borderline tumors combined; estimates were unstable in other histologic subgroups.

In analyses that examined HT among normal-weight (BMI <25) and overweight/obese (BMI ≥25) women, ET was associated with an increased risk only among women who were not overweight; e.g., ORs associated with ever use among women who had only used ET were 1.9 (95% CI, 1.2-2.9) among women with BMI <25 and 1.0 (95% CI, 0.6-1.4) among women with BMI ≥25. In contrast, reduced risk associated with EPT was most evident among women who were overweight or obese (Table 5).

Discussion

Strengths of the current study include its population-based design, relatively large size, and the common use of HT (particularly EPT). Assessing risk among women who only used a single regimen may serve to clarify differing effects of ET and EPT. Detailed life histories were available on HT as well as potentially confounding factors. However, some subgroup analyses were limited by sample size.

It is possible that women who agreed to take part in the study may have had a prevalence of current or past HT use that was not representative of their source population. To impact our findings, such selective participation would have had to occur to a different extent among controls than cases. We have no information regarding the use of HT among eligible cases or controls who refused to participate. However, cases and controls were unaware of the hypotheses of this study, and among cases, the large majority of refusals were among women who were too ill to be interviewed. Also, during the course of the study, we observed reductions in HT use that were of similar magnitude among cases and controls and consistent with national trends (17, 19). For example, among controls with reference dates in 2002, 56% of women who had ever taken EPT were currently using the drug, whereas in 2005, the corresponding figure was 27%. Among women with ovarian cancer who had ever taken EPT, 75% and 46% were current users in 2002 and 2005, respectively. For ET, the proportion of current users declined from 71% to 30% among controls and from 79% to 33% among cases, from 2002 to 2005. Given that observed associations with HT varied according to regimen, it seems unlikely that our findings can be explained by the selective loss of potential controls or cases who were HT users and/or by differential reporting of HT among participating cases and controls.

Older studies (many of which were individually interpreted as lacking evidence of association) of the relation of HT and risk ovarian cancer have been the subject of combined reanalyses and meta-analyses (26-28); these reports, as well as additional studies published through 2003 (10-15), have been extensively reviewed (2, 3) and, in aggregate, support the presence of a small to moderate increase in risk among women who have used ET for a relatively long duration. Studies published since 2004 further support an increased risk

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among women with substantial exposure to ET. Increased risk among women who had used ET for at least 10 years was observed in one recent cohort [ref. 5; relative risk (RR), 1.89; 95% CI, 1.22-2.95] and one case-control (6) study (OR, 2.2; 95% CI, 1.2-4.1). Danforth (4) reported an association with ET in the Nurses Health Study (RR, 1.25 for a 5-year increment of use; 95% CI, 1.12-1.38); in analyses restricted to women exclusively using one formulation, use of 5 years or more of ET was associated with a doubling in risk (RR, 2.04; 95% CI, 1.41-2.97). Pike (9) also observed an increased risk among women who had used ET for more than 5 years relative to women who reported up to 1 year of use (OR, 1.56; 95% CI, 0.72-3.41).

However, the impact of extended duration of ET has been difficult to disentangle from recency. In the NIH-AARP cohort (5), 24 of 26 cases with 10 years or more of use were current users. Other recent studies (4, 6) have not presented analyses of ET duration stratified by recency. In the Million Women Study (1), 2,273 ovarian cancers occurred over an average 5.3 years of follow-up among nearly 1 million women in the United Kingdom; of 242 cases observed among current users of ET, 196 had used for at least 5 years, with a RR of 1.53 (95% CI, 1.27-1.84), whereas the RR for <5 years of use among current ET users was 0.89 (95% CI, 0.64-1.25). No estimate was provided for the past use of ET. The RR among current HT users was greater for serous (1.53; 95% CI, 1.31-1.79) than for mucinous, endometrioid, or clear cell tumors.

In contrast to an increased risk with long duration of ET that may be particularly evident among current and recent users, several studies have not observed increased risks for EPT. However, most studies have lacked sufficient long-term or past EPT users to address associations with duration and recency. Glud (7) assessed risk associated with cumulative grams of oral menopausal estrogen or progestogen in a Danish case-control study and observed an increasing risk with increasing intake of estrogen but no association with progestogens. In a cohort study of 44,241 postmenopausal U.S. women (11), no increase in risk was observed among women who had only used EPT (RR, 1.1; 95% CI, 0.6-1.7); only 18 of 329 cases had exclusively used EPT. In a Swedish study of 655 women with invasive epithelial ovarian cancer and 3,899 controls aged 50 to 74 years, increased risk was observed among users of sequential EPT (RR, 1.54; 95% CI, 1.15-2.05), but no increase in risk was seen among users of CC-EPT (RR, 1.02; 95% CI, 0.73-1.43), and no trend was observed with increasing duration of CC-EPT (12). In a Norwegian cohort of 30,115 postmenopausal women aged 45 to 64 years, 74 ovarian cancers occurred; EPT was the most common type of HT used, and 30 of 34 cases using HT were current users. Relative risks associated with ever use of ET and EPT were 0.9 (95% CI, 0.2-3.9; two exposed cases) and 1.5 (95% CI, 0.9-2.6; 23 exposed cases; ref. 8).

Three recent cohort studies (1, 4, 5), a case-control study (6), and the WHI primary prevention trial (10) provide additional inconsistent findings regarding EPT. The NIH-AARP cohort (5), with 214 ovarian cancers occurring among 97,638 women aged 50 to 71 years, reported an increased risk associated with EPT used for ≥10 years (RR, 2.15; 95% CI, 1.28-3.62) among women who had not had a hysterectomy; of the 50 cancers that occurred among women who used EPT, all but eight were in current users. Risk was somewhat higher for sequential (<15 days P monthly; n = 21 cases) than CC-EPT (≥15 days P monthly; n = 28), and former users of CC-EPT were not at increased risk (OR, 0.97; 95% CI, 0.31-3.10). In contrast, the Nurses Health Study investigators (4) observed no association with duration of EPT (RR, 1.04 for a 5-year increment of use; 95% CI, 0.82-1.32) and no increase in analyses restricted to women exclusively using EPT (0.93; 95% CI, 0.47-1.83) or women with an intact uterus. Small numbers precluded evaluation of particular EPT regimens and limited the analysis of recency. Moorman (6) reported no association of risk with duration of EPT in an analysis comparing postmenopausal women who only used EPT to women who never used HT. In that study, the large majority of HT users were using within 12 months of the reference date, although these data were not provided for specific regimens. In the WHI primary prevention trial (10), in which almost 17,000 postmenopausal women aged 50 to 64 years were assigned to 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate or to placebo, the ovarian cancer RR was 1.58 (95% CI, 0.74-3.24), based on 32 cancers over a mean follow-up of 5.6 years.

In the Million Women Study (1), the RRs of ovarian cancer among current users of EPT were 1.09 (95% CI, 0.91-1.30) and 1.17 (95% CI, 1.02-1.34) for <5 and ≥5 years of use, respectively, with 404 cancers occurring among current EPT users. Risks were similar among current users of continuous combined and sequential EPT (1.13 and 1.14). EPT with medroxyprogesterone acetate, by far the most commonly used progestogen in the United States, as the progestogen component was not associated with an increased risk among current users (RR, 0.99; 95% CI, 0.77-1.26, based on 69 exposed cases). Although no increase in risk was observed among past users of HT overall (RR, 0.98; 95% CI, 0.88-1.11), no results were presented regarding risk of particular regimens (ET versus EPT) of use in former HT users.

Can the results of the various studies of HT and ovarian cancer risk be reconciled? The more recent introduction of EPT, differences between populations in available formulations and in the prevalence and typical duration of use, time trends in the use of specific EPT regimens—with the CC-EPT pill, since its introduction in 1995, largely accounting for subsequent HT increases in the United States (17, 29)—as well as mixed use by individuals of both ET and EPT, may have impacted various studies in uncertain ways. Also, if, as our results suggest, the relation of ET and EPT with ovarian cancer risk varies by body mass, differences between study populations and over calendar time in the prevalence of overweight and obesity may contribute to inconsistent results.

Beyond differences between studies in patterns of HT exposure, differing analytic strategies could also account for differences in findings. However, we noticed no impact on our results of limiting the study to women with no prior cancer or to menopausal women. Also, we observed little indication that adjustment for menopausal status or age at vasomotor symptoms (because age at

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menopause could not be determined in a substantial proportion of women) importantly influenced results. We examined the impact of prior hysterectomy through adjusted and restricted analyses; whereas Beral (30) has argued that failure to adjust for hysterectomy may mask an increased risk associated with HT, hysterectomy was not associated with risk in the current study, and adjustment for it had no meaningful impact on our results.

Conceivably, ovarian tissue may respond differently to HT depending on the age, menopausal status, or underlying hormonal status of a user. Roughly three quarters of women in our study began HT within a few years after vasomotor symptoms began, and many women began use before menstrual function ceased; thus, it is difficult to directly compare our results with the WHI intervention, in which HT was taken by menopausal women >50 years of age and typically initiated many years after menopause. The increases in risk we observed among ET users were largely confined to women who were not overweight, whereas the reduced risk among EPT users was most evident in women who were overweight or obese. These latter findings parallel those reported in studies of endometrial cancer (31, 32) and raise the possibility that the impact of specific HT regimens may depend on levels of endogenous estrogens which, after menopause, are principally supplied by adipose tissue. Few studies of ovarian cancer have addressed this hypothesis. In the Million Women Study (1), there was no clear difference in the strength of association among women with BMI <25, 25 to 29, and ≥30; however, this analysis examined only current use of HT and combined ET, EPT, and other regimens as a single category.

In the current study, risk of ovarian cancer varied by HT regimen. An increased risk among women using ET became apparent only after many years of use and was of moderate strength. Also, even among women who had used ET for ≥5 years, no clear increase in risk was evident several years after stopping. These results are generally consistent with and extend the findings of other recent studies. We observed no increase in risk among users of EPT, a result that is consistent with some, but not all, recent studies; also, we observed a reduction in risk among former users of EPT. Our finding of reduced risk among former users of EPT, but not ET, is consistent with (*a*) the hypothesis that estrogens may increase and progestogens may reduce risk of epithelial ovarian cancer, possibly through differential influences of these hormones on cell proliferation and apoptosis (33, 34); and (*b*) the prolonged protection, apparent many years after exposure, afforded by childbearing and prior use of combined estrogen/progestogen oral contraceptives.

Long-term ET may be associated with an increased ovarian cancer risk that wanes after use ceases. We did not observe an increased risk associated with EPT, and with increasing time after stopping, a reduction in risk became increasingly evident. The progestogen component of HT may confer a risk reduction that is masked by an opposing effect of estrogen until, among former users, estrogenic influences have diminished. These findings, if replicated, may have implications both for public health and for the development of chemoprevention strategies.

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