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Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer

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DESPITE CASE-CONTROL STUDIES,¹ pooled analyses,^{2,3} and meta-analyses,^{4,5} the potential association between menopausal hormone replacement therapy (HRT) and ovarian cancer remains unresolved. Most retrospective studies found no association, and the studies that showed increased risks predominantly included weak, nonsignificant associations and an absence of dose response.⁶ Small size⁷ and incomplete information about other ovarian cancer risk factors⁸ limited the few available prospective studies of incident ovarian cancer. A large, prospective study recently reported a significant 2-fold increased risk of ovarian cancer mortality among long-term users of estrogen replacement therapy (ERT), but did not include exposure information after 1982.⁹ Although use of combined estrogen-progestin replacement therapy (EPRT) has increased recently,¹⁰ epidemiological data on EPRT and ovarian cancer are limited^{8,11,12}; most studies have assessed HRT use without distinguishing between ERT and EPRT. To explore the potential association between ERT and EPRT and ovarian cancer, we analyzed data from

See also p 368 and Patient Page.

Context The association between menopausal hormone replacement therapy and ovarian cancer is unclear.

Objective To determine whether hormone replacement therapy using estrogen only, estrogen-progestin only, or both estrogen only and estrogen-progestin increases ovarian cancer risk.

Design A 1979-1998 cohort study of former participants in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program.

Setting Twenty-nine US clinical centers.

Participants A total of 44 241 postmenopausal women (mean age at start of follow-up, 56.6 years).

Main Outcome Measure Incident ovarian cancer.

Results We identified 329 women who developed ovarian cancer during follow-up. In time-dependent analyses adjusted for age, menopause type, and oral contraceptive use, ever use of estrogen only was significantly associated with ovarian cancer (rate ratio [RR], 1.6; 95% confidence interval [CI], 1.2-2.0). Increasing duration of estrogen-only use was significantly associated with ovarian cancer: RRs for 10 to 19 years and 20 or more years were 1.8 (95% CI, 1.1-3.0) and 3.2 (95% CI, 1.7-5.7), respectively (*P* value for trend <.001), and we observed a 7% (95% CI, 2%-13%) increase in RR per year of use. We observed significantly elevated RRs with increasing duration of estrogen-only use across all strata of other ovarian cancer risk factors, including women with hysterectomy. The RR for estrogen-progestin use after prior estrogen-only use was 1.5 (95% CI, 0.91-2.4), but the RR for estrogen-progestin-only use was 1.1 (95% CI, 0.64-1.7). The RRs for less than 2 years and 2 or more years of estrogen-progestin-only use were 1.6 (95% CI, 0.78-3.3) and 0.80 (95% CI, 0.35-1.8), respectively, and there was no evidence of a duration response (*P* value for trend=.30).

Conclusion Women who used estrogen-only replacement therapy, particularly for 10 or more years, were at significantly increased risk of ovarian cancer in this study. Women who used short-term estrogen-progestin-only replacement therapy were not at increased risk, but risk associated with short-term and longer-term estrogen-progestin replacement therapy warrants further investigation.

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the Breast Cancer Detection Demonstration Project (BCDDP) follow-up study, a large prospective cohort. Multiple data collections between 1979 and 1998 included specific information on ERT and EPRT.

METHODS

Study participants were selected from the BCDDP, a mammography screening program conducted at 29 US screening centers between 1973 and 1980 by

the American Cancer Society and the National Cancer Institute.¹³ In 1979, the National Cancer Institute initiated a follow-up study of 64 182 of the original 283 222 participants: (1) all 4275

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women diagnosed as having breast cancer during the BCDDP; (2) all 25 114 women who underwent breast surgery during the BCDDP, but had no evidence of malignant disease; (3) all 9628 women who were recommended by the BCDDP for surgical consultation, but for whom neither biopsy nor aspiration was performed; and (4) 25 165 women sampled from participants who had neither surgery nor recommendation for surgical consultation during screening.¹⁴ An institutional review board at the National Cancer Institute approved the study. All participants provided informed consent.

The BCDDP follow-up study consisted of 4 phases. Phase 1 (1979-1986) involved a baseline telephone interview (completed by 61 431 women, or 96%) and up to 6 (usually 4) annual telephone follow-up interviews through 1986. Phases 2, 3, and 4 each used single, self-administered, mailed questionnaires between 1987 and 1989, 1993 and 1995, and 1995 and 1998, respectively. Respondents who were not known to be deceased at the end of the previous phase were sent each subsequent questionnaire. Nonrespondents to mailed questionnaires were interviewed by telephone, if possible.

Phase 1 interviews collected information on age at first use and duration of use of female hormones (excluding creams), but did not distinguish ERT from EPRT. The phase 2 questionnaire included use of menopausal hormones in the form of injections, creams, patches, or pills since the last interview. For pill use, this questionnaire queried menopausal ERT and EPRT, duration of ERT and EPRT, and number of days in the month progestins were used. Phases 3 and 4 updated these data for pill users and collected pill names and doses. Each phase included questions about current menopausal status, gynecologic surgeries (including hysterectomy, partial or complete unilateral or bilateral oophorectomy, and dates for each reported surgery) and other risk factors. Interviews during the screening phase (1973-1980) collected demographic data (eg, education level and ethnicity) and

measured height and weight, which were updated during phase 2.

Analytic Data Set

We excluded 12 581 women who reported a bilateral oophorectomy, 4 women who died, 30 women diagnosed as having ovarian cancer, and 4086 women diagnosed as having breast cancer before the start of follow-up. We limited analysis to the remaining women who were menopausal before the start of follow-up or who became menopausal during follow-up. We defined menopause as no menstrual period for at least 3 months or as a result of hysterectomy with at least 1 ovary retained. Women who stopped menstruating because of hysterectomy, but who retained at least 1 ovary or whose ovarian status was uncertain were considered to have reached menopause at age 57 years (the 75th percentile for age at menopause in the study population) or their age at hysterectomy, whichever was later. They maintained an unknown value for analysis of age at menopause. We excluded 483 women whose menopausal status remained unknown throughout the follow-up study. Analysis therefore included 44 247 participants who completed a phase 1 interview. The numbers who subsequently completed phase 2, 3, and 4 questionnaires were 37 657 (85%), 32 891 (74%), and 31 354 (71%), respectively. Death (998; 2%), refusal (1609; 4%), and illness or inability to contact before the end of the questionnaire period (3977; 9%) accounted for missing phase 2 questionnaires. Respective numbers and proportions for missing phase 3 and phase 4 questionnaires were 3572 (8%), 1263 (3%), and 6515 (15%); and 5462 (12%), 1974 (4%), and 5451 (12%).

Case Ascertainment

Lifetime history of ovarian cancer was first ascertained in phase 2. Phases 3 and 4 ascertained ovarian cancer diagnoses since the previous interview. We verified reported ovarian cancer diagnoses through medical record review. Trained personnel completed standardized abstract forms when records were re-

trieved, and 2 of the authors (J.V.L. Jr and M.E.S.) reviewed those original records for this analysis. We linked the cohort to state cancer registries to identify additional cancer diagnoses and to the National Death Index to identify deaths during follow-up (with death certificate retrieval for study deaths). A total of 44 139 women (72% of the 61 431 women who completed a baseline interview; 85% of the women who completed a phase 2 questionnaire) were linked against state cancer registries.

The final analytic cohort included 329 women who developed ovarian cancer identified from medical records (n=118), registry data (n=79), death certificates (n=114), and self-report (n=18). Medical records were not available for those 18 because they were not received by the end of the study period, nonresponse of physicians or hospitals, or participants did not grant permission for record retrieval. We further classified tumors according to histological data from records or cancer registries: 65 serous, 40 endometrioid, 13 mucinous, 8 clear cell, 71 other unclassified, and 132 unavailable (for cancers identified via death certificates or because medical records were not available). Fifty-seven additional women reported ovarian cancer, but medical record review revealed another primary tumor (n=43), metastatic tumors (n=2), benign lesions or tumors of low malignant potential (n=6), or nonepithelial cancer (n=6). We excluded the 6 women who developed nonepithelial cancer during follow-up. We defined diagnosis date hierarchically from medical records, state cancer registry data, or self-report. When only death certificate information was available, we used time since cancer onset to estimate diagnosis date or used the date of death.

Analysis

Follow-up began at the baseline interview date or menopause date, whichever was later. Person-years accrued until the earliest of the following dates: ovarian cancer diagnosis, bilateral (or second) oophorectomy, death from any cause, phase 4 questionnaire comple-

tion, or end of study date. For women without a phase 4 questionnaire, but with whom we had some contact (eg, telephone or notice of refusal) during phase 4, the end of study date was that contact date. We assumed all other women without a phase 4 questionnaire whom we could not contact and whom our National Death Index search did not identify as deceased were still alive. We assigned their study end date by calculating the mean intervals between questionnaire completion dates for phases 2 through 4 (for all women who completed those questionnaires)

and adding those mean intervals to the date of last completed questionnaire for these nonrespondents. To avoid biased end point ascertainment among these participants, deaths from National Death Index and cancer diagnoses from state cancer registries were included only if they occurred before the study end date.

Poisson regression modeled the rate of developing ovarian cancer during follow-up and generated rate ratios (RRs) with 95% confidence intervals (CIs) for categorized variables using standard likelihood ratio methods.¹⁵ Likelihood-based methods produced CIs for the lin-

ear excess RR model.¹⁶ We assessed statistical significance of trends via score tests.

We based the time-dependent HRT variables on the reported ages at which exposure occurred. To calculate person-years for each woman, we updated time-dependent HRT and age covariates at 1-year intervals, but we used 5-year intervals for attained age in Poisson models. Women who had more than 1 exposure type during follow-up could contribute person-time to multiple exposure categories during follow-up. When exposure status or duration be-

Table 1. Prevalence of HRT Use by Selected Factors*

Factor	% of Person-Years†						Total Person-Years‡
	None	ERT Only	EPRT Following ERT	EPRT Only	ERT, Unknown Use of Progestins	Unknown HRT	
Attained age, y							
<55	65	24	1	2	1	6	22 437
55-59	56	25	3	7	3	6	67 667
60-64	48	27	6	11	4	5	123 359
65-69	43	31	7	9	5	5	128 771
70-74	41	34	7	7	7	5	104 005
75-79	40	35	7	5	8	5	70 405
≥80	46	32	4	2	10	6	72 566
Menopausal type							
Natural	52	19	6	9	8	5	408 625
Surgical§	30	57	6	3	0	4	170 464
Unknown	55	30	6	5	0	4	10 123
Age at menopause, y							
<45	35	49	5	4	2	5	168 809
45-49	49	28	6	7	6	5	172 312
50-53	52	20	6	9	7	6	181 859
≥54	43	19	10	15	7	5	10 433
Unknown	52	19	6	11	7	5	55 799
Oral contraceptive use							
None	48	31	5	5	6	4	429 785
≤2 y	39	30	8	11	5	6	74 234
>2 y	40	26	9	12	5	8	85 193
Body mass index, kg/m ²							
≤21.4	43	30	8	10	6	5	157 696
21.5-23.4	43	32	7	8	6	5	150 056
23.5-26.6	46	31	5	6	6	5	147 898
>26.6	53	29	3	4	5	6	133 563
BCDDP participant type							
Breast surgery; no malignant disease	45	32	6	7	5	5	246 385
Recommended for surgery	46	30	6	7	6	5	248 813
No surgery performed or recommended	49	28	6	7	6	5	94 015

*HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; EPRT, estrogen-progestin replacement therapy; and BCDDP, Breast Cancer Detection Demonstration Project.

†Percentages may not sum to 100 because of rounding.

‡Excludes 3884 person-years among women with progestin-only use and 402 person-years among women with "progestin, estrogen unknown" use.

§Hysterectomy with or without unilateral oophorectomy at menopause; see "Methods" section.

||Includes 1851 person-years among women with unknown oral contraceptive use.

came unknown, subsequent person-years were assigned to the “unknown” category. Use of HRT was calculated to 1 year prior to attained (or current) age to eliminate exposure that was most likely not causal. Because information on progestin use was not collected until the phase 2 questionnaire, progestin use was unknown for the 6586 participants who did not answer this interview (and for other participants who could not recall whether they had used progestin replacement therapy). For these women, exposed person-time and cancers among ERT users were included in the category ever use of ERT with unknown use of progestins if the woman reported a natural menopause; otherwise, they were included in the ERT-only category because women with a surgical menopause are less likely to use progestins.

We calculated body mass index (BMI) in kilograms per meters squared from measurements obtained during the screening visit closest in time to the baseline follow-up interview. To assess potential confounding by BMI, parity, and other suspected risk factors, we assessed associations between exposure and ovarian cancer and then evaluated parameter estimate changes in models before and after stratification by (ie, adjustment for) confounding variables. Fully adjusted models included stratification on age, menopause type (natural, surgical, or unknown), and duration of oral contraceptive use (none, ≤ 2 years, or > 2 years).

RESULTS

The 44241 women accrued 589213 person-years of follow-up, with a mean follow-up of 13.4 years (range, 1 month to 19.8 years). The mean age at the start of follow-up was 56.6 years (range, 36-89 years).

Risk Factors

Ovarian cancer was inversely associated with parity, oral contraceptive use, and hysterectomy, and not associated with age at menopause or BMI in our data. Family history of ovarian cancer was not collected until the phase 4 ques-

Table 2. Use of Hormone Replacement Therapy (HRT) and Ovarian Cancer*

	None	ERT Only	EPRT After ERT Only	EPRT Only
Person-years	270 520	179 065	34 619	42 400
No. of ovarian cancers	120	116	21	18
RR (95% CI)				
Age-adjusted	1.0 (Referent)	1.4 (1.1-1.8)	1.4 (0.85-2.2)	1.0 (0.61-1.6)
Multivariate-adjusted†	1.0 (Referent)	1.6 (1.2-2.0)	1.5 (0.91-2.4)	1.1 (0.64-1.7)

*EPRT indicates estrogen-progestin replacement therapy; ERT, estrogen replacement therapy; RR, rate ratio; and CI, confidence interval.

†Adjusted for attained age, menopause type (natural, surgical, or unknown), and duration of oral contraceptive use (none, ≤ 2 years, or > 2 years).

tionnaire and was therefore unavailable for 29% of the cohort (data not shown). One quarter of women who developed ovarian cancer reported breast or ovarian cancer in first-degree relatives.

Women who were older, had a surgical menopause, or had a younger age at menopause were more likely to use ERT. Women who had a natural menopause, an older age at menopause, oral contraceptive use for longer durations, or a lower BMI were more likely to use EPRT (TABLE 1). Person-years associated with HRT use did not differ by parity.

ERT Use

Compared with no HRT use, ever use of ERT only was significantly associated with ovarian cancer in models adjusted for attained age, menopause type, and oral contraceptive use (RR, 1.6; 95% CI, 1.2-2.0; TABLE 2). Use of ERT only with unknown use of progestins (32565 person-years and 40 ovarian cancers) was also significantly associated with ovarian cancer (RR, 2.6; 95% CI, 1.8-3.7). The person-year weighted mean durations of ERT use in these 2 categories were 6.2 and 4.4 years, respectively. The RR for unknown HRT use (30043 person-years and 14 ovarian cancers) was 1.1 (95% CI, 0.63-1.9).

The RRs increased with increasing duration of ERT-only use, and the RR for 20 or more years of use was 3.2 (95% CI, 1.7-5.7; TABLE 3). The RR increased by 0.07 (95% CI, 0.02-0.13) for each additional year of use. Risk estimates in Table 3 reflect ERT-only use, but models that included duration of ERT use with unknown use of progestins generated similar associations

(RR, 3.4; 95% CI, 2.0-5.7 for ≥ 20 years of use; $P = .001$ for trend).

Duration of ERT Use and Hysterectomy Status

Most women who reported long-term ERT use reported a prior hysterectomy (TABLE 4). Total person-years for less than 10 years of ERT-only use were equally distributed according to hysterectomy status, but almost all person-years and ovarian cancers for 10 or more years of ERT-only use were attributed to women with a hysterectomy. Among women with a hysterectomy, the RR was 2.0 (95% CI, 0.96-4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6-7.5) for 20 or more years of use ($P = .001$ for trend). The RR increased 0.08 per year of use (95% CI, 0.02-0.18). Among women without a hysterectomy, the RR was 1.4 (95% CI, 0.92-2.0) for ERT-only use for less than 4 years and 2.1 (95% CI, 1.3-3.5) for between 4 and 9 years. As expected, long-term ERT-only use was less frequent among women without a hysterectomy.

Duration of ERT Use and Tumor Histology

The associations with ERT did not appear to be restricted to particular histological subtypes of ovarian cancer.¹⁷ Ten or more years of ERT-only use was positively associated with serous tumors (6 ovarian cancers among long-term users; RR, 2.2 [95% CI, 0.78-6.1]), endometrioid tumors (7 ovarian cancers among long-term users; RR, 5.5 [95% CI, 1.9-16.2]), tumors with unavailable histology (16 ovarian cancers among long-term users; RR, 1.9

[95% CI, 0.98-3.5]), and other unclassified tumors (7 ovarian cancers among long-term users; RR, 1.6 [95% CI, 0.63-4.3]). Only 2 ovarian cancers with mucinous histology occurred in women who had ERT-only use.

Time Since Last ERT Use

Compared with never use, the RR for recent ERT-only use (ie, current use or last use <2 years ago) was 2.0 (95% CI, 1.4-3.0). For last ERT-only use, the RR was 0.64 (95% CI, 0.24-1.7) for between 2 and 4 years ago; 1.5 (95% CI, 0.88-2.5) for between 5 and 9 years ago; 1.1 (95% CI, 0.59-2.2) for between 10 and 14 years ago, and 1.3 (95% CI, 0.82-2.1) for 15 or more years ago. Similar associations emerged in analyses for current users vs all former users. Because long-term use and recent use are often correlated, we assessed duration in recent vs former users. The RR for between 10 and 19 years of ERT-only

use was 1.7 (95% CI, 0.78-3.5) among recent users and 1.8 (95% CI, 1.0-3.0) among former users. The RR for 20 or more years of use was 2.1 (95% CI, 1.2-3.8) among recent users and 1.7 (95% CI, 0.90-3.4) among former users.

EPRT Use

We classified EPRT use on the basis of prior ERT use (Table 2). Compared with no HRT use, the RR for ERT-only use followed by EPRT use was 1.5 (95% CI, 0.91-2.4). The RR for EPRT-only use was 1.1 (95% CI, 0.64-1.7). The person-year weighted mean durations of EPRT use in these 2 categories were 3.6 years and 3.5 years, respectively.

The person-year weighted average duration of ERT-only use before EPRT use was 5.7 years. Among women who used ERT only for less than 5 years (person-year weighted average=2.5 years) and then used EPRT, the RR associated with ever use of EPRT was 1.5 (95% CI,

0.70-3.3). Among women with ERT-only use for at least 5 years (person-year weighted average=11.2 years), the RR associated with ever use of EPRT was 1.9 (95% CI, 0.89-3.9).

The RR was 1.6 (95% CI, 0.78-3.3) for less than 2 years of EPRT-only use and 0.80 (95% CI, 0.35-1.8) for 2 or more years of EPRT-only use (TABLE 5). There was no evidence of a duration response (P=.30). The mean person-year-weighted duration was 5.6 years for EPRT-only use for 2 or more years. Three ovarian cancers occurred among women with EPRT-only use for 4 or more years (RR, 0.64 [95% CI, 0.20-2.0]).

We observed no association with duration of EPRT use when we combined women with EPRT-only use and women with EPRT use after less than 5 years of ERT-only use. For EPRT use, the RR was 1.3 (95% CI, 0.65-2.5) for less than 2 years, 1.3 (95% CI, 0.51-

Table 3. Duration of ERT-Only Use*

	None	Duration of ERT-Only Use, y†				P Value for Trend	Increase in RR (95% CI) per Year of Use
		<4	4-9	10-19	≥20		
Person-years	270 520	93 804	40 451	30 058	11 567		
No. of ovarian cancers	120	51	25	21	16		
RR (95% CI)							
Age-adjusted	1.0 (Referent)	1.2 (0.87-1.7)	1.4 (0.89-2.1)	1.5 (0.93-2.4)	2.5 (1.5-4.3)		
Multivariate-adjusted‡	1.0 (Referent)	1.3 (0.96-1.9)	1.6 (1.0-2.6)	1.8 (1.1-3.0)	3.2 (1.7-5.7)	<.001	0.07 (0.02 to 0.13)

*ERT indicates estrogen replacement therapy; RR, rate ratio; and CI, confidence interval.

†Duration of use was unknown for 3185 person-years and for 3 women who developed ovarian cancer.

‡Adjusted for attained age, menopause type (natural, surgical, or unknown), and duration of oral contraceptive use (none, ≤2 years, or >2 years).

Table 4. Duration of ERT-Only Use by Hysterectomy Status at Baseline*

	None	Duration of ERT-Only Use, y†				P Value for Trend	Increase in RR (95% CI) per Year of Use
		<4	4-9	10-19	≥20		
No Hysterectomy							
Person-years	213 869	50 884	17 280	7 798	1305		
No. of ovarian cancers	99	33	17	4	1		
Mean duration‡	0	1.4	6.1	13.1	24.0		
RR (95% CI)§	1.0 (Referent)	1.4 (0.92 to 2.0)	2.1 (1.3 to 3.5)	0.99 (0.36 to 2.7)	1.2 (0.17 to 8.7)	.26	0.04 (-0.02 to 0.13)
Hysterectomy 							
Person-years	51 045	41 292	22 535	21 800	10 068		
No. of ovarian cancers	14	15	7	15	14		
Mean duration‡	0	1.5	6.5	14.1	25.4		
RR (95% CI)§	1.0 (Referent)	1.2 (0.59 to 2.6)	1.0 (0.40 to 2.5)	2.0 (0.96 to 4.3)	3.4 (1.6 to 7.5)	.001	0.08 (0.02 to 0.18)

*ERT indicates estrogen replacement therapy; RR, rate ratio; and CI, confidence interval.

†Duration of use was unknown for 3185 person-years and for 3 women who developed ovarian cancer.

‡Mean person-year weighted duration of ERT-only use.

§Adjusted for attained age and duration of oral contraceptive use (none, ≤2 years, or >2 years).

||Includes simple hysterectomy and hysterectomy with unilateral oophorectomy. Does not include women whose hysterectomy status was unknown (8526 person-years and 14 ovarian cancers).

3.1) for between 2 and 3 years, and 1.0 (95% CI, 0.51-2.4) for 4 or more years.

Almost all women with EPRT use, regardless of prior ERT use, had a natural menopause. Among women with a natural menopause, the RR for ERT-only use for less than 5 years followed by EPRT use was 1.4 (95% CI, 0.55-3.4). The RR for ERT-only use for at least 5 years followed by EPRT use was 2.0 (95% CI, 0.81-5.0).

Too few women recalled the number of days each month they used progestins to compare sequential vs continuous combined EPRT regimens (data not shown). The RR for recent EPRT-only use was 0.62 (95% CI, 0.27-1.4) and 2.8 (95% CI, 1.4-5.7) for former EPRT-only use. Too few women used EPRT to assess associations by duration and time since last use.

Other Results

Excluding women who reported any use of menopausal hormone injections, patches, or creams (n=5830; including 34 women who developed ovarian cancer) did not affect the associations with ERT-only use (RR, 2.6 [95% CI, 1.3-5.2] for ≥ 20 years of use; an increase in RR of 0.06 [95% CI, 0.02-0.13] per year of use) or EPRT-only use (RR, 0.81 [95% CI, 0.33-2.0] for ≥ 4 years of use).

Almost all HRT users who provided pill names and doses, which were queried only after 1992, reported use of conjugated equine estrogens at 0.625 mg or medroxyprogesterone acetate at doses of 2.5 mg, 5.0 mg, or 10.0 mg. Missing or unknown pill names and doses for approximately two thirds of HRT users precluded further analyses of specific preparations or doses.

The RRs for HRT were similar after further stratification by parity or BMI. Similar associations for duration of ERT emerged after excluding women whose age at menopause was unknown or assigned to 57 years, women whose menopause type was unknown, women whose ovarian cancer was based on self-report only, or women whose cancers were identified via death certificates only. We found identical results after restrict-

Table 5. Duration of EPRT-Only Use and Ovarian Cancer*

	None	Duration of EPRT-Only Use, yr	
		<2	≥ 2
Person-years	270 520	12 809	19 521
No. of ovarian cancers	120	8	6
RR (95% CI)			
Age-adjusted	1.0 (Referent)	1.5 (0.71-3.0)	0.71 (0.31-1.6)
Multivariate-adjusted†	1.0 (Referent)	1.6 (0.78-3.3)	0.80 (0.35-1.8)

*EPRT indicates estrogen-progestin replacement therapy; RR, rate ratio; and CI, confidence interval.

† $P=.30$ for trend. Duration of EPRT-only use was unknown for 10 070 person-years and for 4 women who developed ovarian cancer.

‡Adjusted for attained age, menopause type (natural, surgical, or unknown), and duration of oral contraceptive use (none, ≤ 2 years, or > 2 years).

ing the analyses based on method of case ascertainment (medical records, registry data, death certificates, and self-report) and after considering only HRT exposures that occurred 2 or more years before attained age. Including the participants diagnosed as having breast cancer before follow-up did not change the results.

COMMENT

We observed significant associations between ERT use and incident ovarian cancer in this prospective study of 44 241 postmenopausal US women who provided multiple exposure assessments over approximately 20 years. In time-dependent analyses that adjusted for other ovarian cancer risk factors and included relatively large numbers of long-term ERT users, risk increased significantly and consistently with increasing duration of use.

Cohort⁷ and case-control^{2,12,17-26} studies have reported positive associations with ERT use, although numerous inverse²⁷⁻³⁰ and null^{1,8,31-34} associations have been published. One meta-analysis of 15 studies concluded ERT does not increase risk,⁵ but another meta-analysis of 9 studies reported statistically significant summary odds ratios (ORs) for ever use of ERT (OR, 1.15; 95% CI, 1.05-1.27) and more than 10 years of ERT use (OR, 1.27; 95% CI, 1.00-1.61).⁴ A recent prospective study of 944 fatal ovarian cancers among 211 581 postmenopausal women who reported ERT exposure through 1982 and were followed-up for 14 years identified 2-fold increased risks associated with 10 or more

years of ERT use.⁹ That study, which excluded women who reported a hysterectomy before baseline, and another recent report,¹² concluded that long-term ERT use increased ovarian cancer risk for women without hysterectomy. Our results showed an increased risk among ERT users without hysterectomy, but also revealed increased risks for long-term ERT use in women who had received a hysterectomy.

Use of EPRT only was not associated with ovarian cancer in our data, but our results were based on only 18 women with EPRT-only use who developed ovarian cancer. Although our analysis captured HRT use through 1998, few women developed ovarian cancer after EPRT-only use for more than 4 years. Whether longer durations of EPRT use are associated with ovarian cancer remains unclear.

Women with ERT-only use had nearly identical increases in risk and similar average durations of ERT use compared with women with EPRT use after prior ERT-only use. If ERT-only use increases ovarian cancer risk and that risk remains elevated for many years,⁹ then the prior ERT-only use could account for the increased risk among women with EPRT use after using ERT. Additional studies will need to clarify subsequent cancer risk among women who used more than 1 type of HRT.

Two case-control studies reported that risk associated with ERT exceeded risk associated with EPRT, and a record linkage study from Sweden observed no association between ovarian cancer incidence and EPRT.⁸ Our results resemble

the OR of 1.06 (95% CI, 1.01-1.10) for each year of ERT use and 1.02 (95% CI, 0.91-1.13) for each year of EPRT use from 1 US study of 327 nonmucinous cases and 564 controls.¹⁷ A Swedish study of 655 cases and 3899 controls reported an elevated OR of 1.4 (95% CI, 1.0-2.0) for ever use of ERT, 1.5 (95% CI, 1.2-2.1) for EPRT with sequential progestins, and an OR of 1.0 (95% CI, 0.73-1.4) for EPRT with continuous progestins.¹² Whether the progestin regimen explains the lack of increased risk among women with EPRT-only use or influences the increased risk among women who used EPRT after ERT-only use in our study is not clear. More data are required to elucidate the specific contributions to ovarian cancer risk of ERT duration, EPRT duration, and EPRT regimen.

In our study, adjustment for hysterectomy and oral contraceptive use had minimal effect on ever-use risk estimates, but consistently increased duration risk estimates. Incomplete control for hysterectomy, oral contraceptive use, and other risk factors may account for null or inverse associations in other studies. One meta-analysis³ reported a summary OR for ever use of ERT of 1.1 (95% CI, 0.9-1.3) from 15 heterogeneous studies and a significant OR of 1.3 (95% CI, 1.0-1.6) from 4 similarly designed US studies,^{17,24-26} which used population-based controls and adjusted for hysterectomy and other risk factors. A pooled analysis³ showed no association with ever use (pooled OR, 1.0; 95% CI, 0.9-1.2) in 5 studies,^{1,27,30,35} which were unadjusted for hysterectomy, but a significant positive association (pooled OR, 1.3; 95% CI 1.1-1.5) in 4 studies^{2,17,22,36} that included adjustment. Those 4 studies also reported positive, but not significant, associations with increasing ERT duration. Similar reanalysis² of 4 European studies^{19-21,23} generated a statistically significant OR for ever use; control for confounders increased the OR in that reanalysis.

Declining ERT use in the late 1970s³ reduced the number of potential long-term users and may have prevented earlier studies from detecting an asso-

ciation with ovarian cancer, which develops over many years. A pooled analysis of 6 case-control studies that used population controls reported elevated, but nonsignificant ORs for 10 or more years of ERT use based on 35 exposed cases and 66 exposed controls.¹ Three other case-control studies included small numbers of long-term ERT users.^{17,30,31} Compared with results published after 7 years,³⁶ follow-up for 14 years doubled the number of ovarian cancer deaths and produced stronger associations with ERT in the prospective mortality study.⁹ We also observed stronger associations with long-term ERT use after almost 20 years of follow-up than in analyses censored in 1986 (phase 1), 1989 (phase 2), or 1995 (phase 3; data not shown). Although earlier studies seemed to indicate that there was no association with ERT, this recent emergence of an increased risk in long-term users should remind investigators that it is premature to conclude that EPRT has no association with ovarian cancer until other large studies specifically assess ovarian cancer risk among persons with short-term or long-term EPRT use.

In addition to the inconsistent epidemiological data, lack of functional steroid receptors and demonstrable estrogen effects *in vitro*³⁷ raised questions about biologic plausibility of an association with ERT. Recent data, however, provide biologic support for a relationship. In a rabbit model, estrogen induced ovarian cancer cell-line growth³⁸ and directly stimulated the ovarian surface epithelium—the suspected pathological origin of most epithelial ovarian carcinomas.^{39,40} Normal ovarian surface epithelial cells also proliferated when stimulated by estrogen.⁴¹ Epithelial ovarian cancer cell lines expressed estrogen receptors,⁴² and recent work demonstrated estrogen-receptor α , estrogen-receptor β , and androgen-receptor expression in both normal and malignant ovarian epithelial cells.⁴³ Confirmation that progestins account for the reduced risk associated with oral contraceptive use and pregnancy³⁷ could provide a biologic basis for weak or null

associations with HRT formulations that include progestins.

Several analytic issues warrant mention. Adjustment for family history of breast cancer did not change our results, but we lacked data to fully address potential confounding by family history of ovarian cancer because information on this variable was collected only in the phase 4 questionnaire. Among women who completed that questionnaire, however, HRT associations did not change after adjustment for family history of ovarian cancer. Use of ERT that leads to adverse effects and hysterectomy could theoretically introduce a detection bias for ovarian cancers detected at hysterectomy. However, only 4 of the 23 women who developed ovarian cancer and reported a hysterectomy during follow-up had used ERT. Inaccurate reporting of hysterectomy could compromise the ability to adjust for confounding, but a subset of BCDDP participants reported gynecologic surgery with reasonable accuracy in a previous study.⁴⁴ Inclusion of women with unknown age at menopause can bias analyses of breast cancer and HRT.^{45,46} However, age at menopause was not associated with ovarian cancer in our data, and our results were identical after excluding participants whose age at menopause was unknown or assigned to 57 years.

The HRT preparations used today differ from the HRT used during this study's early years, but our repeated exposure assessment through 1998 ensured current and generalizable data on HRT. Much of the long-term ERT use likely included higher average daily doses of estrogen than what is currently recommended.⁴⁷ Our analysis could not determine whether duration, dose, or duration and dose explained the elevated risks among long-term ERT users. Whether long-term use of lower-dose ERT increases the risk of ovarian cancer is not known.

In this large prospective study, women who used ERT, particularly for 10 or more years, were at significantly increased risk of ovarian cancer. We observed an elevated risk of ovarian can-

cer among long-term ERT users with hysterectomy and among ERT users without hysterectomy who had switched to EPRT. Women with short-term EPRT-only use were not at increased risk in this study, but risk associated with EPRT remains unclear. Use of ERT and EPRT differentially affects both breast¹⁴ and endometrial⁴⁸ cancer risk and may do the same for ovarian cancer. Additional data on long-term ERT and EPRT use, with particular attention to duration, dose, and regimen, will be necessary to confirm these observations.

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