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Increased Ovarian Cancer Risk Associated with Menopausal Estrogen Therapy is Reduced by Adding a Progestin

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Abstract

Background—It has become increasingly clear that use of menopausal hormone therapy (HT) is associated with an increased risk of ovarian cancer, however, the effects by type of formulation and duration of use are less clear. A systematic review of the HT and ovarian cancer literature was conducted to identify population-based case-control studies, cohort studies, and randomized trials which examined effects by formulation of HT (estrogen-alone [ET] and estrogen plus progestin [EPT]) and duration of use.

Methods—Pub-Med (www.pubmed.gov) was used to identify relevant publications through December 2007; 14 studies were identified. We abstracted relative risks (RRs) and 95% confidence intervals (CIs) in relation to duration of HT use (ET and EPT separately). We used the risk estimates per year of HT use if they were provided, otherwise, we calculated a duration-response for a log-linear model of the duration of HT use against risk.

Results—Ovarian cancer risk was increased among ET users (RR per five years of use, RR_5=1.22, 95% CI 1.18–1.27, p<0.0001) and a lower, but still statistically significant, increased risk was seen with EPT use (RR_5=1.10, 95% CI 1.04–1.16, p=0.001). The increased risk in ET users was statistically significantly higher than the increased risk in EPT users (p=0.004).

Conclusions—ET use increases risk of ovarian cancer in a duration-dependent manner and it appears that the addition of progestins block this effect, at least to some extent. Whether the effect of estrogens would be completely blocked if progestins were given every day is unclear.

Keywords

Ovarian Cancer; Hormone Therapy; Meta-analysis; Systematic Review

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BACKGROUND

The beneficial role of exogenous hormones in the form of oral contraceptives (OCs) on ovarian cancer was first reported more than 25 years ago.[1, 2] OC use has been consistently found to be associated with an approximately 25% reduction in risk of ovarian cancer per five years of use. The mechanism through which OCs protect against ovarian cancer is unclear; hypotheses include blocking ovulation[3] and increasing exposure to progestins.[4] There is some suggestion that OCs containing high-dose progestins are associated with a greater reduction in risk than lower-dose progestin OCs.[5, 6]

Additional evidence that increased exposure to progestins may be associated with reduced risk of ovarian cancer includes the protective effect of pregnancy,[6–8] which is associated with high exposure to progesterone, and *in vitro* experiments which show that progesterone reduces proliferation of both benign and malignant ovarian tumor cells.[9] Lastly, in macaques, a progestin, given with or without estrogen, increased apoptosis of normal ovarian surface epithelium,[10] the epithelium considered by many investigators to be the tissue of origin of ovarian cancers.

The situation with the other major form of exogenous hormone use, namely, menopausal hormone therapy (HT) is less clear. In a recent overview, Greiser and colleagues found that menopausal estrogen (alone) therapy (ET) and menopausal estrogen progestin therapy (EPT) were associated with an increased risk of ovarian cancer; there was “a suggestion of greater risk with ET” but the difference was not statistically significant.[11] In the discussion of their ET results, the authors remarked that the ET results differed by whether or not the studies were population based and that many more studies of EPT were population based than studies of ET. They did not pursue this issue further, did not relate it to the comparison of the results for ET and EPT use, or give the results in a form for the reader to make such a comparison. The results of a detailed evaluation of any difference in risk between ET and EPT use is of major importance for our understanding of the hormonal etiology of ovarian cancer as well as for a proper evaluation of the comparative risks and benefits of ET and EPT use. A significant number of recent studies[12–15] of the effects of HT on ovarian cancer risk were not included in the Greiser et al. review. Approximately 30% of the data included in our meta-analysis was not part of their review.

We have undertaken a systematic review of the relationship between ET and EPT use and ovarian cancer risk, restricting ourselves to population-based studies (case-control and cohort studies, and randomized trials). Studies which used hospital controls were not included because heterogeneous groups served as control subjects in these studies and HT use may be related to the controls' health conditions and unrepresentative of the usage pattern of the underlying populations from which the cases arose. The results of the systematic review are presented herein.

METHODS

Identification of Studies

Pub-Med (www.pubmed.gov) was used to identify relevant population-based case-control studies, cohort studies, and randomized trials using the MeSH search terms “ovarian cancer” with “hormone replacement therapy”, “estrogen replacement therapy”, “estrogen progestin replacement therapy” and “estrogen progestin combination therapy” through December 2007. Identified publications were reviewed to ascertain additional articles. Also, the “related articles” link was used to identify potentially relevant articles. The search was limited to English-language publications. Studies which used hospital controls were not included for the reasons discussed above. A total of 25 publications from population-based case-control studies, cohort studies, and a randomized clinical trial were identified and reviewed.[6, 12–35] Publications which did not provide information on duration of use[16, 19, 27, 31, 33, 35] or by formulation (ET versus EPT)[18, 20, 21, 24, 29] were excluded.

A total of 14 studies provided information on duration by formulation (ET versus EPT) and were included in the meta-analysis: eight population-based case-control studies, five cohort studies, and one clinical trial. The population-based case-control studies included those conducted in Australia[28], Boston[34], Canada[32], Los Angeles[6], North Carolina[17], Sweden[25], western Washington[15], and eight SEER areas[30]. The cohort studies included the American Cancer Society Cancer Prevention Study II (CPS-II; a mortality study)[26], the Breast Cancer Detection Demonstration Project (BCDDP)[23], the NIH-AARP study (NIH-AARP)[14], the Million Women's Study (MWS)[12], and the Nurses' Health Study (NHS)[13]. The clinical trial is the Women's Health Initiative (WHI)[22]. Studies were included if they were restricted to invasive epithelial ovarian cancers or if they combined invasive and borderline epithelial ovarian cancers in their analysis. Three studies[26, 30, 34] included in the meta-analysis were conducted at a time when sequential EPT (sEPT) was beginning to be used (early 1980s), and they did not distinguish between ET and EPT use. These studies were included in the ET only analysis because it is estimated that only ~5% of HT at that time included a progestin component[36] making it unlikely that EPT accounted for an appreciable proportion of HT use in these studies. Each of the 14 studies evaluated potential confounders and adjusted as appropriate in their data analysis.

Statistical Analysis

From the 14 studies included in the meta-analysis, we abstracted relative risks (RRs) and 95% confidence intervals (CIs) in relation to duration of HT use (ET and EPT separately). We used the risk estimates for per year of HT use if they were provided in the paper. Otherwise, we calculated a duration-response for a log-linear model of the duration of HT use against the estimated risk using the method of Greenland and Longnecker.[37] When duration was reported as a range, the midpoint of the range was used; when duration was reported as greater than a certain number of years, we added to this lower bound half the number of years of the immediately shorter duration category. Five studies[14, 17, 25, 28, 34] included a duration category of ≤ 1 year of use. We have combined use of ≤ 1 year duration with never users in our calculations for these five studies because it is most unlikely that such short duration use could increase or decrease risk to an appreciable extent and the

recording of such short duration of use is subject to the possibility of differential recall of cases and controls.

Fixed and random effects models were fitted using STATA (Version 9, StataCorp, College Station, Texas) for ET and EPT use separately. The effect estimates were the same for both the ET and EPT analyses and the statistical significance differed only slightly between the two models; the fixed effects model results are presented here. All statistical significance levels (p values) quoted are two-sided. All RRs are expressed per five years of HT use, RR_5. We also formally tested the difference in effect estimates between ET and EPT use by comparing the estimates within each of the 10 studies which provided information across both of these formulations and combining the results in a formal weighted analysis.

Potential publication bias in this meta-analysis was assessed by measuring `funnel plot' asymmetry.[38] In this method, the log of the odds ratio divided by its standard error (standard normal deviate) for each individual study is regressed against the inverse of its standard error (precision). If the 90% confidence interval for the intercept includes zero this is generally considered as evidence that there is little or no publication bias. We also present the funnel plot where the RR_5 on a log scale is plotted against the precision of $\log(RR_5)$.

RESULTS

Table 1 shows the characteristics of each of the 14 studies included in this meta-analysis as well as the associated RRs per five years of ET and EPT, RR_5, use associated with ovarian cancer risk.

ET Use

Thirteen of the 14 studies provided data on ET use with regard to duration. Figure 1 is a forest plot of the logarithm of the RR_5 by study and overall. The overall estimate of RR_5 was 1.22 (95% CI 1.18–1.27, $p<0.0001$). There was no evidence of heterogeneity of effect across the studies (p=0.91). There was no evidence of publication bias as assessed by asymmetry of the funnel plot (intercept= 0.53, 90% CI= −0.18 – 1.24, p= 0.21; Figure 3). Table 2 shows the RRs by duration categories from the original papers for studies which presented their data in this format. Seven of the 13 studies included in the ET analysis did not provide information by type of menopause. The study from Rodriguez and colleagues[26] was restricted to women with a natural menopause. Of the remaining five studies, three studies[6, 14, 28] found a bigger effect of natural menopause, one study[23] found a smaller effect and one reported the results as similar[13]. There is thus no evidence that the bigger effect of ET is due to the greater proportion of ET use in hysterectomized women.

EPT Use

EPT duration data were available from 11 of the 14 studies. Overall a 10% increased risk of ovarian cancer per five years of EPT use was observed (RR_5=1.10, 95% CI 1.04–1.16, p=0.001; Figure 2). Heterogeneity of effect was not observed (p=0.24). There was no evidence of publication bias based on asymmetry in the funnel plot analysis (intercept= 0.48, 90% CI −0.57 – 1.53, p= 0.42; Figure 3). The RRs by duration categories as presented in the

original publications are shown in Table 3 for the studies which presented their data in this format.

Comparison of ET and EPT Use

The effect estimate for ET use per five years of use was 1.22 compared to 1.10 for EPT. The same difference was observed when restricting the data to the 10 studies[6, 12–15, 17, 23, 25, 28] which provided results for both formulations (Table 1); this difference was statistically highly significantly (p=0.004). This difference was not influenced by longer duration of use of ET compared to EPT. Analysis of differences in effect in the five studies[12, 14, 15, 17, 28] which presented their original data for ET and EPT in the same duration categories found the same difference (p=0.011; see Tables 2 and 3 for original data).

CONCLUSION

This meta-analysis provides highly statistically significant evidence of an increased risk of ovarian cancer associated with ET use; the overall estimate is that risk increases 22% (95% CI 18%–27%) per five years of use. There is a clear duration-response relationship between ET use and ovarian cancer risk (Table 2). Twelve of the 13 studies showed increased risk; the Purdie et al.[28] study showed a 1% decreased risk, but the study was small and the associated confidence limits were wide (Figure 1).

Use of EPT was associated with a statistically significant 10% increase in risk of ovarian cancer per five years of use (95% CI 4%–16%; Figure 2). This increase is statistically significantly less than the increase with ET use (overall effect of within study differences, p=0.004) providing strong evidence that the progestin component ameliorates the effect of the estrogen. This result can not be explained by longer duration of ET use compared to EPT use. This is the key conclusion that can be drawn from this more comprehensive analysis than was undertaken by Greiser and colleagues.[11]

There are two aspects of the risk from EPT exposure that need further consideration: the number of days per 28 day treatment cycle the progestin is taken and the daily dose of the progestin. Four[12, 14, 15, 25] of the 11 studies included in the meta-analysis for EPT provide some information on this. The MWS[12] found comparable increased risks with ever use of sequential EPT (sEPT) and ever use of continuous-combined EPT (ccEPT); duration of use of sEPT and ccEPT were not presented in the report. Rossing and colleagues[15] found a reduction in risk for ever use of sEPT and ccEPT, but duration data was only provided for ccEPT. Data from the NIH-AARP study[14] suggest that sEPT was associated with a higher risk of ovarian cancer (RR_5=1.84, 95% CI 1.14–2.97) than was ccEPT (RR_5=1.40, 95% CI 0.90–2.18), but both were associated with increased risk. These studies (MWS, NIH-AARP, and Rossing) were conducted in either the U.K. or U.S., where we previously noted that the daily dose of progestin (on the days it is taken) is less with ccEPT (2.5 mg/d medroxyprogesterone acetate, MPA) than with sEPT (10 mg/d MPA), rendering the total dose per 28 day cycle higher with sEPT (100 mg versus 70 mg).[39] In contrast, the daily dose of progestin tended to be the same in ccEPT and sEPT regimens in Sweden (1 mg/d of norethisterone acetate, NETA; equivalent to ~10 mg/d of MPA[40]).[39] In the single study from Sweden[25] an increased risk of ovarian cancer was associated with use of sEPT

(RR_5=1.29, 95% CI 1.01–1.66), but no increased risk was associated with use of ccEPT (RR_5=1.02, 95% CI 0.70–1.47). This Swedish study result suggests that 1 mg/d of NETA given every day may completely block the effect of the estrogen.

We made several decisions in carrying out the meta-analysis that may affect the results. First, we included studies conducted in the late 1970s/early 1980s[26, 30, 34] that did not distinguish ET from EPT in the ET alone analysis, assuming that only a very small proportion of HT users at this time would be taking EPT (estimated to be approximately 5%[36]). The results from these three studies are consistent with the others in the meta-analysis and any bias would result in an attenuation of the effect of ET we observed given that EPT has less effect on risk than ET. Second, while some of the studies included in the meta-analysis consist of both invasive and borderline tumors[12, 13, 17, 34] and others did not specify whether borderline tumors were included[14, 28, 30], we included all studies. The results for the studies restricted to invasive tumors are very close to those which included invasive and borderline cases and the proportion of borderline cases in any study which included both would be relatively small (~20%). One of the 14 studies included in the meta-analysis provided association information by invasive[25] versus borderline[41] tumor type and in this study the risk associated with HT for borderline tumors was larger, but not statistically significantly so and the confidence intervals were wide.

There are several additional questions that could not be addressed by this meta-analysis: the association between HT use and risk of ovarian cancer may vary by histological sub-type, the effect of HT may differ between current and past use, and the association by stage of disease is not clear. Each of these questions warrants further study.

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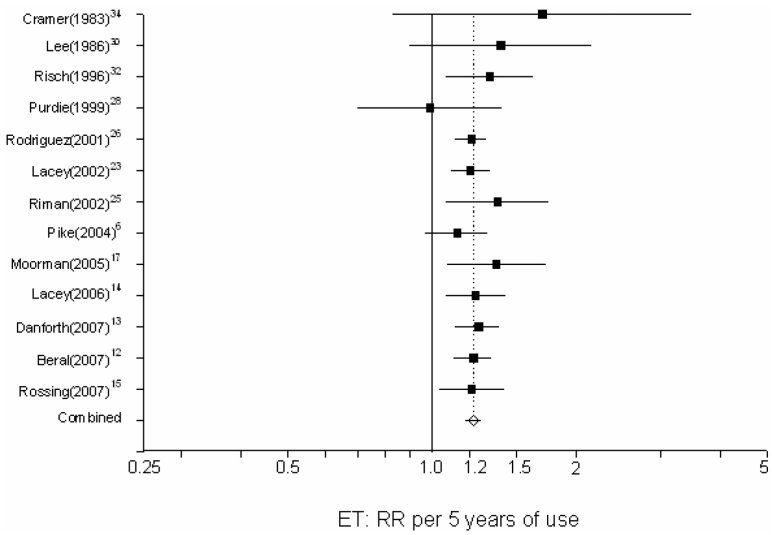

Figure 1.

Forest plot of the study-specific (boxes) and summary (diamond) relative risk and 95% confidence intervals (lines) for ovarian cancer risk per five years of estrogen therapy use. The overall summary ovarian cancer risk per five years of estrogen therapy use is 1.22 (95% CI 1.18–1.27, $p<0.0001$). First author for each study is given on the vertical axis, together with the study reference number.

ET – estrogen-alone therapy.

RR – relative risk

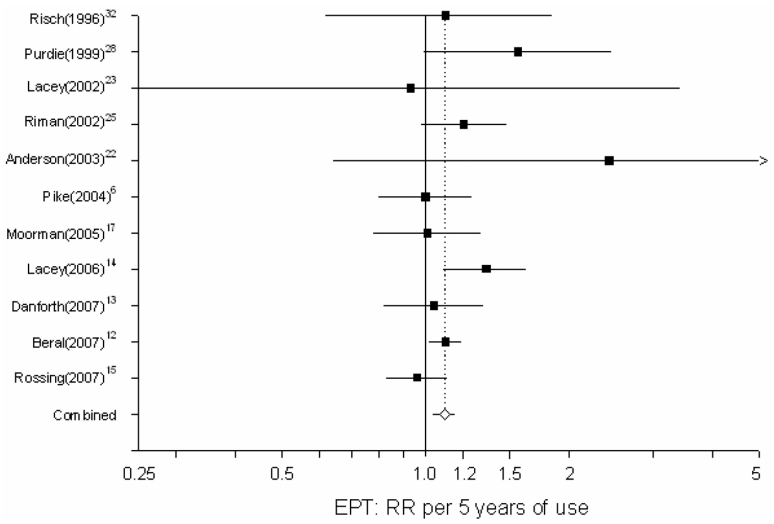

Figure 2.

Forest plot of the study-specific (boxes) and summary (diamond) relative risk and 95% confidence intervals (lines) for ovarian cancer risk per five years of estrogen plus progestin therapy use. The overall summary ovarian cancer risk per five years of estrogen plus progestin therapy use is 1.10 (95% CI 1.04–1.16, p=0.001). First author for each study is given on the vertical axis, together with the study reference number.

EPT – estrogen plus progestin therapy

RR – relative risk

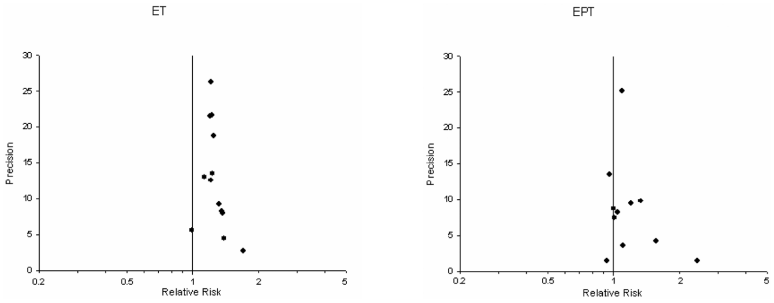

Figure 3.

Funnel plot analysis to evaluate publication bias where the data points represent each study. The vertical axis is the precision (inverse of the standard error) of the log (RR_5) and the horizontal axis is the relative risk per five year of use, (RR_5), plotted on a log scale. In the absence of publication bias, the small, less precise studies will have odds ratios that show more scatter, but are still consistent with the larger, more precise studies. There was neither evidence of publication bias for ET (intercept= 0.53, 90% CI −0.18 – 1.24, p= 0.21) nor for EPT (intercept= 0.48, 90% CI −0.57 – 1.53, p= 0.42).

EPT – estrogen plus progestin therapy

ET – estrogen-alone therapy

Table 1

Description of population-based case-control studies, cohort studies, and the clinical trial used in the meta-analysis.

First Author (year of publication)	Study Type (Cohort name)	Location	Years Conducted	Control Source	Case Ascertainment	Formulation Information	Tumor Behavior Type	Data Collection Method	n Cases/n Controls ET Analysis	RR (95% CI) per 5 years of use of ET	n Cases/n Controls EPT Analysis	RR (95% CI) per 5 years of EPT use
Cramer (1983)[34]	Case-Control	Boston, Massachusetts	1978–1981	Population registry	Greater Boston	ET	Invasive and LMP	In-person interview	172/173	1.70 (0.83–3.48)	nd	nd
Lee (1986)30	Case-Control	US multicenter	1980–1983	Random digit dialing	8 SEER sites	ET	Not given	In-person interview	160/1210	1.39 (0.90–2.15)	nd	nd
Risch (1996)[32]	Case-Control	Canada	1989–1992	Population registry	Cancer registry	ET and EPT	Invasive only	In-person interview	np***	1.39 (0.90–2.15)	np***	1.10 (0.62–1.84)
Purdie (1999)[28]	Case-Control	Australia	1990–1993	Electoral role	Major gynecological treatment centers	ET and EPT	Not given	In-person interview	732/784	0.99 (0.70–1.40)	703/749	1.56 (0.99–2.46)
Rodriguez (2001)[26]	Cohort (CPS-II)	US-wide	1982–1989	CPS-II	National Death Index linkage	ET	Invasive only	Self-administered questionnaire	944/211581**	1.21 (1.12–1.30)	nd	nd
Lacey (2002)[23]	Cohort (BCDDP)	US multicenter	1979–1998	BCDDP	Self-report, cancer registry linkage, death certificates followed by chart review	ET and EPT	Invasive only	Self-administered questionnaire and telephone	233/44241**	1.20 (1.10–1.32)	134/44241**	0.93 (0.25–3.41)
Riman (2002)[25]	Case-Control	Sweden	1993–1995	Population registry	Cancer registry	ET and EPT	Invasive only	Self-administered questionnaire	636/3771	1.37 (1.07–1.75)	632/3746	1.20 (0.98–1.48)
Anderson (2003)[22]	Clinical Trial (WHI)	US multicenter	1993–1998	WHI	Self-report followed by chart review	EPT	Invasive only	Randomized clinical trial	nd	nd	30/16608**	2.42 (0.64–9.12)
Pike (2004)[6]	Case-Control	Los Angeles, California	1992–1998	Neighborhood	Cancer registry	ET and EPT	Invasive only	In-person interview	332/369	1.13 (0.97–1.31)	332/369	1.00 (0.80–1.25)
Moorman (2005)[17]	Case-Control	North Carolina	1999–2003	Random digit dialing	Cancer registry	ET and EPT	Invasive and LMP	In-person interview	226/225	1.36 (1.08–1.73)	195/232	1.01 (0.78–1.31)
Lacey (2006)[14]	Cohort (NIH-AARP)	US multicenter	1995–2000	NIH-AARP	Cancer registry and National Death Index linkage	ET and EPT	Not given	Self-administered questionnaire	136/97638**	1.23 (1.07–1.43)	123/97638**	1.34 (1.09–1.63)
Danforth (2007)[13]	Cohort (NHS)	11 US states	1976–2002	NHS	Self-report, death certificates followed by chart review	ET and EPT	Invasive and LMP	Self-administered questionnaire	137/82905**	1.25 (1.12–1.38)	82/82905**	1.04 (0.82–1.32)
Beral (2007)[12]	Cohort (MWS)	UK	1996–2004	MWS	National Health Service Central Registers	ET and EPT	Invasive and LMP	Self-administered questionnaire	1378/948576**	1.22 (1.11–1.33)	1546/948576**	1.10 (1.02–1.19)
Rossing (2007)[15]	Case-Control	western Washington	2002–2005	Random digit dialing	Cancer registry	ET and EPT	Invasive	In-person interview	393/781	1.21 (1.04–1.42)	426/936	0.96 (0.83–1.11)
All Studies Combined										1.22 (1.18–1.27)		1.10 (1.04–1.16)

BCDDP - Breast Cancer Detection Demonstration Project

CI - confidence intervals

CPS-II - American Cancer Society Cancer Prevention Study II

EPT - estrogen plus progestin therapy

ET - estrogen-alone therapy

MWS - Million Women's Study

NHS - Nurses' Health Study

NIH-AARP – National Institutes of Health - American Association of Retired Persons

RR - relative risk

SEER - Surveillance Epidemiology and End Results

WHI - Women's Health Initiative

* nd - not done

** total cohort size

*** np - not provided

Table 2

Adjusted relative risks by duration of ET use categories for 10 of the 13 studies* included in the meta-analysis.

Author	Duration Categories**	Cases	Controls/Person Years	Adjusted RR	95% CI
Cramer (1983)[34]	0	145	153	1.0	
	2–5	9	10	1.01	0.41 – 2.47
	6+	9	4	2.83	0.87 – 9.26
Lee (1986)[30]	0	134	1007	1.0	
	<2	9	83	1.1	0.5 – 2.3
	2–5	8	63	1.3	0.6 – 2.8
	6+	9	57	1.7	0.8 – 3.6
Purdie (1999)[28]	0	663	707	1.0	
	1–3	27	26	1.13	0.85 – 1.50
	4+	22	28	0.92	0.67 – 1.25
Rodriguez (2001)[26]	0	689	2185876	1.0	
	<10	189	527202	1.11	0.94 – 1.30
	10+	66	98677	1.85	1.44 – 2.38
Lacey (2002)[23]	0	120	270520	1.0	
	1–3	51	93804	1.3	0.96 – 1.9
	4–9	25	40451	1.6	1.0 – 2.6
	10–19	21	30058	1.8	1.1 – 3.0
	20+	16	11567	3.2	1.7 – 5.7
Riman (2002)[25]	0	583	3531	1.0	
	1	5	34	1.07	0.40 – 2.88
	2–4	8	58	0.99	0.45 – 2.15
	5–9	11	38	1.8	0.86 – 3.75
	10+	12	36	2.14	1.03 – 4.46
Moorman (2005)[17]	0	129	152	1.0	
	1–4	23	24	1.2	0.6 – 2.3
	5–9	17	11	1.5	0.6 – 3.5
	10+	52	32	2.2	1.2 – 4.1
Lacey (2006)[14]	0	87	176376	1.0	
	<10	23	43458	1.15	0.72 – 1.82
	10+	26	27501	1.89	1.22 – 2.95
Beral (2007)[12]	0	1142	474700	1.0	
	1–4	40	20300	0.89	0.64 – 1.25
	5+	196	62500	1.53	1.27 – 1.84
Rossing (2007)[15]	0	299	614	1.0	
	1–4	25	67	0.8	0.5 – 1.4
	5–9	17	26	1.4	0.7 – 2.6
	10+	52	74	1.7	1.1 – 2.7

CI - confidence intervals

ET - estrogen-alone therapy

RR - relative risk

* three studies[6,13,32] presented per year of use estimates and are therefore not shown in this table.

** years of use

Table 3

Adjusted relative risks by duration of EPT use categories for six of the 11 studies* included in the meta-analysis.

Author	Duration Categories**	Cases	Controls	Adjusted RR	95% CI
Purdie (1999)[28]	0	663	707	1	
	1–3	16	14	1.36	0.92–2.00
	4+	15	14	1.33	0.88–2.00
Lacey (2002)[23]	0	120	270520	1	
	<2	8	12809	1.6	0.78–3.3
	2+	6	19521	0.8	0.35–1.8
Moorman (2005)[17]	0	129	152	1.0	
	1–4	29	31	1.0	0.6–1.9
	5–9	14	14	1.1	0.5–2.6
	10+	20	28	1.0	0.5–2.0
Lacey (2006)[14]	0	73	150413	1	
	2–4	11	22625	1.24	0.65–2.39
	5–9	13	25647	1.30	0.71–2.39
	>=10	19	20472	2.15	1.28–3.62
Beral (2007)[12]	0	1142	474700	1	
	<5	141	58700	1.09	0.91–1.30
	5+	263	106100	1.17	1.02–1.34
Rossing (2007)[15]	0	299	614	1	
	1–4	39	131	0.6	0.4–0.8
	5–9	41	83	1.0	0.6–1.5
	10+	47	108	0.9	0.6–1.4

CI - confidence intervals

EPT - estrogen-progestin therapy

RR - relative risk

ccEPT - continuous combined estrogen-progestin therapy

sEPT - sequential estrogen-progestin therapy

* three studies[6,13,32] presented per year of use estimates and are therefore not shown in this table, one study[25] presented results separately by ccEPT and sEPT and is therefore not included, and one study[22] provided the overall hazard ratio and is therefore not included.

** years of use