Association Between Menopausal Estrogen-Only Therapy and Ovarian Carcinoma Risk

Alice W. Lee MPH[1], Roberta B. Ness MD, MPH[2], Lynda D. Roman MD[3], Kathryn L. Terry ScD[4,5], Joellen M. Schildkraut PhD[6], Jenny Chang-Claude PhD[7,8], Jennifer A. Doherty PhD[9], Usha Menon MD[10], Daniel W. Cramer MD, ScD[4,5], Simon A. Gayther PhD[11,12], Harvey Risch MD, PhD[13], Aleksandra Gentry-Maharaj PhD[10], Marc T. Goodman PhD[14,15], Francesmary Modugno PhD[16-18], Ursula Eilber[7], Kirsten B. Moysich PhD[19], Andrew Berchuck MD[20], Mary Anne Rossing DVM, PhD[21,22], Allan Jensen PhD[23], Kristine G. Wicklund PhD[22], Kara L. Cushing-Haugen MS[22], Estrid Hogdall PhD, DMSc[23,24], Anja Rudolph PhD[7], Pamela J. Thompson MPH[14,15], Lynne R. Wilkens DrPH[25], Susanne K. Kjaer MD, DMSc[23,26], Michael E. Carney MD[27], Daniel O. Stram PhD[1], Susan J. Ramus PhD[1], Anna H. Wu PhD[1], Malcolm C. Pike PhD[1,28], Celeste Leigh Pearce PhD, MPH[*1,29] on behalf of the Ovarian Cancer Association Consortium

[1] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2] University of Texas School of Public Health, Houston, TX, USA; [3] Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [4] Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA; [5] Harvard T.H. Chan School of Public Health, Boston, MA, USA; [6] Department of Public Health Sciences, The University of Virginia, Charlottesville, VA, USA; [7] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [8] University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [9] Department of Epidemiology, The

Geisel School of Medicine at Dartmouth, Hanover, NH, USA; [10] Women's Cancer, Institute for Women's Health, University College London, London, United Kingdom; [11] Center for Cancer Prevention and Translational Genomics, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [12] Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [13] Department of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, CT, USA; [14] Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [15] Community and Population Health Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [16] Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Gynecologic Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [17] Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA; [18] Womens Cancer Research Program, Magee-Womens Research Institute and University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA; [19] Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA; [20] Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA; [21] Department of Epidemiology, University of Washington, Seattle, WA, USA; [22] Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA [23] Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; [24] Molecular Unit, Department of Pathology, Herley Hospital, University of Copenhagen, Copenhagen, Denmark; [25] Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA; [26] Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [27] Department of Obstetrics and Gynecology, John A.

Burns School of Medicine, University of Hawaii, Honolulu, HI, USA [28] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [29] Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

[*] Corresponding author: Celeste Leigh Pearce, PhD, 1415 Washington Heights, SPH Tower Office #4642, Ann Arbor, MI 48109-2029. Phone: 734-764-3835, Fax: 734-764-3192. lpearce@umich.edu

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Precis

Menopausal estrogen-only therapy use is significantly associated with increased risk of serous and endometrioid ovarian carcinomas, especially among current, long-term users.

Abstract

Objective: To describe the association between postmenopausal estrogen-only therapy use and risk of ovarian carcinoma, specifically with regard to disease histotype and duration and timing of use.

Methods: We conducted a pooled analysis of 906 women with ovarian carcinoma and 1,220 controls; all 2,126 women included reported having had a hysterectomy. Ten population-based case-control studies participating in the Ovarian Cancer Association Consortium (OCAC), an international consortium whose goal is to combine data from many studies with similar methods so reliable assessments of risk factors can be determined, were included. Self-reported questionnaire data from each study were harmonized and conditional logistic regression was used to examine estrogen therapy's histotype-specific and duration and recency of use associations.

Results: 43.5% of the controls reported previous use of estrogen therapy. Compared to them, current-or-recent estrogen therapy use was associated with an increased risk for the serous (51.4%, OR=1.63, 95% CI 1.27-2.09) and endometrioid (48.6%, OR=2.00, 95% CI 1.17-3.41). In addition, statistically significant trends in risk according to duration of use were seen among current-or-recent postmenopausal estrogen therapy users for both ovarian carcinoma histotypes ($p_{trend}<0.001$ for serous and endometrioid). Compared to controls, current-or-recent users for ten years or more had increased risks of serous ovarian carcinoma (36.8%, OR=1.73, 95% CI 1.26-2.38) and endometrioid ovarian carcinoma (34.9%, OR=4.03, 95% CI 1.91-8.49).

Conclusions: We found evidence of an increased risk of serous and endometriod ovarian carcinoma associated with postmenopausal estrogen therapy use, particularly of long duration. These findings emphasize that risk may be associated with extended estrogen therapy use.

Introduction

Menopausal hormone therapy (HT) containing estrogens is used to relieve climacteric symptoms and prevent osteoporosis among postmenopausal women. Prior to the results of the Women's Health Initiative (WHI) in 2002,[1] approximately 13 million women in the United States used HT, and while this number declined after the WHI, there are still approximately 5 million HT users.[2]

A comprehensive meta-analysis by Pearce et al, which included 14 population-based studies of women ages 18 to 79, showed that use of estrogen-only therapy (ET) was associated with increased risk of ovarian carcinoma (relative risk per 5 years of use=1.22).[3] Recent studies since then have shown similar results[2,4-6] , but important aspects remain unclear including whether differences exist by disease histotype or by duration and timing of use. The recent pooled analysis by the Collaborative Group on Epidemiological Studies on Ovarian Cancer (Collaborative Group)[2] did report histotype-specific findings for serous and endometrioid cancers, but not for mucinous and clear cell cancers. They also found little trend in association with duration of use, contrary to the results of several studies.[3,4,6-9] Notably, the Collaborative Group's analysis included the majority of studies in Pearce et al's meta-analysis in which a duration association was found. Clarifying these features could have important implications clinically and for risk stratification purposes.

Estrogen-only therapy is one of the most commonly used HT types, hence a more complete characterization of the ET-ovarian carcinoma association is warranted. We have undertaken a pooled analysis of data from the Ovarian Cancer Association Consortium (OCAC) to assess ET's histotype-specific, duration and recency of use associations with risk of ovarian carcinoma.

Materials and Methods

The OCAC is an international multidisciplinary consortium founded in 2005 (http://apps.ccge.medschl.cam.ac.uk/consortia/ocac/index.html). Since many groups worldwide are conducting studies to identify risk factors and genetic variation associated with ovarian carcinoma risk, the goal of the OCAC is to provide a forum in which data from many individual studies with similar methods can be combined so reliable assessments of the risks associated with these factors can be determined. Data were sent by each study investigator to the consortium data coordinating center at Duke University, which cleaned and harmonized these data.

For the pooled analysis presented here, 10 population-based case-control studies that were individually conducted and contributed data to the OCAC were included, with seven conducted in the United States and three in Europe. Details regarding each study have been published previously,[10-20] but their main characteristics as well as any overlap with the Collaborative Group's pooled analysis are presented in Table 1. Cases were women with initial diagnoses of primary ovarian carcinoma (women with primary fallopian tube and peritoneal tumors were excluded). Eligible tumor types included serous, mucinous, endometrioid, and clear cell ovarian carcinomas as well as other epithelial tumor types that were not classified as one of these four main ovarian carcinoma histotypes including mixed cell and Brenner tumors; borderline-malignant tumors were excluded. Controls were women with ovaries (a single ovary was acceptable), who had not been diagnosed with ovarian carcinoma at the time of interview. Reference dates for the women in the studies were usually the dates of diagnosis for the cases and the dates of interview for the controls. The data used in this analysis considered events

occurring only prior to the reference dates. All studies included in this analysis had approval from ethics committees and written informed consent was obtained from all study participants.

There was a total of 8,095 ovarian carcinoma patients and 13,434 controls across the ten OCAC studies. However, only women who reported having had a simple hysterectomy (without bilateral oophorectomy) were included in our analysis since estrogen-only therapy use is very infrequent among women with intact uteri as it is a confirmed risk factor for endometrial cancer,[21,22] leaving us with 1,432 cases and 1,995 controls. Additional exclusions included women who were less than 50 years of age at reference date (n=387), had a prior primary cancer diagnosis (excluding non-melanoma skin cancer) (n=399), or were missing or had unknown HT information (n=141). We also excluded women who had used HT in an estrogen-progestin combined form (n=246) for simplicity of presentation and since its use is likely to skew the primary effect of estrogen-only therapy. Only women classified as non-Hispanic white, Hispanic white, or black were considered, hence our final subject set consisted of 2,126 women who had undergone hysterectomy, with 906 ovarian carcinoma cases and 1,220 controls (Figure 1).

Information regarding HT use in all forms as well as potential confounding variables selected a priori, including age, race-ethnicity, education, oral contraceptive (OC) use, parity, endometriosis, tubal ligation, age at menarche, and body mass index (typically one year before the reference date), was reported by means of self-completed questionnaires or in-person or phone interviews; we did not have information on previous salpingectomy or *BRCA* status at the time of this analysis. The questions used to ascertain HT use and, more specifically, estrogen-only therapy use are presented in Appendix 1, available online at http://links.lww.com/xxx.

Age at menopause among women who have had a simple hysterectomy cannot be determined since the women are no longer menstruating but may still have functioning ovaries.

Hence, in our primary analysis here, we have only considered estrogen-only therapy use after age 50 given that 50 is the approximate average age at menopause for women in these populations.[23] The majority of estrogen-only therapy use before age 50 is thus likely to be use when the women were still having regular ovulatory cycles. Given that menopause plays a central role in ovarian carcinoma etiology, it is possible that the added estrogen exposure during the period when endogenous levels of estrogen are naturally high (i.e., before menopause) is less important than exposure at older ages, the majority of which will be in the postmenopausal period.[24] Hence, for the analysis presented here, we have defined estrogen-only therapy use as use after age 50, with women who only used estrogen-only therapy before age 50 included in the baseline 'never' users group. We also conducted sensitivity analyses to see if the results were affected if true 'never' users were used as the baseline comparison group and if estrogen-only therapy use was considered regardless of age at use.

A common approach to dealing with the problem of an unknown age at menopause for women who had a hysterectomy is to use their age at simple hysterectomy as their age at menopause. Hence, we conducted a sensitivity analysis to assess the association between estrogen-only therapy use and ovarian carcinoma risk using such an approach. We also conducted sensitivity analyses using ages 48 and 52 instead of 50 as the age at menopause.

Estrogen-only therapy use was categorized in terms of its recency and its duration of use (in years). Current use was defined as having last used estrogen-only therapy within the past year, recent use as within the last one to four years, and past use as five or more years before the reference date. Because current and recent estrogen-only therapy users showed similar effects, they were combined in the analyses presented here. Duration of estrogen-only therapy use was summed over all episodes of use and the total categorized into the following groups: 'never'

(including <1 year), 1 to <5 years, 5 to <10 years, and 10 or more years of use. Women who used estrogen-only therapy for less than one year were included in the baseline 'never' users group as the recall of such short-term use may be greater in cases than controls. All data were cleaned and checked for internal consistency and clarifications were requested from the study investigators when needed.

Study, age, race-ethnicity, education, and OC use were included in all statistical models. We conditioned on study, age in five-year groups (50-54, 55-59, 60-64, 65-69, 70-74, 75+; finer stratification after age 75 was not warranted due to small numbers), race-ethnicity (non-Hispanic white, Hispanic white, and black), and education (less than high school, high school, some college, and college graduate or higher) and we adjusted for OC use in categories as ordinal variables ('never' (including <1 year), 1 to <2 years, 2 to <5 years, 5 to <10 years, and 10 or more years for OC use). Tubal ligation, endometriosis, parity, body mass index, and age at menarche were also considered, but their inclusion did not change the beta coefficients for the association between ET use and ovarian carcinoma (including overall, serous, or endometrioid) by more than 10% so the results given below are only adjusted for OC use. Overall, cases were missing 1.7% and 1.1% and controls 1.4% and 0.7% for OC use and education, respectively; missing categories were created for these women so their data could be used in the analysis.

Conditional logistic regression was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for the association between estrogen-only therapy use and risk of ovarian carcinoma. This was done for all ovarian carcinoma cases combined and for its four main histotypes. Similar analytic approaches were applied when assessing the effects of recency and duration of use. All p-values reported are two-sided. All analyses were performed using SAS 9.4.

Results

Data from 906 women with ovarian carcinoma (567 serous, 113 endometrioid, 49 mucinous, 42 clear cell, 135 epithelial but not specified as one of the four main histotypes) and 1,220 controls, all of whom had a simple hysterectomy, were included in our analysis. Of these women, 460 cases (50.8%) and 531 controls (43.5%) reported ever having used estrogen-only therapy after age 50. Compared with the women in the control group, wmen who had used estrogen-only therapy after age 50 had a 30% increased risk of ovarian carcinoma as shown in Table 2 (50.8%, OR=1.30, 95% CI 1.06-1.59). Most of this risk elevation was observed among long-term users of estrogen-only therapy for 10 years or more (both current or recent and past users).

In addition, the estrogen-only therapy-ovarian carcinoma association appeared to show distinct histotype-specific associations as presented in Table 3 (serous and endometrioid) and Appendix 2, available online at http://links.lww.com/xxx (mucinous and clear cell). Compared with the women in the control group, current or recent estrogen-only therapy use was statistically significantly associated with an increased risk of both serous (51.4%, OR=1.63, 95% CI 1.27-2.09) and endometrioid (48.6%, OR=2.00, 95% CI 1.17-3.41) histotypes, but not mucinous (31.3%, OR=0.93, 95% CI 0.43-2.00) and clear cell (39.0%, OR=0.87, 95% CI 0.40-1.88) histotypes, although the confidence limits for the mucinous and clear cell effect estimates were wide due to small numbers of cases. When we looked at high-grade (moderately differentiated, poorly differentiated, undifferentiated) and low-grade (well differentiated) serous ovarian carcinomas separately, we found increased risks for both and hence the results for all serous cases combined are given.

Trends in association with duration of estrogen-only therapy use were observed for the serous ($p_{trend}<0.001$) and endometrioid ($p_{trend}<0.001$) histotypes among current or recent estrogen-only therapy users. Across all histotypes and duration and timing categories, estrogen-only therapy appeared to have the strongest association with risk of endometrioid ovarian carcinoma; compared with the women in the control group, current or recent, long-term users of estrogen-only therapy for 10 years or more had over a four-fold increased risk (34.9%, OR=4.03, 95% CI 1.91-8.49). Current or recent, long-term users also had nearly a two-fold increased risk of serous ovarian carcinoma (36.8%, OR=1.73, 95% CI 1.26-2.38) when compared with women in the control group. In addition, there appeared to be elevated risks of 1.49, 2.07, and 1.82 for overall, serous, and endometrioid ovarian carcinoma, respectively, when we compared past, long-term ET users to our baseline 'never' user group (Tables 2 and 3).

Because we assumed that all women in our analysis had an age at menopause of 50, we conducted a sensitivity analysis in which each woman's age at simple hysterectomy was used as her age at menopause, with the duration and timing of use variables re-categorized as such. The results by duration, timing of ET use, and histotype slightly attenuated with ORs of 1.46, 1.64, and 3.72 among current-or-recent ET users of 10 years or more for ovarian carcinoma overall and the serous and endometrioid histotypes, respectively (Appendix 3, available online at http://links.lww.com/xxx). Sensitivity analyses that used a true 'never' user baseline group and redefined ET use regardless of age at menopause or with ages 48 and 52 as the age at menopause did not affect the overall findings (data not shown).

Discussion

Most population-based case-control studies and cohort studies have shown that estrogen-only therapy use is associated with an increased risk of ovarian carcinoma and considering our findings together with those recently published by the Collaborative Group,[2] it seems clear that estrogen-only therapy is associated with risk for the serous and endometrioid histotypes of the disease. We found greater increased risk for those who used estrogen-only therapy for 10 years or more, including those who last used it more than 5 years in the past, whereas the Collaborative Group[2] did not. This was surprising given that the individual studies that contributed the most statistical information to their analysis (the Million Women Study (MWS)[7] and the Danish Sex Hormone Register Study (DaHoRS)[4]) reported duration associations with estrogen-only therapy use in their primary publications. The meta-analysis from Pearce el al[3] showed evidence of an estrogen-only therapy duration-ovarian carcinoma risk association as well.

From a biological standpoint, an elevated risk of endometrioid ovarian carcinoma with estrogen-only therapy use is not surprising given that the cells of origin are histologically similar to endometrial tissue,[25] and estrogen-only therapy use is a confirmed risk factor for endometrial cancer.[21] Danforth et al[26] had suggested that estrogen-only therapy may act through similar biologic mechanisms in the development of endometrioid tumors as it does in endometrial cancer. Given the increased risk we see for endometrioid ovarian carcinoma and the well-established association between endometriosis and the endometrioid and clear cell histotypes,[27] we assessed the estrogen-only therapy risk association according to previous history of endometriosis or not, but did not see any heterogeneity in risk (data not shown).

Although the exact mechanism by which estrogen-only therapy might affect serous and endometrioid ovarian carcinoma risk remains unknown, estrogens have long been implicated as etiologic factors.[28] Ovarian carcinogenesis may be a result of the direct effects of unopposed

estrogen and an estrogen-rich environment, which would potentially be enhanced by estrogen-only therapy use. The use of estrogen-only therapy may also directly stimulate the growth of premalignant or early malignant cells with long-term use increasing the risk of transformation or proliferation.[29] In addition, the fallopian tube fimbriae , a proposed cell of origin for high-grade serous carcinoma, have been shown to proliferate at times when estrogenic influences are greater during the menstrual cycle,[30,31] and this increased activity results in greater cell proliferation which may enhance the risk of mutations and malignant transformation. Estradiol has also been shown to increase ovarian carcinoma cell proliferation in vitro[32] and influence the growth of ovarian tumors in a transplanted mouse model.[33] Therefore, while several hypotheses have been put forth to explain ovarian carcinoma etiology, unopposed estrogen appear to play an important role.

Limitations of our analysis include the self-reported nature of our data. Because case-control studies inquire about previous exposures when subjects are already aware of their disease status, recall bias is possible as cases may be more likely to search for explanations for their disease and assign greater significance to past events than controls. However, studies have shown high agreement between self-reported estrogen use and prescription data.[34] In addition, case patients have not been shown to preferentially report HT use more than controls.[35] We considered estrogen-only therapy use only after age 50 to be relevant in an attempt to mainly consider only use after ovarian function had ceased. Sensitivity analysis showed little effect when changing this to age 48 or 52, the latter which will only include use that is almost all in the postmenopausal period.

A potential concern with case-control studies such as those included in our analysis is that some ineligible women (those who had a bilateral oophorectomy) could have been recruited

as controls even though they would not be at risk of developing ovarian carcinoma. However, oophorectomy results in a loss of estrogen production, which may make such women more likely to use estrogen-only therapy, thus potentially biasing our findings towards the null. If this type of bias is present, any association between estrogen-only therapy use and risk of ovarian carcinoma would be underestimated.

Our analysis offers evidence of an increased risk of ovarian carcinoma with ET use after the age of 50. This is especially true for risk of serous and endometrioid tumors for long durations of use, shedding light on the distinct histotype-specific etiologies. Although ET use has declined since the WHI, a significant number of women continue to use it today. Physicians and patients should be aware of the risk of ovarian carcinoma associated with its long-term use.

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Table 1. Description of studies included in analysis

Study Name	Time Period	Location	Case Ascertainment	Control Ascertainment	Controls (mean/IQR for age)	Cases (mean/IQR for age)	Serous	Muci-ous	Endom-etrioid	Clear cell
Connecticut Ovary Study (CON) [19]	2002-2009	USA; CT	Cancer registry or hospital records	Random digit dialing, Health Care Financing Administration records	49 (60.9/13)	54 (62.2/12)	28	4	12	4
Disease of the Ovary Study and their Evaluation (DOV) [18]	2002-2009	USA; WA	Cancer registry	Random digit dialing	224 (66.8/12)	159 (62.7/8)	108	3	15	3
German Ovarian Cancer Study (GER) [10, *]	1992-1998	Germany	Admissions to all hospitals serving the study regions	Population registries	89 (60.9/11)	34 (61.5/12)	17	2	2	1
Hawaii Ovarian Cancer Study (HAW) [12]	1994-2007	USA; HI	Cancer registry	Department of Health Annual Survey, Health Care Financing Administration records	40 (67.3/16)	32 (66.1/17)	18	1	5	2
Hormones and Ovarian Cancer Prediction (HOP) [13, *]	2003-2008	USA; western PA, northeast OH, western NY	Cancer registries, pathology databases, physicians' offices	Random digit dialing	201 (65.5/16)	100 (66.6/15.6)	57	5	17	4
Malignant Ovarian Cancer Study (MAL) [20]	1994-1999	Denmark	Cancer registry, gynecological departments	Random digit dialing	84 (62.6/13)	47 (61.7/11)	25	4	8	5
North Carolina Ovarian Cancer Study (NCO) [14]	1999-2008	USA; NC	Cancer registry	Random digit dialing	126 (62.7/11)	153 (62.9/10)	94	5	16	11
New England Case-Control Study of Ovarian Cancer (NEC) [16]	1999-2008	USA; NH and eastern MA	Cancer registries, hospital tumor boards	Random digit dialing, town books, drivers' license lists	67 (63.2/11)	50 (63.4/12)	38	1	6	1
United Kingdom Ovarian Cancer Population Study (UKO) [11]	2006-2007	United Kingdom	Gynecological Oncology NHS centers	Women in the general population participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)	116 (64.0/9)	56 (67.0/12)	30	7	12	4
University of Southern California. Study of Lifestyle and Women's Health (USC) [15,17, *]	1993-2005	USA; Los Angeles, CA	Cancer registry	Neighborhood controls	224 (62.9/12.5)	217 (64.7/12)	152	17	20	7
				Total:	1220	906[†]	567[†]	49[†]	113[†]	42[†]

Note: All studies used in-person interviews except GER, which used self-completed questionnaires. MAL used either in-person or phone interviews.

[*] Some of the study's data were included in the Collaborative Group's[2] analysis.

[†] Sum of numbers do not equal total number of cases because some cases were not classified as one of the four main histotypes considered.

Table 2. Association between estrogen-only therapy use over age 50 and risk of ovarian carcinoma overall

Categories of ET Use	Number of controls	Number of cases	Median duration (years)	OR*	95% CI	p-value
Never used	689	446	--	1.00	--	--
Ever	531	460	9.20	1.30	1.06 – 1.59	0.013
1 to<5 years	149	92	2.70	1.00	0.72 – 1.39	0.99
5 to<10 years	155	135	7.45	1.27	0.93 – 1.72	0.13
10+ years	227	233	15.12	1.54	1.18 – 2.01	0.002
					p-trend:	0.001
Current-or-recent users†	432	392	10.00	1.35	1.09 – 1.67	0.006
1 to <5 years	103	67	3.00	1.00	0.68 – 1.48	0.99
5 to <10 years	120	112	7.20	1.35	0.96 – 1.90	0.087
10+ years	209	213	15.20	1.53	1.17 – 2.02	0.002
					p-trend:	<0.001
Past users	99	68	6.20	1.07	0.74 – 1.56	0.72
1 to <5 years	46	25	2.20	1.01	0.59 – 1.74	0.97
5 to <10 years	35	23	8.20	1.03	0.57 – 1.86	0.93
10+ years	18	20	13.28	1.49	0.71 – 3.13	0.29
					p-trend:	0.95

Note: OR=odds ratio, CI = confidence interval.

* Adjusted for oral contraceptive use (never (including <1), 1 to <2, 2 to <5, 5 to <10, 10+ years) and conditioned on age (50-54, 55-59, 60-64, 65-69, 70-74, 75+), education (less than high school, high school, some college, college graduate or higher), race-ethnicity (non-Hispanic white, Hispanic white, black), and study.

† Current-or-recent users included those who used estrogen-only therapy within the last five years prior to their reference age.

Table 3. Association between estrogen-only therapy use after age 50 and risk of serous and endometrioid ovarian carcinoma

		SEROUS (N=567)				ENDOMETRIOID (N=113)			
Categories of ET Use	Number of controls	Number of cases	OR*	95% CI	p-value	Number of cases	OR*	95% CI	p-value
Never used	689	252	1.00	--	--	54	1.00	--	--
Ever	531	315	1.57	1.23 – 2.00	<0.001	59	1.82	1.10 – 3.03	0.021
1 to <5 years	149	62	1.26	0.86 – 1.83	0.24	10	0.98	0.45 – 2.15	0.97
5 to <10 years	155	92	1.58	1.11 – 2.25	0.012	17	1.64	0.78 – 3.47	0.19
10+ years	227	161	1.79	1.31 – 2.43	<0.001	32	3.58	1.74 – 7.36	<0.001
				p-trend:	<0.001			p-trend:	<0.001
Current-or-recent users†	432	267	1.63	1.27 – 2.09	<0.001	51	2.00	1.17 – 3.41	0.011
1 to <5 years	103	46	1.37	0.88 – 2.14	0.16	7	0.88	0.35 – 2.19	0.78
5 to <10 years	120	74	1.69	1.14 – 2.52	0.010	15	1.72	0.76 – 3.87	0.19
10+ years	209	147	1.73	1.26 – 2.38	<0.001	29	4.03	1.91 – 8.49	<0.001
				p-trend:	<0.001			p-trend:	<0.001
Past users	99	48	1.28	0.83 – 1.96	0.27	8	1.20	0.48 – 3.01	0.69
1 to <5 years	46	16	1.05	0.55 – 2.01	0.89	3	1.35	0.37 – 4.94	0.66
5 to <10 years	35	18	1.26	0.65 – 2.43	0.50	2	1.46	0.25 – 8.66	0.68
10+ years	18	14	2.07	0.89 – 4.79	0.091	3	1.82	0.40 – 8.19	0.44
				p-trend:	0.46			p-trend:	0.35

Note: OR=odds ratio, CI=confidence interval

* Adjusted for oral contraceptive use (never (including <1), 1 to <2, 2 to <5, 5 to <10, 10+ years) and conditioned on age (50-54, 55-59, 60-64, 65-69, 70-74, 75+), education (less than high school, high school, some college, college graduate or higher), race-ethnicity (non-Hispanic white, Hispanic white, black), and study.

† Current or recent users included those who used estrogen-only therapy within the last five years prior to their reference age.

Figure 1. Flowchart of analysis exclusions