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Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis

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Abstract

Objective—There is a rapidly evolving debate on the indications and appropriate duration of therapy for postmenopausal hormone therapy. The objective of this meta-analysis was to examine the specific relationships of postmenopausal estrogen therapy (ET), postmenopausal combined (estrogen-progestogen) hormone therapy (CHT), and the incidence of breast cancer.

Design—We performed computerized searches of MEDLINE and CancerLit through September 2003 and reviewed reference lists of retrieved studies and meta-analyses. We included English-language studies that identified noncontraceptive postmenopausal hormone use; reported on the risks of “current use” of ET and/or CHT and breast cancer incidence; were case-control, cohort, or experimental; and reported either an odds ratio (OR), relative risk (RR), or HR with CIs. Two investigators were involved during all stages of study selection and independently extracted all data selected for inclusion in meta-analyses.

Results—Meta-analysis of 13 studies of ET and breast cancer (700,000 women) resulted in an OR of 1.16 (95% confidence limits [CL] 1.06, 1.28), with estimates for less than 5 years use 1.16 (1.02, 1.32) and more than 5 years use 1.20 (1.06, 1.37). Meta-analysis of eight studies of CHT and breast cancer (650,000 women) resulted in an OR of 1.39 (95% CL 1.12, 1.72), with estimates for less than 5 years use 1.35 (1.16, 1.57) and more than 5 years use 1.63 (1.22, 2.18).

Conclusions—Data from observational studies support the association of increased but considerably different risks for breast cancer incidence among current users of ET and CHT. These represent the first pooled estimates for ET. CHT estimates correspond to those from randomized trials.

Keywords

Hormone therapy; Breast cancer; Menopause

There is a rapidly evolving debate on the indications and appropriate duration of therapy for postmenopausal hormone therapy (HT). Initially, use focused on the treatment of perimenopausal symptoms, but the purported benefits were quickly broadened to include protection from cardiovascular disease, age-related dementias, osteoporosis, and colon cancer.

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¹ Most recently, the perceived role of HTs has shifted from one of broad indications, long-term use, and substantial optimism to narrow indications, short-term use, and great skepticism.
²

Since the publication of the results of the Women's Health Initiative (WHI),^{3,4} a primary prevention trial of HT and coronary heart disease, and the follow-up to the Heart and Estrogen/Progestin Replacement Study (HERS II),⁵ a secondary prevention trial on the same topic, concerns have focused on whether the potential risks of HT outweigh the benefits for selected patients, many patients, or even a majority of patients. HERS II⁵ found increased rates of venous thromboembolism and biliary tract surgery in the group assigned to receive 0.625 mg/day of conjugated estrogens and 2.5 mg/day of medroxyprogesterone acetate (MPA). Rates of cancer, however, were not elevated in treated women relative to controls. One arm of the WHI was stopped early because of a finding of increased breast cancer risk among users of combined conjugated estrogens and MPA, with an unadjusted hazard ratio (HR) of 1.26 (95% confidence limits [CL] 1.00, 1.59). A second arm of the WHI that was stopped more recently, due to the relative certainty that a beneficial cardiovascular effect would not be demonstrated with longer follow-up, found no increased risk of breast cancer among users of estrogen-alone preparations, with an HR of 0.77 (95% CL 0.59, 1.01).

The Agency for Healthcare Research and Quality (AHRQ) has also completed a report on HT.
⁶ They found an association between the "current use" of HT and breast cancer as well as conflicting evidence of increased risk for long-term use. They concluded that there was no evidence of increased risk for combined estrogen-progestogen regimens over estrogen-alone regimens. This report, however, based many of its findings on meta-analyses that were confounded by the inclusion of premenopausal oral contraceptive use.⁷⁻⁹ The US Preventive Services Task Force concluded that there was fair to good evidence that HT increases the incidence of breast cancer, with best evidence for estrogen plus progestogen.¹⁰

The role of HT has been re-evaluated since the publication of the WHI, HERS II, and AHRQ reports. The US Food and Drug Administration codified its revised position on HT by requiring changes to the package inserts for all female hormonal therapies.¹¹ Meanwhile, numerous new reports from observational studies have been published on the association between specific regimens of HT and breast cancer, providing the opportunity for a closer examination of the topic which can better incorporate duration of use into estimates of risk, examine different regimens, and provide more generalizable results than trials alone. Especially when absolute risk is small, individual studies may be ill-equipped to estimate risks precisely because of random error. Meta-analysis of such studies may help average out the "noise," albeit not correcting for any potential systematic biases in the original data.

For these reasons, we undertook a systematic review that differs from previous work in four ways. First, it excludes contraceptive use from systematic assessment of HT and breast cancer risk. Second, it separates estimates for estrogen-alone therapy (ET) and combined estrogen-progestogen hormone therapy (CHT) regimens. Third, it looks at the duration of use, separated into less than 5 years or greater than 5 years. Fourth, it relies solely on estimates of ET/CHT "current use."

METHODS

Data sources

Studies and review articles relating postmenopausal hormone therapy and cancer were identified in the MEDLINE (1966 through September 2003) and CancerLit (1975 through September 2003) databases. Search terms included *hormone replacement therapy*, *estrogen replacement*, *cancer*, and *neoplasm* (see Appendix 1 for the complete search strategy).

Study selection criteria

Studies had to be conducted in postmenopausal women with the title available in English to be considered for this systematic review. Data on cancer incidence, mortality, pathology, or stage had to be reported. Studies selected for inclusion met the following requirements: 1) the study was observational or interventional with a comparison group (eg, case-control, cohort, quasi-experimental, or experimental, but not case series); 2) the study incorporated longitudinal ascertainment of exposure and disease (ascertainment could be prospective or historical, but not cross-sectional); 3) the study reported data on rates of cancer in at least two groups (“never” and “current” users), or the study included a summary estimate (eg, odds ratio, relative risk) with reported CIs or a precise *P* value; and 4) the study had to distinguish between noncontraceptive and contraceptive estrogen use in its presentation of results. Reports selected for meta-analyses additionally had to provide estimates of risk for women using ET or CHT at study inception (current use). Estimates for “current use” of HT among women enrolling in a study, as compared with “past use” or “ever use,” have consistently found the greatest risk associations with breast cancer and are also most comparable to estimates from randomized trials such as HERS and WHI that start women on HT or placebo at study inception.^{12,13} Two investigators reviewed all titles and studies included in meta-analyses. The full text of the citation was retrieved for those with no abstract available. We excluded editorials, letters, and nonsystematic reviews. For datasets that were presented in multiple publications, we selected those with the most up-to-date results, longest follow-up, or most pertinent outcomes. We did not pursue unpublished data because several prior meta-analyses conducted in this area found no contribution from this added step. We conducted a separate search to identify prior meta-analyses of HT and cancer and used their reference lists to find additional studies not identified by database searches. Appendix 2 summarizes the findings of the literature search.

Data extraction

We abstracted included studies into evidence tables modeled on those of the AHRQ report.⁶ Pertinent data were initially abstracted by one investigator, compared with results found by the AHRQ reviewers where available, and independently abstracted by another investigator. Discrepancies were resolved by consensus.

Data synthesis

We conducted meta-analyses of studies on the “current use” of ET/CHT and its relationship to incident cases of breast cancer. We used the methods of DerSimonian and Laird¹⁴ to compute point estimates and 95% CIs with Stata software (version 7) using the “meta” command. Because no meaningful differences were found between the random effects and fixed effects analyses, only random effects results are presented. When results from observational studies and randomized trials were available on the same topic, separate meta-analyses were conducted because of different potentials for bias among studies versus trials.¹⁵ Heterogeneity was assessed using the Q test, *I*² and further evaluated with exploratory meta-regression.^{16,17} Whenever possible, adjusted odds ratios or RRs were used as estimates of the true relation between HT and breast cancer. We present “study quality” ratings based on methods described by the US Preventive Services Task Force,¹⁸ but limit our use of these ratings because they do not take account of bias directions and so are potentially misleading.¹⁹ To assess publication bias we used the “trim and fill” method (“metatrim” in Stata).²⁰

RESULTS

Search results

From a sample of 2,474 titles reviewed (1,669 MEDLINE, 594 CancerLit, and 211 from prior meta-analyses) we identified 10 meta-analyses, 56 reports of case-control studies, 41 reports

of cohort studies, and 4 reports of randomized trials with data on the relationship between breast cancer and HT. Studies that are included in the meta-analyses are listed in Table 1. Other studies that met all the inclusion criteria but were not included in meta-analyses (because they did not provide data on “current use” of ET/CHT, or are presented in other publications of the same dataset) are listed in Appendix 3. Other than updated reports of data presented earlier, all exclusions were of studies that only provided data on HT “ever use” or “past use.” Both of these classifications of exposure are subject to considerable recall bias on type of agent and duration of use, and hence may underestimate risks compared to estimates based on “current use.” All data elements relative to the meta-analyses had two reviewers who came to consensus on all items. Studies included in prior meta-analyses but excluded in this review are listed in Appendix 4 along with reasons for their exclusion.

Postmenopausal hormone therapy formulations

There are numerous formulations of HT that vary by agent and dose. In general, women used estradiol-based regimens in European studies and conjugated estrogens in US studies. Earlier studies report higher doses of estrogen (eg, >1.25 mg/day conjugated estrogens³²) than more recent studies (eg, 0.625 mg/day of conjugated estrogens⁵). The use of opposed estrogens (ie, in combination with a progestogen) gained widespread acceptance in the 1980s after many studies found estrogen-alone regimens were associated with high rates of endometrial cancer in women with a uterus.³³ In a nationally representative cohort of US women, use of CHT increased from 7% in 1979–1983 to 37% in 1992–1995.³¹ Hence, studies of women on HT conducted in the 1970s or earlier are presumed to have women exposed to estrogen alone unless explicitly stated otherwise. Combined hormone therapy consists of a form of estrogen delivered either sequentially or simultaneously with a form of progestogen. Early CHT formulations delivered estrogen for most days of the cycle with a progestogen (eg, levonorgestrel or MPA) added during the final week—sequential CHT; however, most of the CHT studies identified in this review are of estrogen and progestogen delivered simultaneously—continuous CHT. If a study listed the progestogen type and dose used, which occurred infrequently, this information was abstracted. All but one study¹² included in the CHT meta-analysis were conducted in the United States, where MPA is the predominant progestogen.³⁴ The Million Women Study, conducted in Europe, had approximately 17% of progestogen users taking MPA, 39% taking norethisterone, and 44% taking norgestrel/levonorgestrel.¹²

Estrogen therapy and risk of breast cancer

Eight cohort and five case-control studies addressed the association of ET and breast cancer (see Table 2). Meta-analysis of these 13 studies including 701,160 women results in a pooled OR of 1.16 (95% CL 1.06, 1.28), with the Q test $P = 0.003$ suggesting heterogeneity and $I^2 = 53\%$ (see Figure 1). Exploratory meta-regression analyses to determine potential sources of this heterogeneity did not detect a relation of the odds ratio to design (case control versus cohort), location (US versus Europe), enrollment or publication year, study size, quality rating (good versus poor/fair), years of follow-up, or adjustment for socioeconomic status.

Nine studies provided estimates for less than 5 years of ET use: OR 1.16 (1.02, 1.32) with the Q test $P = 0.09$ and $I^2 = 27\%$. Ten studies provided data for 5 or more years of use: OR 1.20 (1.06, 1.37) with the Q test $P < 0.001$ and $I^2 = 70\%$.

Nonparametric tests for publication bias resulted in no studies being trimmed or filled (see Appendix 5), suggesting no significant likelihood of missed studies. Furthermore, any studies not published would have to be large with highly protective findings to influence the statistical pooling in light of the over 700,000 women included in this meta-analysis.

We identified one randomized trial that met all inclusion criteria. The Women's Health Initiative showed an unadjusted HR of 0.77 (95% CL 0.59, 1.01) and an adjusted HR of 0.77 (95% CL 0.57, 1.06), with an average of 6.8 years of follow-up.³

Combined estrogen-progestogen therapy and risk of breast cancer

We conducted a meta-analysis of observational studies of CHT and breast cancer (four cohort and four case-control studies) that excluded two randomized trials: WHI and HERS (see Table 2). Meta-analysis of these eight "good quality" studies with 655,559 women yields a pooled OR of 1.39 (95% CL 1.12, 1.72) with a heterogeneity P of < 0.001 and $I^2 = 87\%$ (see Fig. 2). Exploratory meta-regression analyses to determine potential sources of this heterogeneity did not detect a relation of the OR to design (case control versus cohort), enrollment or publication year, years of follow-up, or adjustment for socioeconomic status. The only factors that relate to the OR are predominant type of progestogen (MPA versus other), study location (US versus Europe), and sample size ($P < 0.001$). By excluding the Million Women Study (RR 2.00, 95% CL 1.91, 2.09) the pooled OR for seven studies is 1.32 (95% CL 1.19, 1.46) with a heterogeneity $P = 0.36$ and $I^2 = 0\%$. For this meta-analysis, the Million Women Study is the only one conducted in Europe, it is the largest study, and the only one that had norgestrel/levonorgestrel as the predominant type of progestogen.

Six studies provided estimates for less than 5 years of CHT use: OR 1.35 (1.16, 1.57) with the Q test $P = 0.17$ and $I^2 = 11\%$. Five studies provided data for 5 or more years of use: OR 1.63 (1.22, 2.18) with the Q test $P < 0.001$ and $I^2 = 74\%$. Nonparametric tests for publication bias resulted in no studies being trimmed or filled (see Appendix 5). If small positive studies are more likely to be reported than small negative studies, then the "trim and fill" method would compensate and "fill in" the missing studies and create an adjusted pooled estimate.²⁰

We identified two randomized trials that met all inclusion criteria. The Heart and Estrogen/progestin Replacement Study (HERS) study⁵ (the fully randomized and blinded trial excluding the open-label observational cohort portion of HERS II) showed an HR of 1.30 (95% CL 0.77, 2.19) and the WHI showed an adjusted HR of 1.26 (95% CL 0.83, 1.92) and an unadjusted HR of 1.26 (95% CL 1.00, 1.59).⁴

What types of progestogens in CHT are associated with higher risk for breast cancer?

Available data are limited with respect to explicit comparisons of breast cancer risk by type of progestogen used. AHRQ found insufficient evidence to conclude that elevated risk is associated with certain types of progestogens relative to others. HERS II showed a trend toward increased risks associated with a regimen with 2.5 mg/day MPA. The same oral regimen was used in the WHI and showed increased risk. In cohort and case-control studies, MPA was the most common agent taken by women exposed to CHT, and most studies found increased risk for CHT regimens. Although the Million Women Study found a higher risk associated with CHT use than all the studies conducted in the United States, whether this can be attributed to the predominant type of progestogen used or another as-yet-unidentified confounder has not been determined.

DISCUSSION

In this meta-analysis of observational studies of postmenopausal hormone use, there is an increased risk of breast cancer incidence associated with the current use of ET (1.16, 95% CL 1.06, 1.28) and a considerably larger risk associated with the current use of CHT (1.39, 95% CL 1.12, 1.72). Data from randomized trials do not give a conclusive answer for breast cancer risk from postmenopausal HT (see Fig. 3). Results from HERS with approximately 4 years of follow-up and WHI with about 5 years of follow-up correspond well to the pooled results

obtained from observational studies of CHT with less than 5 years duration of use. In Fig. 3, there are trends in the pooled observational results toward both a dose-response relationship (with longer durations of use corresponding to larger risks) and greater risk associated with the addition of a progestogen to the hormone therapy regimen. That the observational evidence reinforces data from two randomized trials of CHT helps give credence to the pooled estimates for ET.

However, the risk of breast cancer reported in the ET arm of the WHI appears to contradict the risk estimates we derived from a substantial sample of pooled observational data. The WHI investigators concluded “Women considering taking CEE should be counseled about an increased risk of stroke but **can be reassured about no excess risk of heart disease or breast cancer** for at least 6.8 years of use”³ (emphasis added). We believe the data suggest that differences exist between estrogen-alone and combined estrogen-progestogen regimens, but would recommend full disclosure to potential HT users about even minor elevations in breast cancer risk.

Prior observational studies led us to recommend HT based on biased results from “past use” and “ever use” estimates (not just “current use”), inclusion of pre-menopausal women, and mixing of exposures attributed to HT from ET and CHT. The present meta-analysis represents the least confounded and most specific one to date, including several large studies that were missed or omitted by prior meta-analyses. The authors of the AHRQ summary concluded that there was no evidence of increased risk for CHT regimens over ET regimens and conflicting evidence of increased risk for long-term use.⁶ They did not, however, conduct new meta-analyses on these questions. Their conclusions were based on the results of three prior meta-analyses,^{7–9} which did not differentiate between ET and CHT. Furthermore, these prior meta-analyses had significant limitations: 1) the Collaborative Group’s reanalysis of 51 epidemiologic studies⁷ (OR 1.21, $P < 0.001$) includes 10 studies of premenopausal women using oral contraceptives (see Appendix 4) and we identified five cohort studies^{12,13,29–31} and six case-control studies^{22–25,35,36} that were published since the time of their pooling; 2) the Sillero-Arenas meta-analysis⁸ (RR 1.23, 95% CL 1.12, 1.35) was based on only six studies (which they did not explicitly identify); and 3) the meta-analysis by Colditz et al⁹ (RR 1.40, 95% CL 1.20, 1.63) included only three studies, one of which explicitly states that it included women on oral contraceptives.³⁷

Several studies included in this analysis were conducted during the 1980s, a time of transition from estrogen-alone regimens to estrogen plus progestogen for women who had not had a hysterectomy. Confounding (or self-selection) bias among women or their physicians might have been strongest during this period. Hence, any presumptions on type of agent relative to effect on breast cancer risk are most susceptible to bias. Furthermore, a “healthy user” bias has been well-documented among studies of HT and cardiovascular disease.³⁸ Despite the potential for a “healthy user” bias, we still found an increased risk for breast cancer among “current users” of ET and CHT relative to “never users” of any HT. An earlier meta-analysis of HT and cardiovascular disease³⁹ found that higher socioeconomic status (and its associated better health) accounted for most of the observed protective association from HT^{40,41}. We found no such association with breast cancer incidence and socioeconomic status for either the ET meta-analysis ($P = 0.756$) or the CHT meta-analysis ($P = 0.678$).

Although factors such as the type of estrogen (derived from equine or “natural” sources), type of progestogen (testosterone based or not), and other factors might help provide biologic explanations for this heterogeneity,^{42,43} there were insufficient data in the reports included in the current analyses to further evaluate their specific roles. The sensitivity analysis that included seven of eight studies (which had MPA as the predominant agent) found that the type of progestogen explained a substantial portion of the heterogeneity observed in the CHT meta-

analysis. But this might also be attributable to study size, study location, or other factors. Future research in this area should clearly differentiate premenopausal and postmenopausal estrogen and progestogen exposure, attempt to quantify lifetime estrogen (and progestogen) exposure patterns, and attempt to address specific risks by type of estrogen and progestogen.

The meta-analysis of ET in the current report represents the “first look” at such significant HT data without the inclusion of progestogen, and provides clinically meaningful estimates for patients and providers on the risks of this specific type of postmenopausal hormone therapy. The present report suggests that a woman taking ET for a few (<5) years of perimenopausal use will have considerably different risks compared to a woman needing CHT or long-term (>5 years) treatment. Women with disabling menopause symptoms might find that risk acceptable for the short term. Until this report, recommendations for HT use did not differ for these women with clinically different risk profiles and needs.

CONCLUSIONS

In conclusion, our analysis shows that current use of ET and CHT are associated with increased but different risks of breast cancer. Our conclusions differ from prior reports because we excluded studies confounded by premenopausal oral contraceptive use, included numerous studies published since the time of the last review, and focused on estimates of ET/CHT “current use.” We believe these new findings should be thoughtfully considered as policy and clinical decision making undergo re-evaluation.

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Appendix 1. MEDLINE search strategy

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#1 Search hormone replacement therapy
#2 Search estrogen replacement
#3 Search #1 OR #2
#4 Search cancer
#5 Search neoplasm
#6 Search #4 OR #5
#7 Search #3 AND #6
#8 Search #3 AND #6 Field: All Fields, Limits: English, Human
#9 Search (#8) AND (randomized controlled trial [PTYP] OR drug therapy [SH] OR therapeutic use [SH:NOEXP] OR random* [WORD])
#10 Search (#8) AND (cohort studies [MESH] OR risk [MESH] OR (odds [WORD] AND ratio* [WORD]) OR (relative [WORD] AND risk [WORD])
OR (case control* [WORD] OR case-control studies [MESH]))
#11 Search #9 OR #10

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Strategy adapted from Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Inform Assoc* 1994;1:447–458.

APPENDIX 2. Hormone therapy systematic review flow chart. *Presented in detail in Appendix 3, with reports of 56 case-control, 41 cohort, and 4 randomized trial datasets. †Rejected articles presented data that was

updated in another article or did not provide estimates for “current use” of ET/CHT compared with “never use.”

Appendix 3.

See Appendix 3 table in Figures and Tables section.

Appendix 4. Studies included in other meta-analyses but excluded in this report

Author, Year	Journal	Reason for rejection
Siskind, 1989	Am J Epidemiol	no HT data
Ravnihar, 1979	Eur J Cancer	OCPs not HT
Hislop, 1986	Cancer Detect Preven	no HT data
Lawson, 1981	Am J Epidemiol	no differentiation between OCPs and HT
Byrd, 1977	Ann Surg	case series
Thomas, 1982	J Natl Cancer Inst	case series
Hoover, 1976	N Engl J Med	case series
Craig, 1974	J Natl Cancer Inst	cross-sectional study
Burch, 1975	Front Hormone Res	case series
Dupont, 1999	Cancer	case series
Dupont, 1989	Cancer	case series
La Vecchia, 1995	Br J Cancer	did not differentiate HT into ET and CHT
Levi, 1996	Eur J Cancer Prev	did not differentiate HT into ET and CHT
Lee, 1987	Included in Collaborative Group's meta-analysis	
Paul, 1990	J Natl Cancer Inst	OCPs not HT
Ursin, 1992	Int J Cancer	OCPs not HT
Rookus, 1994	Epidemiology	OCPs not HT
White, 1994	Lancet	OCPs not HT
Brinton, 1995	J Natl Cancer Inst	OCPs not HT
Morabia, 1993	J Natl Cancer Inst	OCPs not HT
Vessey, 1983	Prev Med	OCPs not HT
Ravnihar, 1988	Br J Cancer	OCPs not HT
WHO Collab, 1990	Neoplasia	OCPs not HT
	Br J Cancer	OCPs not HT

OCPs, oral contraceptives; HT, (postmenopausal) hormone therapy; ET, (postmenopausal) estrogen therapy; CHT, (postmenopausal) combined hormone therapy.

APPENDIX 5. Funnel plots for publication bias

FIG. 1.

Current use of estrogen therapy and breast cancer risk. Forest plot of observational studies on the association between “current use” of estrogen therapy and the incidence of breast cancer. Each square represents the point estimate of a study, with the size of the square corresponding to the study size. Thirteen studies (see Table 2 for corresponding references) result in a pooled OR of 1.16 (95% CL 1.06, 1.28).

FIG. 2.

Current use of combined (estrogen-progestogen) hormone therapy and breast cancer risk. Forest plot of observational studies on the association between “current use” of combined therapy and the incidence of breast cancer. Each square represents the point estimate of a study, with the size of the square corresponding to the study size. Eight studies (see Table 2 for corresponding references) result in a pooled odds ratio of 1.39 (95% CL 1.12, 1.72).

FIG. 3.

Comparisons between randomized trials and observational studies of hormone therapy and breast cancer incidence by duration of hormone therapy use. Plots of point estimates and adjusted 95% CL for the association observed in individual randomized trials and pooled observational studies of estrogen therapy and combined estrogen-progestogen therapy.

TABLE 1

Studies included in the meta-analyses

Design/ Quality ^a	Author	Study name or location	Setting	Country	Years enrolled	Study size	Baseline age range (mean), y
CC/G	Stanford 1995 ²¹	Washington state	Population based	United States	1988–90	942	50–64
CC/F	Henrich 1998 ²²	Yale	Hospital based	United States	1987–92	654	47–88 (66)
CC/G	Chen 2002 ²³	Group Health Cooperative	Population based	United States	1990–95	1,397	50–74
CC/G	Newcomb 2002 ²⁴	3 State	Population based	United States	1992–94	10,869	50–79
CC/G	Weiss 2002 ²⁵	CARES	Population based	United States	1994–98	3,823	35–64
Cohort/G	Mills 1989 ²⁶	7th-Day Adventist	Population based	United States	1976–82	20,341	(55.4)
Cohort/G	Colditz 1995 ²⁷	Nurses Health	Population based	United States	1976–86	69,586	30–55
Cohort/G	Folsom 1995 ²⁸	Iowa	Population based	United States	1986–91	41,837	55–69
Cohort/G	Lucas 1998 ²⁹	Osteoporotic Fractures	Population based	United States	1986–92	7,250	>65
Cohort/P	Sourander 1998 ³⁰	Finland	Population based	Finland	1987–95	6,433	57–65
Cohort/G	Schäirer 2000 ³¹	BCDDP ^b	Population based	United States	1973–80	2,082	(58)
Cohort/G	Porch 2002 ¹³	Women's Health Study (WHS)	Population based	United States	1993–00	17,835	>45
Cohort/G	Beral 2003 ¹²	Million Women	Population based	United Kingdom	1996–01	>1 mill	50–64
RCT/G	Hulley 2002 ⁵	HERS II	Population based	United States	1993–00	2,763	(67)
RCT/G	Rossouw 2002 ⁴	Women's Health Initiative	Population based	United States	1993–98	16,608	50–79 (63)

^aCC, case-control; RCT, randomized controlled trial; G, good; F, fair; P, poor; according to rating system of Harris et al.¹⁸^bBreast Cancer Detection Demonstration Project.

TABLE 2
Point estimates and 95% confidence limits for studies included in the meta-analyses

Author/Year	Study	<5 years use	≥5 years use	Study size	Overall
Estrogen therapy					
Mills 1989	7th-Day Adventist	1.88 (1.30, 2.73)	2.05 (1.15, 3.63)	7,839	1.69 (1.12, 2.55)
Colditz 1995	Nurses Health	1.18 (1.02, 1.36)	1.46 (1.28, 1.66)	69,586	1.32 (1.14, 1.54)
Folsom 1995	Iowa	1.45 (1.03, 2.06)	1.21 (0.92, 1.60)	36,942	1.24 (0.99, 1.56)
Stanford 1995	Washington	1.00 (0.69, 1.43)	0.77 (0.53, 1.13)	662	0.90 (0.70, 1.30)
Henrich 1998	Yale	—	—	654	1.52 (0.77, 2.99)
Lucas 1998	Osteoporotic Fractures	—	—	5,278	1.33 (0.75, 2.35)
Sourander 1998	Finland	—	—	6,560	0.57 (0.27, 1.20)
Schraier 2000	BCDDP	—	1.10 (1.00, 1.30)	37,084	1.10 (1.00, 1.30)
Chen 2002	Group Health	1.29 (0.87, 1.91)	1.84 (1.04, 3.27)	757	1.17 (0.85, 1.60)
Newcomb 2002	3 State	1.07 (0.84, 1.37)	1.34 (1.12, 1.59)	9,200	1.25 (1.08, 1.45)
Porch 2002	WHS	0.96 (0.58, 1.58)	0.99 (0.65, 1.53)	12,219	0.96 (0.65, 1.42)
Weiss 2002	CARES	0.92 (0.72, 1.17)	0.81 (0.63, 1.04)	2,354	0.84 (0.67, 1.06)
Beral 2003	Million Women	1.05 (0.69, 1.59)	1.34 (1.24, 1.44)	512,025	1.30 (1.22, 1.38)
Pooled ET		1.16 (1.02, 1.32)	1.20 (1.06, 1.37)	701,160	1.16 (1.06, 1.28)
Combined estrogen-progestin therapy					
Colditz 1995	Nurses Health	—	—	69,586	1.41 (1.15, 1.74)
Stanford 1995	Washington	1.40 (0.70, 2.70)	0.50 (0.10, 1.70)	572	0.90 (0.60, 1.20)
Schraier 2000	BCDDP	1.40 (1.10, 1.90)	—	21,323	1.40 (1.10, 1.90)
Chen 2002	Group Health	—	—	700	1.49 (1.04, 2.12)
Newcomb 2002	3 State	1.32 (1.02, 1.70)	1.50 (1.09, 2.06)	8,490	1.39 (1.12, 1.71)
Porch 2002	WHS	1.11 (0.81, 1.52)	1.76 (1.29, 2.39)	12,211	1.37 (1.05, 1.78)
Weiss 2002	CARES	1.02 (0.69, 1.51)	1.37 (1.06, 1.77)	2,222	1.22 (0.99, 1.50)
Beral 2003	Million Women	1.63 (1.37, 1.93)	2.21 (2.09, 2.34)	540,455	2.00 (1.91, 2.09)
Pooled CHT		1.35 (1.16, 1.57)	1.63 (1.22, 2.18)	655,559	1.39 (1.12, 1.72)

Notes:

- Mills 1989 includes patients followed up until 1982, at which time combined regimen use was negligible in the United States.
- Mills 1989 ET duration estimates based on age-adjusted pooled estimates for <1 and 1–5 years, and 6–10 and ≥10 years.
- Colditz 1995 ET duration estimates based on pooled estimates for data for 1–23 and 24–59 months, and 60–119 and ≥120 months.
- Overall CHT data from Nurses Health Study are also presented in Grodstein 1997 with RR 0.76 (0.56–1.02).
- Folsom 1995 classified as ET (follow-up ended 1991, when most HT was still ET; they estimate <20% CHT).
- Henrich 1998 ET estimate includes approximately 5% of women on CHT.
- Schraier 2000 CHT <5 years estimate based on 3.6 years average use given for overall CHT users.
- Schraier 2000 ET ≥5 years estimate based on 10.3 years average use given for overall ET users.
- Chen 2002 ≥5 years ET estimate based on 60 continuous months of “recent” use in the past 5 years.
- Weiss 2002 ET and CHT <5 year data based on pooled estimates for data from 0–6, 6–23, and 24–59 months.
- Beral 2003 duration data based on pooled estimates for data for <1 and 1–4 years, and 5–9 and ≥10 years.

Appendix 3. All studies that met inclusion criteria

Design	Author	Year	Journal	Setting	Country	Years enrolled	Study size ^a	Baseline age range (mean) , y
CC	Boston Collaborative	1974	N Engl J Med	Hospital based	United States	1972	825	45-69
CC	Brinton	1981	Cancer	Population based	United States	1973-77	1,960	35-74
CC	Brinton	1986	Br J Cancer	Population based	United States	1977-80	4,218	35-74
CC	Brinton	1998	Menopause	Population based	United States	1990-92	1,950	<55
CC	Brownson	1988	Arch Intern Med	Population based	United States	1979-86	2,149	(63)
CC	Byrne	2000	Cancer	Population based	United States	1976-92	743	30-55
CC	Casagrande	1976	J Natl Cancer Inst	Population based	United States	1969-73	266	50-64
CC	Chen	2002	JAMA	Population based	United States	1990-95	1,397	50-74
CC	Daling	2002	Cancer	Population based	United States	1994-98	3,602	<65
CC	Etinger	1996	Obstet Gynecol	Population based	United States	1969-73	454	55-69
CC	Ewertz	1988	Int J Cancer	Population based	Denmark	1983-84	990	<70
CC	Fioretti	1999	Brit J Cancer	Hospital based	Italy	1983-94	1,247	22-80
CC	Grodstein	1997	N Engl J Med	Population based	United States	1976-94	40,000	30-55
CC	Harris	1992	J Natl Cancer Inst	Hospital based	United States	1987-89	1,124	(55)
CC	Henrich	1998	J Clin Epidemiol	Hospital based	United States	1987-92	654	47-88 (66)
CC	Hiatt	1984	Cancer	Population based	United States	1971-79	239	37-56
CC	Hoover	1981	J Natl Cancer Inst	Population based	United States	1969-75	956	(57.3)
CC	Horwitz	1984	Am J Med	Hospital based	United States	1976-79	921	>45 (63)
CC	Huang	1999	Int J Cancer	Hospital based	Taiwan	1995-96	300	26-82 (49.6)
CC	Hulk	1982	Am J Obstet Gynecol	Hospital based	United States	1977-78	772	(64.8)
CC	Jack	1980	Am J Epidemiol	Hospital based	United States	1975-78	236	45-64
CC	Kaufman	1984	JAMA	Hospital based	United States	1976-81	1,317	<70 (51)
CC	Kaufman	1991	Am J Epi	Hospital based	United States, Canada	1980-86	3,763	40-69 (59)
CC	Kelsey	1981	J Natl Cancer Inst	Hospital based	United States	1977-79	1,173	45-74
CC	Kirsh	2002	Cancer Causes Control	Population based	Canada	1995-96	807	20-74
CC	La Vecchia	1992	Int J Cancer	Hospital based	Italy	1983-85	5,606	<75
CC	La Vecchia	1986	Int J Cancer	Hospital based	Italy	1983-85	1,524	<75
CC	La Vecchia	1995	Br J Cancer	Hospital based	Italy	1991-94	5,157	23-74
CC	Levi	1996	Eur J Cancer Prev	Hospital based	Swiss	1990-95	737	23-70
CC	Li	2002	Cancer	Population based	United States	1992-94	769	30-74
CC	Li	2000	Cancer	Population based	United States	1988-90	1,029	50-64
CC	Lipworth	1995	Int J Cancer	Hospital based	Greece	1983-94	2,368	(56.4)
CC	Magnuson	1999	Int J Cancer	Population based	Sweden	1993-95	5,408	50-74
CC	McDonald	1986	Breast Cancer Res Treat	Population based	United States	1977-78	714	50-74
CC	Moorman	2000	Am J Pub Health	Population based	United States	1993-96	804	20-74
CC	Newcomb	2002	Cancer Epidemiol Biomarkers Prev	Population based	United States	1992-94	10,869	50-79
CC	Newcomb	1995	Am J Epidemiol	Population based	United States	1989-91	6,828	<75
CC	Nomura	1985	NCI Monogr	Hospital based	United States	1975-80	344	45-74
CC	Nomura	1986	Int J Cancer	Hospital based	United States	1975-80	344	45-74
CC	Olsson	2001	Br J Cancer	Population based	Sweden	1990-92	29,508	25-65
CC	Palmer	1991	Am J Epidemiol	Population based	Canada	1982-86	1,821	<70
CC	Persson	1997	Int J Cancer	Population based	Sweden	1990-92	2,175	40-74
CC	Pike	2000	Steroids	Population based	United States	1987-96	3,534	55-64
CC	Rohan	1988	Med J Aust	Population based	Australia	1982-84	569	20-74
CC	Ross	2000	J Natl Cancer Inst	Population based	United States	1987-96	3,534	55-64
CC	Ross	1980	JAMA	Population based	United States	1971-77	414	50-74
CC	Sartwell	1977	J Natl Cancer Inst	Hospital based	United States	1969-72	651	20-74
CC	Sherman	1983	Cancer	Hospital based	United States	1974-78	226	(60)
CC	Stanford	1995	JAMA	Population based	United States	1988-90	942	50-64
CC	Talamini	1985	Int J Epidemiol	Hospital based	Italy	1980-83	741	27-79
CC	Tavani	1997	Cancer Epidemiol Biomarkers Prev	Hospital based	Italy	1981-94	5,984	22-74
CC	Weinstein	1993	Int J Epidemiol	Population based	United States	1984-86	1,697	20-79

Design	Author	Year	Journal	Setting	Country	Years enrolled	Study size ^a	Baseline age range (mean), y
CC	Weiss	2002	Obstet Gynecol	Population based	United States	1994-98	3,823	35-64
CC	Wingo	1987	JAMA	Population based	United States	1980-82	3,014	25-54
CC	Wynder	1978	Cancer	Hospital based	United States	1969-75	897	>30
CC	Yang	1992	Cancer Causes Control	Population based	United States	1988-89	1,384	<75
Cohort	Adami	1989	Int J Cancer	Population based	Sweden	1977-87	23,244	35 (54.5)
Cohort	Beral	2003	Lancet	Population based	United Kingdom	1996-01	>1 mill	50-64
Cohort	Bland	1980	Cancer	Population based	United States	N/R	405	37-84
Cohort	Buring	1987	Am J Epidemiol	Population based	United States	1976-80	33,335	30-55
Cohort	Chen	2002	Ann Intern Med	Population based	United States	1980-94	44,187	30-55
Cohort	Colditz	1995	N Engl J Med	Population based	United States	1976-86	69,586	30-55
Cohort	Colditz	1990	JAMA	Population based	United States	1976-86	23,607	30-55
Cohort	Colditz	1992	Cancer Causes Control	Population based	United States	1976-86	23,965	30-55
Cohort	Colditz	2000	Am J Epidemiol	Population based	United States	1976-86	58,520	30-55
Cohort	Delignieres	2002	Climacteric	Population based	France	1975-87	3,175	20-59
Cohort	Folsom	1995	Am J Public Health	Population based	United States	1986-91	41,837	55-69
Cohort	Gambrell	1983	Obstet Gynecol	Hospital based	United States	1975-81	5,563	31-92
Cohort	Gapstur	1999	JAMA	Population based	United States	1986-96	37,105	55-69
Cohort	Gapstur	1995	Cancer Epidemiol Biomarkers Prev	Population based	United States	1986-92	37,105	55-69
Cohort	Goodman	1997	Prev Med	Population based	Japan	1979-81	22,200	30+
Cohort	Hammond	1979	Am J Obstet Gynecol	Hospital based	United States	1974	610	(43)
Cohort	Henderson	1991	Arch Intern Med	Population based	United States	1981-85	8,881	(73)
Cohort	Hunt	1987	Br J Obstet Gynaecol	Menopause clinics	United Kingdom	1978-82	4,544	(50)
Cohort	Hunt	1990	Br J Obstet Gynaecol	Menopause clinics	United Kingdom	1978-82	4,544	(50)
Cohort	Lando	1999	Am J Prev Med	Population based	United States	1971-74	5,761	25-74 (55)
Cohort	Lucas	1998	Am J Epidemiol	Population based	United States	1986-92	7,250	>65
Cohort	Manjer	2001	Int J Cancer	Population based	Sweden	1983-92	5,865	(54.1)
Cohort	Miller	1992	Can Med Assoc J	Population based	Canada	1980-85	39,405	50-59
Cohort	Mills	1989	Cancer	Population based	United States	1976-82	20,341	(55.4)
Cohort	Olsson	2001	Br J Cancer	Population based	Sweden	1990-92	29,508	25-65
Cohort	Persson	1996	Int J Cancer	Population based	Sweden	1977-80	22,579	(54.5)
Cohort	Porch	1999	Cancer Causes Control	Population based	Sweden	1977-80	23,246	<70
Cohort	Porch	2002	Cancer Causes Control	Population based	United States	1993-00	17,835	>45
Cohort	Pukkala	2001	Cancer Causes Control	Population based	Finland	1994-97	94,505	All
Cohort	Risch	1994	Am J Epidemiol	Population based	Canada	1976-90	32,790	43-49
Cohort	Schairer	1994	Cancer Causes Control	Population based	United States	1973-80	42,020	(57.4)
Cohort	Schairer	1997	Epi	Population based	Sweden	1977-87	23,246	>35 (54.5)
Cohort	Schairer	1999	J Natl Cancer Inst	Population based	United States	1973-80	2,675	(58)
Cohort	Schairer	2000	JAMA	Population based	United States	1973-80	2,082	(58)
Cohort	Schuurman	1995	Cancer Causes Control	Population based	Netherlands	1986	62,573	55-69
Cohort	Sellers	1997	Ann Intern Med	Population based	United States	1986-93	35,919	55-69
Cohort	Sourander	1998	Lancet	Population based	Finland	1987-95	6,433	57-65
Cohort	Sturgeon	1995	Epidemiology	Population based	United States	1973-80	49,017	(57.4)
Cohort	Vakil	1983	Cancer Detect Prev	20 private practices	Canada	1960-70	1,483	32-62
Cohort	Willis	1996	Cancer Causes Control	Population based	United States	1982-91	676,526	59.2
Cohort/CC	Bergkvist	1989	N Engl J Med	Population based	Sweden	1977-84	23,244	(53.7)
RCT	Hulley	1998	JAMA	Population based	United States	1993-98	2,763	(67)
RCT	Hulley	2002	JAMA	Population based	United States	1993-00	2,763	(67)
RCT	Nachtigal	1992	Obstet Gynecol	Hospital based	United States	1965-88	164	(55)
RCT	Rossouw	2002	JAMA	Population based	United States	1993-98	16,608	50-79

CC, case-control; RCT, randomized controlled trial.

^aStudy size = number of breast cancer cases.