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Current breast cancer risks of hormone replacement therapy in postmenopausal women

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Abstract

The controversies surrounding hormone replacement therapy have left many women confused and afraid. Providers have been faced with long-standing assumptions challenged by an abundance of new data in the past few years, with little guidance on how to interpret these findings. The objective of this paper is to provide a framework for understanding breast cancer risk associated with postmenopausal hormone replacement therapy, with a particular focus on how observational studies and randomised trials provide complementary information. This framework considers the data on risks of various hormonal preparations, the profiles of women at risk, and ends with an expert opinion in this context.

Keywords

breast cancer; estrogen; hormone replacement therapy; progestin

1. Introduction

Menopausal disorders related to estrogen deficiency span the spectrum from short-term symptoms to long-term conditions. Short-term symptoms consist of hot flushes, night sweats, palpitations, irritability and anxiety. Chronic conditions include osteoporotic fractures, cardiovascular disease, colon cancer and dementia. Of all women going through menopause, 80 - 90% will experience symptoms, and 20 - 40% will seek medical care as a result [1].

Estrogen replacement has been found to be effective in the treatment of vasomotor symptoms of menopause, with considerable improvements in symptom frequency and severity within weeks of hormone replacement therapy (HRT) initiation [2]. Symptom relief has been demonstrated with low doses of estrogen, combined estrogen and progestin therapy, and transdermal preparations of estrogen [3,4].

Although controversies surround the discussion of potential harms associated with postmenopausal hormonal replacement, many experts concur that the short-term use of hormone replacement for the treatment of vasomotor symptoms is appropriate [4,5]. With longer use, breast cancer is a primary concern among women on treatment.

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Most perimenopausal women will only experience vasomotor symptoms for a few months. However, some will continue to experience bothersome symptoms for > 10 years. The relative benefits and safety of HRT changes as the duration of use increases. This paper summarises the relative breast cancer risks of estrogen and combined estrogen/progesterone replacement in postmenopausal women [4,6,7].

2. Breast cancer epidemiology, risk factors and mechanisms of disease

2.1 Risk factors

Breast cancer is one of the most common cancers affecting women [8]. Known risk factors for breast cancer include age, obesity, alcohol consumption, breast feeding, genetic predisposition, family history, low or late parity, late menopause, oral contraceptive use and postmenopausal hormone replacement use [9-12]. The breast cancer risk from hormone therapy alone is comparable to that from early menarche or late parity [13], and the annual risk from postmenopausal HRT is comparable to that of each year of delayed menopause [12]. When evaluating the risk of hormone replacement, one must attempt to control for all other confounding risk factors (Table 1). These risk factors are consistently noted in observational studies and randomised controlled trials [12,14-18].

Many of the risks point to a hormonal component in general, and a relationship to estrogen in particular. In fact, epidemiological data suggest a dose-response relationship between the serum level of endogenous sex hormones and the risk of breast cancer [9,19,20]. In addition, some of the therapies for breast cancer target estrogen receptors, further strengthening the causal links between estrogen and breast cancer [21].

2.2 Potential mechanisms of disease: estrogen

The exact mechanism for the association of estrogen to breast cancer has not been fully elucidated. The promotional theory argues that when estrogen binds estrogen receptors, it stimulates cellular proliferation, thus allowing for errors in DNA replication with each cycle. If these errors are not repaired, these mutations lead to transformation that results in breast cancer [22,23]. Another theory argues that estrogen promotes already existing tumours and is not oncogenic. This is supported by the observation that incident cases in hormone users are observed after as short as 1 year and that the risk returns to baseline after discontinuation of HRT [14]. A third theory suggests that the metabolites of oral estrogen react with breast tissue DNA to have an oncological effect [24]. It is very possible that more than one of these mechanisms are involved in breast cancer development [25]. So far, there is still no conclusive data demonstrating that estrogen is a cancer-causing agent [26].

2.3 Potential mechanisms of disease: progestin

Many questions have been raised regarding the role of progesterone in breast cancer development. When combined estrogen/progestin therapy is used, the risk of breast cancer is consistently higher than that of estrogen alone use. Many studies have examined the type of progestin (natural versus synthetic), method of administration (sequential versus continuous) and whether the progestin is testosterone-derived. Some authors have claimed that only the continuous method of administration (e.g., conjugated equine estrogen [CEE] used in the Women's Health Initiative [WHI]) has been linked to increased risk [10,25,27]. In a meta-analysis of observational studies, Campognoli *et al.* suggest that the relative risks of continuous progestin are generally two to three times higher than that of cyclic progestin regimens [28]. Continuous progestin inhibits the sloughing of mammary epithelium that occurs during the withdrawal phase of cyclic regimens [28]. This leads to amenorrhea - which in fact may increase medication adherence of patients - ultimately leading to higher effective exposure to the drug [29].

Different derivatives of progesterone seem to also confer different risks. Some authors point to the non-progesterone properties of synthetic progestins that potentiate breast tissue proliferation, decrease insulin sensitivity and increase insulin-like growth factor activity [28, 30]. A French study showed that natural progestins did not significantly increase breast cancer risk when compared with synthetic progestins for > 2 years of use [31]. Beneficial effects of natural progestins on the endometrium, brain, macrophages and the arterial wall have been reported [32]. Testosterone-derived progestins (e.g., 19-nortesterone) have greater androgenic and estrogenic activities and, thereby, may confer increased risk of breast cancer [10,17]. Levononorgestrel is more androgenic compared with norethisterone, which is more androgenic than medroxyprogesterone acetate (MPA); MPA was the progestin used in the WHI and Heart and Estrogen/Progestin Replacement Study (HERS).

The exact mechanism of how progesterone increases breast cancer is unknown [25]. Maximum mitotic activity in breast tissue occurs in the mid to late luteal phase, at the time of maximum progesterone level [33]. Some claim that the actions of progesterone on estrogen-induced cellular mitotic activity is antagonistic [34], and others claim that it is synergistic [35].

3. Estrogen alone and combined estrogen/progestin replacement therapy

3.1 Pattern of use

There was an exponential increase in the use of postmenopausal HRT from the 1980s to the 1990s [36]. By 2002, hormone replacement therapies were among the most prescribed medications of all classes [37,38].

Much has been published on the risk of breast cancer caused by postmenopausal HRT and discrepancies in results exist. Nonetheless, the majority of the randomised controlled trials, most large observational studies and meta-analyses show a trend towards a small but significant increase in breast cancer risk associated with HRT use. Much of this data was well-known to physicians and the public by the 1990s. Publication of HERS in 1998 and the WHI trial in 2002 did not demonstrate the expected cardiovascular benefits of HRT, and in fact resulted in a global index where harm exceeded benefit [39,40]. In the year immediately following publication of the WHI, HRT prescriptions decreased by > 50% [41].

3.2 Data from observational studies

Observational studies assessing the risk of HRT may classify women in terms of ‘ever’ users, ‘current’ users, or ‘past’ users, compared with ‘never’ users. A woman who has never used any form of hormone therapy in her lifetime is referred to as a ‘never’ user, whereas an ‘ever’ user has used some form of hormone therapy at any point in her life, and a ‘past’ user has taken HRT, but does not at the time of the study. ‘Ever’ and ‘past’ use comparisons rely on a woman’s memory, are prone to all the flaws of recall bias and have the potential of including past oral contraceptive use. A ‘current’ use definition, in contrast, compares women who are actively using HRT at the time of the study with those who have never used HRT, and, hence, is less prone to recall bias. Although use of this definition attempts to eliminate recall bias, it does limit comparisons of risks associated with cumulative life-time use. However, ‘current’ use is also most similar to the HRT regimen of randomised controlled trials, and makes comparisons between observational studies using such a definition and randomised trials more valid.

One of the early major observational studies on the association between HRT use and breast cancer was the Nurses’ Health Study, published in 1995, which followed > 100,000 healthy women of 30 - 50 years of age at enrolment [42]. The investigators found that the risk of ≥ 5 years of ‘current’ use of HRT was 1.2 to 2 times greater than that of ‘never’ users.

A Collaborative Group study published in 1997 attempted to resolve discrepancies seen in prior data [12]. They reanalysed 51 studies from 21 different countries and included > 52,705 patients. Overall, the risk for 'ever' compared with 'never' users was 1.14, and 1.35 for users of > 5 years duration (1.35 for estrogen only and 1.53 for combined therapy). However, these conclusions have little relevance today, as 80% of the studies included were published in the 1980s, when estrogen therapy alone was the accepted practice, even for women with an intact uterus, and higher doses of estrogen were used in available formulations.

Other smaller observational studies also showed a smaller but significant increase in the risk of breast cancer in women using estrogen alone or combined estrogen/progestin therapy [10, 11,15].

The Million Women Study, published in 2003, was one of the largest studies of breast cancer incidence [14]. It included > million UK women of 50 - 64 years of age who presented for a national mammography screening program. Women were followed for an average of 2.6 years and data was collected from questionnaires that asked specifics of hormone use, menopausal status and other relevant information. When compared with 'never' users, the increased risk of estrogen therapy alone was 1.05 and 1.34 for 'current' users of less than and more than 5 years, respectively. For 'current' users of combined therapy, the risk was 1.63 and 2.21 for less than and more than 5 years use, respectively. The risk for combined therapy observed was higher than in most other observational studies, which may in part be explained by the greater use of testosterone-derived progestins in Europe.

The authors' own meta-analysis of observational studies looked at the risk of 'current' use for less than and greater than 5 years duration [43]. The summary risk of 'current' estrogen therapy use was 1.16 and 1.20 for less than and more than 5 years use. The 'current' risk for combined therapy was 1.35 and 1.63 for less than and more than 5 years use, respectively.

3.3 Data from randomised controlled trials

The first large randomised controlled trial of HRT was published in 1998 [40]. The HERS trial compared users of CEE (0.625 mg/day plus MPA 2.5mg/day continuously) to placebo in 2763 postmenopausal women with an average age of 67 and established coronary artery disease. It showed that, in addition to no cardiovascular benefit and more thromboembolic events, HRT was associated with a non-significant trend toward higher breast cancer risk (relative risk [RR] =1.37; 95% CI = 0.84 - 1.94).

The WHI trial randomised > 16,000 postmenopausal women with an average age of 63.3 and no history of coronary artery disease to receive either CEE 0.625 mg/day combined with continuous MPA 2.5 mg/day, or placebo [39,44]. When followed for an average of 5.6 years, the RR of breast cancer was 1.24. *Post hoc* subgroup analyses showed that, even after controlling for an extensive list of potential confounders, a significantly increased risk was seen among women who were users of HRT before entering the study [45]. This may suggest that it is prolonged exposure (i.e., cumulative dose) of HRT that considerably increases risk.

Overall, there are many similarities between the risks reported in observational studies and randomised controlled trials. The summary risks from the above meta-analysis of observational studies [43] correlate well with those from randomised controlled trials [46] (Figure 1).

3.4 Data on estrogen alone versus combined estrogen/progestin therapy

Many studies attempt to separate the risk according to the use of combined estrogen/progestin therapy versus that of unopposed estrogen alone. Large observational studies and recent randomised controlled trials have shown that the risk with combined therapy is higher than

that of unopposed estrogen therapy alone [15,17,39,42,44]. These findings are further supported by meta-analysis [28,43].

Data regarding the risk of unopposed estrogen therapy alone have been less robust than for combined therapy. Some large observational studies, such as the Collaborative, the Million Women Study and the Nurses' Health Study, showed increased risk with unopposed estrogen use [12,14,42]. However, there are many observational studies that found the risk to be small or negligible [11,17,47-50]. A meta-analysis of observational studies found the risk for 'current' estrogen use compared to 'never' use was 1.16 [43]. Another recent meta-analysis found that the pooled odds ratio was 1.08 [27]. The estrogen-alone arm of the WHI, published in 2004, included postmenopausal women in their 60s with no prior coronary artery disease. Women were randomised to receive CEE 0.625 mg/day or placebo. The investigators recently reported that the risk of breast cancer was non-significantly lower in the estrogen group at 6.8 years (RR = 0.77; 95% CI = 0.57 - 1.06) and 7.1 years (RR = 0.80; 95% CI = 0.62 - 1.04) [51,52].

Given the data available at that time, the United States Preventive Services Task Force in 2005 concluded that it could not assess the effects of unopposed estrogen on the incidence of breast cancer [53]. Table 2 and Figure 1 illustrate the odds ratios for estrogen and for combined estrogen/progestin therapy from major observational studies and randomised trials.

3.5 Duration of use

The risk of breast cancer from HRT is related to the duration of use, and becomes more significant after 5 years of use [12,14,18,39,42,54]. A 1991 meta-analysis showed a clear duration-risk response [55]. The annual increase in risk found in the Collaborative study was 2.3% per year after 5 years of use [12]. Subsequent meta-analysis found a duration-response relationship for both combined as well as unopposed estrogen [43]. The RR from this meta-analysis for combined estrogen/progestin therapy of < 5 years use was 1.35 (1.16 - 1.57) and for > 5 years of use was 1.63 (1.22 - 2.18). The RR for estrogen therapy alone of < 5 years use was 1.16 (1.02 - 1.32) and for > 5 years use was 1.20 (1.06 - 1.37). The WHI trial showed a similar strong association, and found an RR of 2.14 (1.15 - 3.94) with < 5 years of previous use and an RR of 4.61 (1.01 - 21.02) with 5 - 10 years of use [39].

A recent subgroup analysis of prior hormone users in the WHI further supports higher breast cancer risk with increased cumulative exposure [48]. This study looked at the differences in breast cancer risk attributed to estrogen/progestin among prior hormone users and never users. It tried to address whether this difference can be explained by potential confounders of prior use and, if not, to determine if this supports the hypothesis of increased risk with longer duration of exposure. Women who used hormone therapy in the past were different from those who had never used hormone therapy. They were on average younger, more often white, had more education, had a lower BMI, were more physically active and more likely to have moderate to severe vasomotor symptoms. After controlling for an extensive list of potential confounders, the estrogen/progestin hazard ratio for prior users was significantly higher than for women without prior HT use.

3.6 Dose and route of administration

Another way to dissect the data of risk associated with HRT use is to look at whether the dose of hormone or the route of administration made a difference in the subsequent risk of breast cancer. The Million Women Study, as well as the Collaborative analysis, did not find that lower doses of estrogen conferred a lower risk of breast cancer [12,14]. Different types of oral estrogens have not been shown to affect the risk [46]. Many argue that CEE/MPA and CEE, which were used in the randomised controlled trials, do not equate to all hormones used for

HRT, and that the risks associated with transdermal, intranasal or 'natural' estrogens may be lower. These hypotheses remain unsubstantiated.

4. Conclusion

A careful review of the evidence suggests that HRT in postmenopausal women is clearly associated with an increased risk of breast cancer, and that this risk is higher for combined estrogen/progesterone therapy than for unopposed estrogen therapy alone.

When evaluating the risk and benefits of HRT, one must take into consideration all the outcomes, as well as patient-specific treatment goals. Outcomes most affected by hormone therapy include cardiovascular, cerebrovascular and thromboembolic events, breast, colon and endometrial cancers, and fractures associated with osteoporosis.

The increase in cardiovascular risk seen in the WHI that so dramatically changed the use of HRT needs to be considered critically. Cardiovascular events in both arms of the WHI varied according to a woman's age. For combined therapy, the RR for cardiovascular outcomes increased with age since menopause (although this was not statistically significant). For women who were < 10 years since menopause, the RR for cardiovascular outcomes was 0.89; from 10 - 19 years since menopause it was 1.22; and for women > 20 years since menopause it was 1.71. The cardioprotective effect in the estrogen-alone arm of the WHI was greater for women who were younger at the start of the study. For women of 50 - 59 years of age, the RR was 0.56, for women of 60 - 69 years of age it was 0.92, and for those women of 70 - 79 of age it was 1.04 [39,44,51,52].

Results of the WHI cannot be generalised to all postmenopausal women. For a woman in her mid-fifties, beginning menopause with severe vasomotor symptoms, the global index of risk will be very different from that reported in the WHI. In fact, the WHI data is insufficient and under-powered to make conclusions regarding cardiovascular risk in this younger age group [56]. The older age of women in the WHI may account for some of the differences in cardiovascular events between past observational studies and recent randomised controlled trials. The Nurses' Health Study included women enrolled while in their 30s to 50s and found almost a 50% decrease in cardiovascular events [42]. Although selection bias (e.g., survivor effect) certainly played a role in observational studies examining cardiovascular risk, considerable differences in enrolment characteristics cannot be discounted.

5. Expert opinion

Decisions on the use of HRT must be made after thorough consideration of a woman's preferences, age, time since menopause, estimated duration of use, and other known risk factors.

One such important consideration is whether a woman has had a hysterectomy. Approximately 20 million women in the US have had a hysterectomy, making it the second-most performed major surgery for women of reproductive age in the US. According to the Centers for Disease Control and Prevention, the rate of hysterectomy was 5.5 per 1000 women from 1994 to 1999 [101]. The only randomised controlled trial that studied women with hysterectomies is the estrogen arm of the WHI, and it only evaluated use of CEE 0.625 mg/day. One must rely on observational data when evaluating risk and benefits for women with hysterectomies.

What advice do we give to perimenopausal women with vasomotor symptoms? Hormone replacement remains the most effective method of providing predictable relief of unwanted hot flushes. Many experts in the field still believe that hormone therapy is safe and effective when used for this purpose, for short durations and at low doses [4,57,58]. The risks of hormone

use must be presented to the patient, who may have a different valuation or level of acceptable risk than perceived by a provider. Women studied in the HERS and the WHI were older, mostly > 10 years postmenopausal, asymptomatic and had poor compliance. Observational studies provide more clinically relevant data for postmenopausal women with vasomotor symptoms.

Future investigations, especially well-conducted observational studies, should examine risks for postmenopausal women with vasomotor symptoms given HRT for short durations, standardised doses of natural estrogens and progestins, and different routes of hormone administration.

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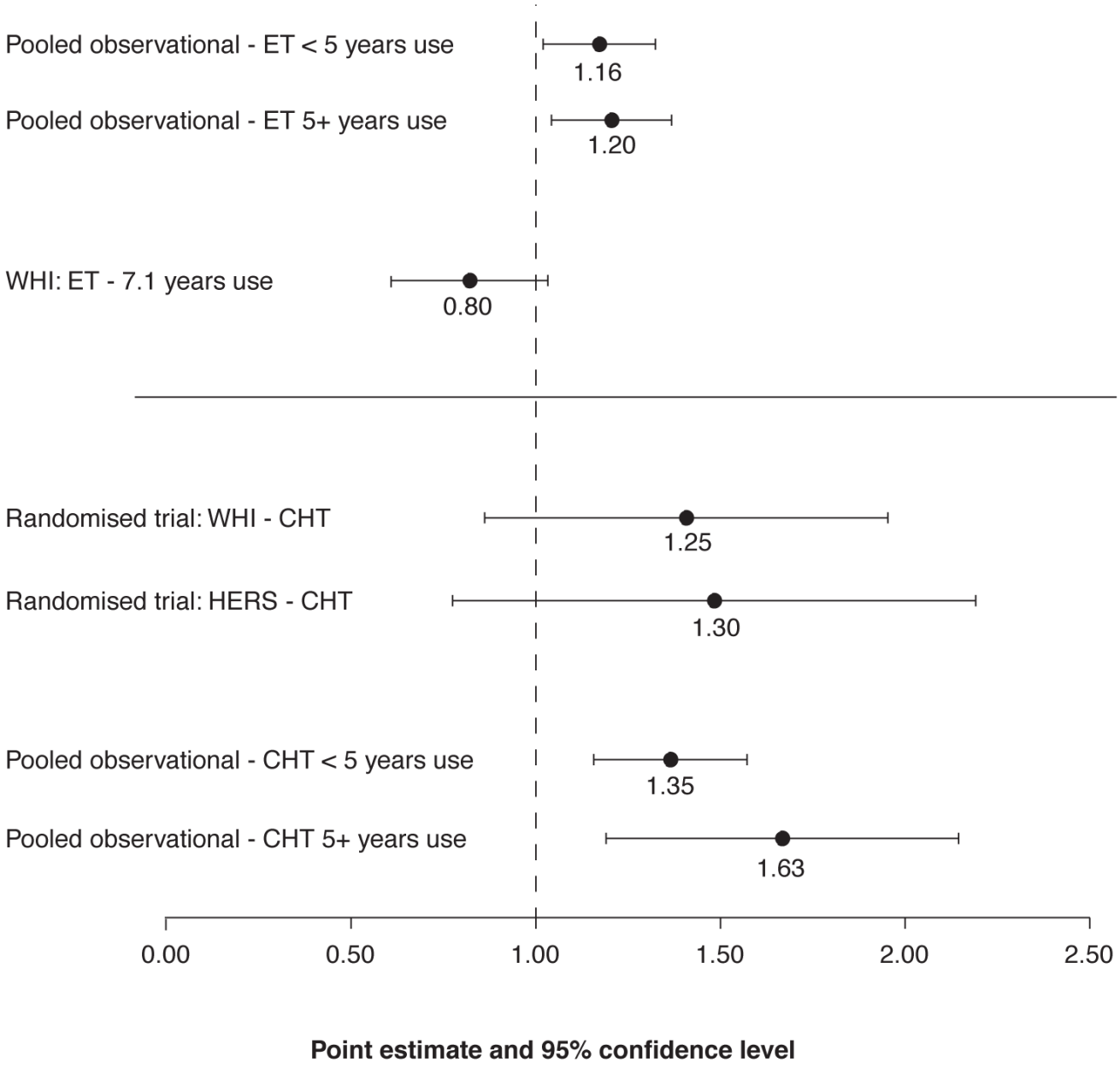

Figure 1. Breast cancer risks by duration of use and type of study

CHT: Combined hormone therapy; ET: Estrogen therapy; HERS: Heart and Estrogen/ Progestin Replacement Study; WHI: Women's Health Initiative.

Table 1

Risk factors for breast cancer and their relative risks

Risk factor	Low-risk group	High-risk group	Relative risk
Age	30 - 34	70 - 74	17.0
Age at menarche	> 14	< 12	1.5
Alcohol	No use	Use	1.22
Use of oral contraceptives	Never	Previous or current	1.07 - 1.20
Age at birth of first child	< 20	> 30	1.9 - 3.5
Breast feeding (months)	> 16	0	1.37
Parity	> 5	0	1.4
Age at oophorectomy	< 35	N/A	3.0
Age at menopause	< 45	> 55	2.0
Postmenopausal BMI	< 22.9	> 30.7	1.6
BRCA1 gene	No	Yes	1.65
BRCA2 gene	No	Yes	1.45
Family history	No	Yes	2.6

Data from [9,59,60].

BMI: Body mass index.

Table 2

Observational studies of hormone replacement therapy and breast cancer

Author/year	Study	< 5 years use	≥ 5 years use	Study size	Overall odds ratio
Estrogen therapy alone					
Mills (1989) [62]	7th-day Adventist	1.88 (1.30 - 2.73)	2.05 (1.15 - 3.63)	7839	1.69 (1.12 - 2.55)
Colditz (1995) [42]	Nurses' Health‡	1.18 (1.02 - 1.36)	1.46 (1.28 -1.66)	69,586	1.32 (1.14 - 1.54)
Folsom (1995) [63]	Iowa	1.45 (1.03 - 2.06)	1.21 (0.92 - 1.60)	36,942	1.24 (0.99 - 1.56)
Stanford (1995) [64]	Washington	1.00 (0.69 - 1.43)	0.77 (0.53 - 1.13)	662	0.90 (0.70 - 1.30)
Henrich (1998) [65]	Yale	-	-	654	1.52 (0.77 - 2.99)
Lucas (1998) [66]	Osteoporotic Fractures	-	-	5278	1.33 (0.75 - 2.35)
Sourander (1998) [67]	Finland	-	-	6560	0.57 (0.27 - 1.20)
Schairer (2000) [15]	BCDDP	-	1.10 (1.00 - 1.30)	37,084	1.10 (1.00 - 1.30)
Ross (2000) [17]	SEER	1.04 (0.87 - 1.25)	1.02 (0.85 - 1.21)	3047	1.03 (0.89 - 1.19)
Chen (2002) [47]	Group Health	1.29 (0.87 - 1.91)	1.84 (1.04 - 3.27)	757	1.17 (0.85 - 1.60)
Newcomb (2002) [68]	3 state	1.07 (0.84 - 1.37)	1.34 (1.12 - 1.59)	9200	1.25 (1.08 - 1.45)
Porch (2002) [50]	WHS	0.96 (0.58 - 1.58)	0.99 (0.65 - 1.53)	12,219	0.96 (0.65 - 1.42)
Weiss (2002) [69]	CARES	0.92 (0.72 - 1.17)	0.81 (0.63 - 1.04)	2354	0.84 (0.67 - 1.06)
Beral (2003) [14]	Million Women	1.05 (0.69 - 1.59)	1.34 (1.24 - 1.44)	512,025	1.30 (1.22 - 1.38)
Li (2003) [70]	Seattle	0.8 (0.6 - 1.2)	1.2 (0.8 - 1.7)	1982	1.0 (0.8 - 1.3)
POOLED*		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) [42]	Nurses' Health‡	-	-	69,586	1.41 (1.15 - 1.74)
Stanford (1995) [64]	Washington	1.40 (0.70 - 2.70)	0.50 (0.10 - 1.70)	572	0.90 (0.60 - 1.20)
Schairer (2000) [15]	BCDDP	1.40 (1.10 - 1.90)	-	21,323	1.40 (1.10 - 1.90)
Ross (2000) [17]	SEER	1.11 (0.91 - 1.36)	1.33 (1.01 - 1.74)	2406	1.18 (0.99 - 1.40)
Chen (2002) [47]	Group Health	-	-	700	1.49 (1.04 - 2.12)
Newcomb (2002) [68]	3 state	1.32 (1.02 - 1.70)	1.50 (1.09 - 2.06)	8490	1.39 (1.12 - 1.71)
Porch (2002) [50]	WHS	1.11 (0.81 - 1.52)	1.76 (1.29 - 2.39)	12,211	1.37 (1.05 - 1.78)
Weiss (2002) [69]	CARES	1.02 (0.69 - 1.51)	1.37 (1.06 - 1.77)	2222	1.22 (0.99 - 1.50)
Beral (2003) [14]	Million Women	1.63 (1.37 - 1.93)	2.21 (2.09 - 2.34)	540,455	2.00 (1.91 - 2.09)
Li (2003) [70]	Seattle	1.3 (0.9 - 2.0)	1.2 (0.8 - 1.7)	1982	1.7 (1.3 - 2.0)
POOLED*		1.35 (1.16 - 1.57)	1.63 (1.22 - 2.18)	655,559	1.39 (1.12 - 1.72)

[*] Pooled estimates do not include data from Ross (2000) or Li (2003), which compared ever use to never use; all other studies included in the pooled estimate compare current users to never users.

[≠] Nurses' Health Study data was also reported in [61], but only included data on estrogen therapy, not combined hormone therapy. Hence, for purposes of the pooling, the data from Colditz (1995) was retained.