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Breast cancer risk with postmenopausal hormonal treatment

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This review was designed to determine from the best evidence whether there is an association between postmenopausal hormonal treatment and breast cancer risk. Also, if there is an association, does it vary according to duration and cessation of use, type of regimen, type of hormonal product or route of administration; whether there is a differential effect on risk of lobular and ductal cancer; and whether hormone treatment is associated with breast cancers that have better prognostic factors? Data sources for the review included Medline, the Cochrane Database of Systematic Reviews (Cochrane Library, 2005) and reference lists in the identified citations. Eligible citations addressed invasive breast cancer risk among postmenopausal women and involved use of the estrogen products with or without progestin that are used as treatment for menopausal symptoms. Abstracted data were demographic groupings, categories of hormone use, categories of breast cancer, two-by-two tables of exposure and outcome and adjusted odds ratios, relative risks (RRs) or hazard rates. Average estimates of risk were weighted by the inverse variance method, or if heterogeneous, using a random effects model. The average risk of invasive breast cancer with estrogen use was 0.79 [95% confidence interval (95% CI) = 0.61–1.02] in four randomized trials involving 12 643 women. The average breast cancer risk with estrogen–progestin use was 1.24 (95% CI = 1.03–1.50) in four randomized trials involving 19 756 women. The average risks reported in recent epidemiological studies were higher: 1.18 (95% CI = 1.01–1.38) with current use of estrogen alone and 1.70 (95% CI = 1.36–2.17) with current use of estrogen–progestin. The association of breast cancer with current use was stronger than the association with ever use, which includes past use. For past use, the increased breast cancer risk diminished soon after discontinuing hormones and normalized within 5 years. Reasonably adequate data do not show that breast cancer risk varies significantly with different types of estrogen or progestin preparations, lower dosages or different routes of administration, although there is a small difference between sequential and continuous progestin regimens. Epidemiological studies indicate that estrogen–progestin use increases risk of lobular more than ductal breast cancer, but the number of studies and cases of lobular cancer remains limited. Among important prognostic factors, the stage and grade in breast cancers associated with hormone do not differ significantly from those in non-users, but breast cancers in estrogen–progestin users are significantly more likely to be estrogen receptor (ER) positive. In conclusion, valid evidence from randomized controlled trials (RCTs) indicates that breast cancer risk is increased with estrogen–progestin use more than with estrogen alone. Epidemiological evidence involving more than 1.5 million women agrees broadly with the trial findings. Although new studies are unlikely to alter the key findings about overall breast cancer risk, research is needed, however, to determine the role of progestin, evaluate the risk of lobular cancer and delineate effects of hormone use on receptor presence, prognosis and mortality in breast cancer.

Key words: breast cancer/duration of use/estrogen/progestin/recency/relative risk

Introduction

A serious adverse event associated with treatment of a common disorder has public health significance. The incidence of breast cancer, which is the most common cancer in women, is highest after the menopause. Menopausal symptoms affect more than 50% of women, and estrogen treatment (E) with or without a progestin is the most effective therapy (Greendale *et al*., 1998). After years of uncertainty, a 1997 review defined the association between hormonal treatment and breast cancer risk based on data from 51 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Breast cancer risk increased by 2.3% per

year of hormone use, compared with an increased risk of 2.8% per year of natural delay in the onset of the menopause. The increased risk of breast cancer was not significant until 5 years of use and declined within a few years of discontinuing hormones. Breast cancers usually take more than 5 years to develop from early carcinogenesis to the clinical stage, therefore, it is thought that hormones do not initiate new tumours, but may increase (promote) the likelihood of tumour growth at a late stage of carcinogenesis (La Vecchia, 2004).

An association between breast cancer and hormone use is plausible because breast cancer incidence is increased by hormonal factors, such as early menarche, delayed menopause and obesity, as well as non-hormonal factors, such as age (by far the most important), breast mass and adult height (ESHRE Capri Workshop Group, 2004). The important hormonal factors are estrogen, progestin, prolactin and other hormones that stimulate breast epithelial growth, thus accumulating DNA damage and increasing the risk of breast cancer (Pike *et al*., 1993; The Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Missmer *et al*., 2004). Early menarche and late menopause increase cancer risk because more menstrual cycles increase exposure to estrogen and progestin and breast gland growth. Breast cancer risk is higher with higher endogenous concentrations of estradiol, a risk that is highest in association with receptor positive and *in situ* cancers (Missmer *et al*., 2004). Breast cancer risk is reduced by hormonal factors that oppose epithelial cell growth: pregnancy and lactation induce terminal differentiation of cells in the breast epithelium and remove those cells from the synthetic pool (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

Since the collaborative report, both randomized controlled trials (RCTs) and epidemiological studies have reported on clinical and epidemiological issues that arise from this association. Several reviews have been published, although there are differing views on the validity of meta-analysis for observational data. A 2001 qualitative review appraised the risk estimates from studies of association, examining the distribution, pattern of the estimates and the strength of the association (Bush *et al*., 2001). The authors found little consistency in breast cancer risks of hormone users compared with non-users or in risks by the duration of use. They did find a consistently lower risk of death from breast cancer in hormone users compared with non-users and concluded that the evidence did not show an increased breast cancer risk with estrogen use or combined hormone estrogen–progestin therapy. A 2002 review summarized evidence on HRT and risks of breast cancer, associations with prognosis and breast cancer mortality and HRT interactions with risk factors, such as family history and benign breast disease (Marsden, 2002). It found that breast cancer risk was increased only for long-term use of HRT and falls when use ceases. Systematic bias and the lack of adequately powered studies prevented any firm clinical recommendations about the prescription of differing HRT regimens and risk or the effect of HRT on breast-cancer proliferation and mortality. A 2002 review of postmenopausal hormone therapy prepared for the U.S. Preventive Services Task Force included a section on breast cancer risk (Nelson *et al*., 2002). It cited three meta-analyses of epidemiological studies including the collaborative analysis and stated that the breast cancer risk was increased with current but not ever use of estrogen. The 2002 Women's Health Initiative (WHI) study (Writing Group for the Women's Health Initiative Investigators, 2002) was cited as evidence of the increased risk with estrogen–progestin. Published effects on breast cancer mortality suggested no increase or a decrease, but effects from duration of use were mixed (Nelson *et al*., 2002).

This review will undertake to provide a quantitative summary of the evidence to date on the breast cancer risk with current, ever and past use of estrogen or estrogen–progestin as treatment for menopausal symptoms. The review also will address effects on risk associated with duration and discontinuation of hormone use. In addition, it will explore whether data exist to show a differential effect from use of different regimens, hormone products and routes of administration or from lower dosages. It will further evaluate evidence that appears to show a differential effect on lobular and ductal cancer incidence and evidence on whether the associated breast cancers have better prognostic factors. The review will not cover studies on the safety of using hormone treatment in women who have been treated for breast cancer, and it does not cover the interaction of hormone treatment with family history of breast cancer as each of these subjects merits a free-standing review.

Methods

This is primarily a narrative review, because it covers several clinical questions, but it will use methods associated with synthetic reviews. The clinical question and the specific methods are identified in each section. Data from English publications were identified in searches of Medline, the Cochrane Database of Systematic Reviews (Cochrane Library, 2004), the authors' files and references from relevant articles. Abstracts were not eligible, and no attempt was made to contact authors. Eligible studies addressed invasive breast cancer risk associated with use of estrogen products with or without progestin for treatment of menopausal symptoms. Studies were identified as RCTs or epidemiological studies, but not otherwise categorized by quality criteria. We abstracted data on demographic groupings, types of hormone use, categories of breast cancer, two-by-two tables of exposure and outcome and adjusted relative rates. Abstraction was not done in duplicate or audited. An adjustment for zero cells involved adding 0.5 to all cells of the two-by-two table. Odds ratios and hazard ratios were considered to be equivalent to relative risks (RRs). Average estimates of RR and/or risk difference were calculated, weighted by the inverse variance method. When the risk estimates were heterogeneous, the random effects model was used (Deeks *et al*., 2001). I squared was estimated to describe the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins *et al*., 2003). Differences between groups of risk estimates were evaluated by partitioning the heterogeneity statistic Q into the heterogeneity explained by the groups and the residual heterogeneity (Deeks *et al*., 2001). In these categorical analyses, the *P* values represent the significance of the heterogeneity between groups. Two questions were considered to be primary analyses: the effects of estrogen alone or estrogen–progestin on invasive breast cancer risk in RCTs. Other analyses are secondary analyses, and the *P* values should be interpreted with caution.

Clinical questions

RCTs and breast cancer risk with menopausal hormone use

Question: In postmenopausal women, does use of estrogen or estrogen–progestin hormones increase the risk of invasive breast cancer?

To address this question, only RCTs in which the intervention was estrogen or estrogen–progestin were considered. The two WHI RCTs were the only trials that were designed with sufficient power to evaluate as a primary outcome the effect of menopause treatment on breast cancer risk in healthy women (Chlebowski *et al*., 2003; Anderson *et al*., 2004). The remaining trials evaluated hormone treatment for primary or secondary prevention of cardiovascular disease in women who were known to have or be at high risk of cardiovascular disease; in these trials, breast cancer was a secondary outcome. Knowing of no effect of cardiovascular disease on breast cancer risk, we combined trials among healthy women with those among women with cardiovascular disease. The trials are reviewed according to exposure: estrogen alone or estrogen with progestin (Table I).

Unopposed estrogen and risk of invasive breast cancer

Four estrogen trials (ETs) contribute to this estimate (Table I). The WHI ET and placebo trial involved 10 739 women who were mainly healthy and free of menopausal symptoms (Anderson *et al*., 2004). The women were randomly allocated to receive either 0.625 mg of conjugated equine estrogens (CEEs) or placebo daily. After an average follow-up of 6.8 years, there were 94 and 124 cases of invasive breast cancer (26 and 33 per 10 000 woman-years) in the ET and placebo groups, respectively. The lower risk with ET was not significant [relative hazard (RH) = 0.77, nominal 95% confidence interval (95% CI) = 0.59–1.01]. Although this estimate has a high level of validity, even in this large trial there were only 94 exposed cases, which was insufficient to provide the precision that is needed to distinguish between no change in breast cancer risk or reduced breast cancer risk.

Three other trials involved patients with cardiovascular disease. The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) randomized 222 women with low density lipoprotein cholesterol levels greater than 3.37 mmol/l to receive either micronized estradiol 17 β 1 mg or placebo daily for 2 years (Hodis *et al*., 2001). One placebo recipient developed breast cancer. The Women's Estrogen for Stroke Trial (WEST) involved 664 women with a recent ischemic stroke who received micronized estradiol 17β 1 mg or placebo daily for 2.8 years (Viscoli *et al*., 2001). There were five cases of invasive breast cancer in each of the estrogen (n = 337) and placebo (n = 327) groups (RR = 1.0, 95% CI = 0.3–3.5). The Estrogen for Prevention of Reinfarction Trial (ESPRIT) involved 1017 women with a recent myocardial infarction who received estradiol valerate 2 mg or placebo daily for 2 years (Cherry *et al*., 2002). There were four cases of invasive breast cancer in each of the estrogen (n = 504) and placebo (n = 513) groups (RR = 0.98, 95% CI = 0.25–3.91).

The weighted-average likelihood of breast cancer for estrogen compared with placebo use, based on 12 643 patients in these four trials was 0.79 (95% CI = 0.61–1.01). The heterogeneity estimate was Q = 0.50 with 3 degrees of freedom (dof), P = 0.92 and I^2 = 0% (Figure 1). The overall risk reduction would be four (95% CI = –1–9) fewer breast cancer cases per 10 000 women using estrogen per annum (P = 0.10, Q = 0.95, 3 dof, heterogeneity P = 0.91 and I^2 = 0%).

Table I. Menopause hormone treatment and breast cancer risk: randomized controlled trials (RCTs)

Authors	Description of patients	Mean age (years)	Duration (years)	Intervention	Total patients		Breast cancer cases		Authors' estimated risk
					Estrogen	Placebo	Estrogen	Placebo	Adjusted RR, RH (95% CI)
Estrogen alone									
Hodis *et al*. (2001)	LDL levels ≥3.37 mmol/l	62.2	2	Estradiol 17β 1 mg or placebo	111	111	0	1	
Viscoli *et al*. (2001)	Recent stroke	71	2.8	Estradiol 17β 1 mg or placebo	337	327	5	5	1.0 (0.3–3.5)
Cherry *et al*. (2002)	Recent myocardial infarction	63	2	Estradiol valerate 2 mg or placebo	513	504	4	4	0.98 (0.25–3.91)
Anderson *et al*. (2004)	Mainly healthy and symptom free	64	6.8	CEE 0.625 mg or placebo	5310	5429	94	124	0.77 (0.59–1.01)
Estrogen and progestin									
Nachtigall *et al*. (1979)	Chronic hospital inpatients	55	10	CEE 2.5 mg + MPA 10 mg 7 days	84	84	0	4	
Angerer *et al*. (2001)	Carotid atherosclerosis	40–70	0.9	Estradiol 17β 1 mg + GSD 1 week or no Rx	107	108	0	1	
Hulley *et al*. (2002)	Coronary artery disease	67	6.8	CEE 0.625 mg + MPA 2.5 mg	1380	1383	49	39	1.27 (0.84–1.94)
Chlebowski *et al*. (2003)	Mainly healthy and symptom free	51–79	5.6	Conjugated equine estrogen, 0.625 mg	8506	8102	199	150	1.24 (1.01–1.54)

CEE, conjugated equine estrogens; CI, confidence interval; GSD, gestodene; LDL, low density lipoprotein cholesterol; MPA, medroxyprogesterone acetate; RH, relative hazard; RR, relative risk; RX, treatment.

Comment: Although estrogen use appears to be associated with a 20% lower risk of breast cancer and might save four cases per 10 000 women per year compared with non-users, the existing RCTs involve only 103 estrogen user patients who developed breast cancer, a number which is too small to provide a precise estimate of the risk.

Estrogen and progestin and risk of invasive breast cancer

Four estrogen–progestin trials contribute to this estimate (Table I). The WHI trial of estrogen–progestin treatment (EP) and placebo involved 16 608 mainly healthy postmenopausal women (Chlebowski *et al*., 2003). The women were randomly allocated to receive either hormones [CEE 0.625 mg with medroxyprogesterone acetate (MPA) 2.5 mg] or placebo daily. During 5.6 years of follow-up, there were 199 and 150 new invasive breast cancer cases (41 and 33 per 10 000 woman-years) in the EP and placebo groups, respectively. The likelihood of breast cancer was significantly higher in EP users (RH = 1.24, 95% CI = 1.01–1.54, P = 0.003). In this intent to treat analysis, there was approximately 50% loss of contrast (42% of EP patients stopped their medication and 11% of placebo patients started a hormone treatment). Considering only the adherent patients in each group (100% contrast), the RH was 1.49 (95% CI = 1.13–1.96, P = 0.0001).

The other three trials involved patients with cardiovascular disease. The Estrogen Replacement Therapy study involved 168 female in-patients in a chronic disease hospital who were randomly allocated to CEE plus MPA and followed for 10 years (Nachtigall *et al*., 1979). After 10 years, they had a choice of treatments and were followed for a further 12 years (Nachtigall *et al*., 1992). Breast cancer was diagnosed in four placebo patients after 4 years, and in 10 after 22 years; no cases were diagnosed in the women randomly allocated to CEE. The authors' estimated Z value for 10 years of hormone use was 2.05 (P = 0.04). The 10-year experience was used for the meta-analysis; substituting that the 22-year experience did not materially change the overall estimates given below.

The Postmenopausal Hormone Replacement against Atherosclerosis trial (PHOREA) was a German trial that involved 321 women with carotid atherosclerosis who received either micronized estradiol 17β 1 mg with 0.025 mg gestodene for 12 days of each 28 (107 women) or placebo (106 women) for 48 weeks (Angerer *et al*., 2001). (A third arm in which the progestin was prescribed every third month has not been included in our data.) Breast cancer developed in one placebo patient.

The Heart and Estrogen/progestin Replacement Study (HERS) involved 2763 women with proven coronary artery disease (Hulley

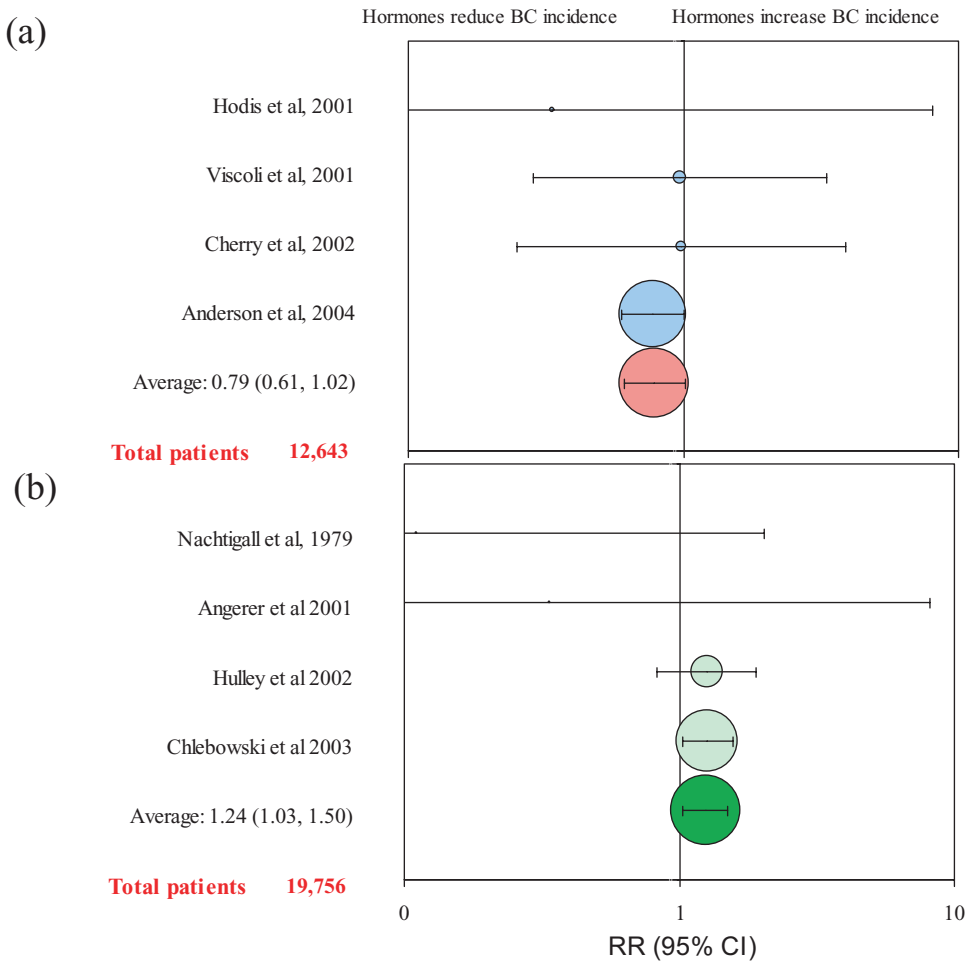

Figure 1. Randomized controlled trial (RCT) estimates of the relative risk (RR) of invasive breast cancer with hormonal treatment. Circles are proportional to weight with 95% confidence intervals (95% CIs) for (**a**) unopposed estrogen and (**b**) estrogen with progestin.

et al., 2002). The women were randomly allocated to receive either CEE 0.625 mg with MPA 2.5 mg or placebo daily. Breast cancer was reported as an adverse event. During 6.8 years of follow-up, there were 49 and 39 new invasive breast cancer cases in the EP and placebo groups, respectively, a non-significant increase in the likelihood of breast cancer for EP users (RH = 1.27, 95% CI = 0.84–1.94).

The weighted-average likelihood of breast cancer for EP compared with placebo use, based on 19 756 patients in these four trials was 1.24 (95% CI = 1.03–1.50). The heterogeneity estimate was Q = 3.32, 3 dof, $P = 0.34$ and $I^2 = 10\%$ (Figure 1). The overall risk increase would be 4.4 more breast cancer cases (95% CI = 0.3–8.5) per 10 000 women using EP per annum ($P = 0.02$, Q =5.35, 3 dof, heterogeneity $P = 0.15$ and $I^2 = 44\%$).

Comment: EP use appears to be associated with a 24% higher risk of breast cancer and would involve four more cases per 10 000 women per year compared with non-users. This group of RCTs involved 248 EP user patients who developed breast cancer, a number which is too small to provide a precise estimate of the risk.

Epidemiological studies on breast cancer risk with menopausal hormone use

Question: In postmenopausal women, is use of estrogen or estrogen–progestin hormones associated with risk of invasive breast cancer?

The question is similar to the question in the above section, because the limited power in the level I evidence from RCTs indicates that epidemiological studies also should be evaluated to supplement RCT evidence.

The Collaborative Study (Collaborative Group on Hormonal Factors in Breast Cancer, 1997) summarized studies up to 1996, studies missing from the collaborative re-analysis and subsequent studies were retrieved from the authors' files and a Medline search on January 5, 2005 (Table II). Where study data were reported more than once, the most recent report was used (Kaufman *et al*., 1984, 1991; Sellers *et al*., 1997; Gapstur *et al*., 1999). Where hormone use was not defined as estrogen or estrogen–progestin, the data were not abstracted for current- and ever-use estimates. We categorized The Iowa Women's Health Study (Gapstur *et al*., 1999) as estrogen exposure from the authors' comment that less than 20% of use was combined estrogen–progestin (Sellers *et al*., 1997). Figures from the collaborative re-analysis are as published. Epidemiological studies that were not covered in the collaborative re-analysis are summarized in Table II and the following text sections. The summary of the average risks in the epidemiological studies is in Table III.

Many of the epidemiological studies present hormone use according to whether a woman ever used menopause hormones (ever use), whereas others offer RRs for current and past use. The latter approach is preferable because the collaborative analysis has shown that past use is not a risk factor, and therefore ever use is a not very meaningful blend of current and past use.

For the epidemiological studies not included in the collaborative re-analysis, the meta-analyses estimate the weighted average of the adjusted RRs reported in the studies for current, past and ever use. Variance was computed from 95% CIs or *P* values. There was significant heterogeneity for most of these analyses, and the random effects model estimates are shown.

The collaborative re-analysis

The collaborative re-analysis involved original data from 52 705 women with breast cancer and 108 411 women without breast

Table II. Recent epidemiological studies of breast cancer risk with menopause hormone treatment

						Exposed		Not exposed	
Authors	Location	Design	Exposure	Age (years)	Follow-up (years)	Cases	Controls	Cases	Controls
Beral *et al*. (2003)	UK	Cohort	HT	50–64	2.6	4246	436 166	2894	392 757
Chen *et al*. (2002)	Washington	CC	HT	50–74		462	243	421	271
Gapstur *et al*. (1999)	Iowa	Cohort	E	55–69	11	492	13 608	740	22 665
Jernstrom *et al*. (2003)	Lund	Cohort	HT	50–64	4.1	74	3849	23	2399
Kaufman *et al*. (1991)	Massachusetts	CC	HT	40–69		393	457	1293	1620
Kerlikowske *et al*. (2003)	USA	Cohort	HT	50–79	5	1399	159 406	1803	211 857
Kirsh and Krieger (2002)	Ontario	CC	HT	20–74		132	120	272	283
Li *et al*. (2000)	Washington	CC	HT	50–64		173	258	159	187
Li *et al*. (2003b)	Washington	CC	HT	65–79		691	668	284	339
Magnusson *et al*. (1999)	Sweden	CC	HT	50–74		663	494	1738	2201
Newcomb *et al*. (2002)	USA	CC	HT	50–79		1471	1439	3827	4132
Olsson *et al*. (2003)	Lund	Cohort	HT	25–65	10.1	87	1650	153	6707
Persson *et al*. (1999)	Sweden	Cohort	HT	<70	5.8	150	*42 504*	48	*17 794*
Porch *et al*. (2002)	USA	RCT	HT	45+	5.9	265	*66 255*	146	*38 762*
Ross *et al*. (2000)	California	CC	HT	55–72		1024	853	873	784
Schairer *et al*. (2000)	USA	Cohort	HT	*58*	10.2	1321	277 021	761	196 666
Stahlberg *et al*. (2004a,b)	Denmark	Cohort	HT	45+	6.3	134	4308	110	6566
Tjonneland *et al*. (2004)	Denmark	Cohort	HT	50–64	4.8	279	11 538	144	11 657
Weiss *et al*. (2002)	USA	CC	HT	35–64		1252	1374	672	655

CC, case control; E, estrogen treatment; HT, E or EP treatment; MPA, medroxyprogesterone acetate; ND, type of HT not defined; RCT, randomized controlled trial (non-hormonal intervention).
Person years of follow-up are given in italics. Age represents mean age or range. Studies that enrolled women from age 45 excluded those who were not menopausal. Gapstur *et al*. (1999) used hormone use from Sellers *et al*. (1997).

Table III. Average estimates of breast cancer risk with hormone use

	Unopposed estrogen		Estrogen–progestin		Estrogen and estrogen–progestin	
	User cases	RR (95% CI)	User cases	RR (95% CI)	User cases	RR (95% CI)
Randomized controlled trials (*inverse variance*)	103	0.78 (0.61–1.01)	248	1.24 (1.03–1.50)		
Adherent women				1.49 (1.13–1.96)		
Collaborative re-analysis (*Mantel-Haenszel*)*						
<5 years use	498	0.99 (0.83–1.15)	136	1.15 (0.78–1.52)		
>5 years use	558	1.34 (1.16–1.52)	58	1.53 (0.88–2.18)		
Epidemiological studies (*random effects*)						
Current use	2862	1.18 (1.01–1.38)	3455	1.70 (1.36–2.13)		
Ever use	4193	1.08 (0.97–1.20)	2221	1.31 (1.12–1.53)		
Past use (*inverse variance*)					1362	1.02 (0.96–1.08)

CI, confidence interval; RR, relative risk.
Meta-analysis methods were given in italics.
*Four thousand six hundred and forty women with known information about hormonal constituents (Table II). Current or last 1–4 years use.

cancer from 51 studies in 21 countries (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). With a risk increase of 2.3% per year of use, the RR did not become significantly higher until after 5 years, but for few users who had taken HRT for 5 years or longer (the average duration of use in this group was 11 years), the RR was 1.35 (95% CI = 1.21–1.49) or 1.34 (95% CI = 1.16–1.52, see Table III). Five years after stopping hormone use, the excess risk disappeared regardless of how long the hormones were used.

Many studies included in the collaborative re-analysis (61% of the subjects) did not specify the type of hormone use. For the remaining 4640 postmenopausal women, only 12% of the known types of hormone use involved estrogen–progestin products. Thus, it is reasonable to consider that the collaborative re-analysis estimates predominately reflect breast cancer risk with use of unopposed estrogen. Among patients using estrogen–progestin, the RRs with current or recent use were 1.15 (95% CI = 0.84–1.51) (or 95% CI = 0.78–1.52, see Table III) and 1.53 (95% CI = 0.90–2.16) (or 95% CI = 0.88–2.18, see Table III), respectively, for less than 5 years and 5 or more years.

The collaborative re-analysis resolved many issues after two decades of ambivalence about breast cancer risk with hormone treatment. Reports of increased and decreased risk were equally plentiful and, not surprisingly, clinicians were confused and uncertain. Figure 2 shows why there were both positive and negative reports: many studies were too small to make a precise estimate of the risk. Thus, the estimates, most of which involved exposure to unopposed estrogen, were randomly distributed around the true risk, which is near unity in the estrogen-dominated collaborative re-analysis data set. Figure 2 is a modified funnel plot of RR against study size (Sutton *et al*., 2000). Study size is usually represented by the weight, or inverse of the variance, but in Figure 2, study size is represented by the number of breast cancer cases who were hormone users. The funnel plot is a technique to determine the likelihood of publication bias. In the collaborative re-analysis data, there are as many negative small studies (often underrepresented) as positive small studies (often overrepresented), ruling out publication bias.

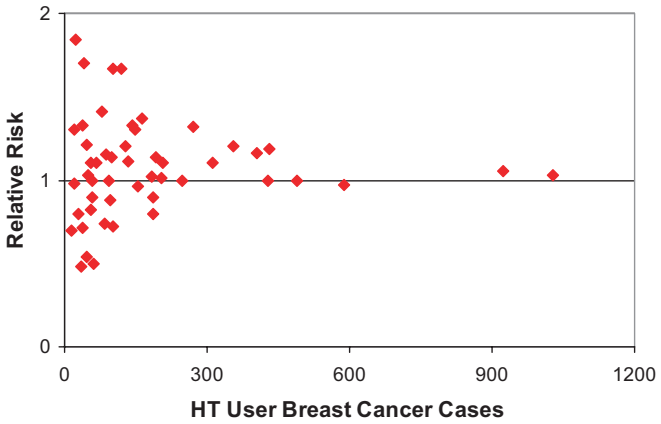

Figure 2. Breast cancer risk estimates with estrogen use among studies summarized in the collaborative re-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Relative risks (RRs) are plotted against sample size represented by the number of hormone users that developed breast cancer.

What Figure 2 also shows is that the results of studies with fewer than 200–300 user cases are more scattered than those of larger studies. Of course, the results of RCTs with fewer than 300 user cases, although less likely to vary because of bias, may demonstrate a similar scattered pattern because of chance. Even the WHI studies that were powered to assess breast cancer risk were at the margin of resolution, as indicated by the 95% CIs that include or approach unity. The true breast cancer risk with estrogen or EP may not be known until more trials have been reported.

Current use of hormones and epidemiological study estimates of invasive breast cancer risk

Unopposed estrogen. Breast cancer risk with current use of unopposed estrogen was reported in nine epidemiological studies listed in Table II (Gapstur *et al*., 1999; Li *et al*., 2000, 2003b; Schairer *et al*., 2000; Chen *et al*., 2002; Porch *et al*., 2002; Weiss *et al*., 2002; Beral and Million Women Study Collaborators, 2003; Stahlberg *et al*., 2004b). The risk estimates for current use ranged from 0.9 for lobular cancer (Li *et al*., 2003b) to 4.42 for favourable prognosis ductal cancers (Gapstur *et al*., 1999), and the estimates

were heterogeneous ($P < 0.001$). In these studies involving more than 2862 estrogen-exposed breast cancer cases, the average inverse variance fixed effects summary risk was 1.23 (95% CI = 1.16–1.29); the random effects risk was 1.18 (95% CI = 1.01–1.38). The combined estimates were strongly influenced by the 991 user cases in the Million Women Study, which accounted for 65% of the overall weight (Beral and Million Women Study Collaborators, 2003). In the remaining studies involving more than 1871 estrogen-exposed breast cancer cases, the average inverse variance fixed effects summary risk was 1.11 (95% CI = 1.01–1.21); the random effects risk was 1.17 (95% CI = 0.97–1.42). The impact of the exclusion appears greater in the fixed effects model because random effects models give proportionately more weight to small studies. The CIs for three of the four summary estimates are close to unity or include unity.

Comment: In epidemiological studies among postmenopausal women, risk of invasive breast cancer among current users of estrogen is approximately 20-fold higher than in non-users. This estimate is higher than the combined estimate from RCTs for unopposed estrogen use (risk reduction of approximately 20%). Whether risk is increased or decreased, the magnitude of the effect of unopposed estrogen on breast cancer risk is small.

Estrogen and progestin. Seven epidemiological studies reported breast cancer risk with current use of estrogen and synthetic progestins (Li *et al*., 2000, 2003b; Chen *et al*., 2002; Porch *et al*., 2002; Weiss *et al*., 2002; Beral and Million Women Study Collaborators, 2003; Stahlberg *et al*., 2004b). The risk estimates for current EP use ranged from 0.7 for ductal cancer (Li *et al*., 2000) to 4.16 for continuous use of estrogen with testosterone-like progestins (Stahlberg *et al*., 2004b). The average EP RR estimates were heterogeneous ($P < 0.001$). In studies involving 3455 EP user breast cancer cases, the inverse variance fixed effects average risk was 1.86 (95% CI = 1.75–1.98); the random effects summary risk was 1.70 (95% CI = 1.36–2.13). The average EP estimate was strongly influenced by the 1934 user cases in the Million Women Study, which accounted for 84% of the overall weight (Beral and Million Women Study Collaborators, 2003). In the remaining studies involving 1521 EP user breast cancer cases, the average inverse variance fixed effects summary risk was 1.53 (95% CI = 1.36–1.72); the random effects risk was 1.67 (95% CI = 1.29–2.17).

Comment: Among postmenopausal women who are current users of estrogen–progestin combinations, the risk of invasive breast cancer is approximately 20% higher than in non-users. This estimate is higher than the estimate from RCTs (breast cancer risk was approximately 24% higher).

Past use of hormones and epidemiological study estimates of invasive breast cancer risk

Few studies estimated breast cancer among past users according to whether the woman used estrogen or estrogen–progestin. For past use of either estrogen or estrogen–progestin, the RR estimates from five studies ranged from 0.92 (Chen *et al*., 2002) (all cases) to 2.68 (favourable prognosis ductal cancers) (Gapstur *et al*., 1999). The past use estimates did not involve significant heterogeneity ($P = 0.28$). In this group of studies which involved more than 1362 breast cancer cases among past users, the fixed effects average risk was 1.02 (95% CI = 0.95–1.09). As with the current use risk estimates above, this estimate is also influenced by the Million Women Study, with 1044 cases, which accounted for 74% of the overall weight (Beral and Million Women Study Collaborators, 2003). The summary risk was not materially changed by excluding that study (1.04, 95% CI = 0.91–1.20).

Comment: As in the collaborative re-analysis, where there was no excess breast cancer risk 5 years after discontinuing hormone use, recent epidemiological studies indicate that past use of menopausal hormone treatment is not associated with continuing breast cancer risk elevation. If, however, past use were dominated by use of unopposed estrogen, that would tend to explain the lack of a significant impact on breast cancer risk.

Ever use of hormones and epidemiological study estimates of invasive breast cancer risk

Unopposed estrogen. Breast cancer risk with ever use of unopposed estrogen was reported in 11 epidemiological studies listed in Table II (Kaufman *et al*., 1991; Gapstur *et al*., 1999; Magnusson *et al*., 1999; Persson *et al*., 1999; Li *et al*., 2000, 2003b; Ross *et al*., 2000; Schairer *et al*., 2000; Kirsh and Kreiger, 2002; Weiss *et al*., 2002; Olsson *et al*., 2003). The risk estimates for ever use ranged from 0.5 for ductal cancer (Li *et al*., 2000) to 2.22 for favourable prognosis ductal cancers (Gapstur *et al*., 1999). The estimates were heterogeneous ($P < 0.001$). In these studies involving approximately 4193 estrogen-exposed breast cancer cases, the average inverse variance fixed effects summary risk was 1.05 (95% CI = 0.99–1.10); the random effects risk was 1.08 (95% CI = 0.97–1.20).

Estrogen–progestin. Eleven epidemiological studies reported breast cancer risk with ever use of estrogen–progestin (Kaufman *et al*., 1991; Magnusson *et al*., 1999; Persson *et al*., 1999; Li *et al*., 2000, 2003b; Ross *et al*., 2000; Schairer *et al*., 2000; Kirsh and Kreiger, 2002; Weiss *et al*., 2002; Jernstrom *et al*., 2003; Olsson *et al*., 2003). The risk estimates for current EP use ranged from 0.65 for less than 6 months use (Weiss *et al*., 2002) to 2.7 for exclusive use of estrogen–progestin (Stahlberg *et al*., 2004b). The RR estimates for ever use of EP were heterogeneous ($P < 0.001$). In studies involving more than 2221 EP user breast cancer cases, the inverse variance fixed effects summary risk was 1.29 (95% CI = 1.20–1.40); the random effects summary risk was 1.31 (95% CI = 1.12–1.53).

Comment: The breast cancer risk with ever use (1.08) of unopposed estrogen is intermediate between the risks associated with current use of unopposed estrogen (1.18) and past use of either estrogen or estrogen–progestin types, if menopausal hormones (1.02). This is not unexpected, given that ever use combines current and past use. The same pattern applies to estrogen–progestin use: the breast cancer risk with ever use (1.08) lies between the risks associated with current use (1.74) and past use of any menopausal hormones (1.02).

To recap the risks of invasive breast cancer with hormone use, Table III summarizes the evidence from RCTs and epidemiological studies. The RCT evidence has greater validity, but the contrast between treated and placebo groups is diminished by noncompliance in the hormone groups and use of hormones in the placebo groups during the long-term WHI studies. Intention to treat analyses, correct as they may be for efficacy, do not convey the full picture about safety, which should be estimated by the most conservative means available. There is, after all, less concern about the safety of those women who are not using the

intervention. In epidemiological studies, however, women who say they are current users are most likely current users, and the contrast with no use is more likely to approach 100%. In the WHI estrogen–progestin trial, the RH among adherent women with 100% contrast was the most conservative estimate of risk (RH = 1.49), and it was not very different from the epidemiological studies combined estimate for current use of estrogen–progestin (1.70).

The applicable absolute risks indicate that the difference in risks between study types may not be clinically relevant. For women 55–60 years of age, the population incidence of breast cancer is approximately 300 per 100 000 women per year (Ries *et al*., 2003). With a RH equal to 1.49, there would be 147 excess cases [(300 × 1.49) – 300] per 100 000 women per year with EP (Table IV). The excess with an RR equal to 1.70 would be approximately 210 cases per 100 000 women per year. The excess cases with use of estrogen–progestin would be approximately one case per 1000 women per year for either of the RCT estimates and approximately two cases per 1000 women per year for the epidemiological study estimate.

When does breast cancer risk rise after starting hormone treatment?

Question: In postmenopausal women, does longer use of estrogen or EP correlate with higher risk of invasive breast cancer?

This section will consider evidence from clinical trials, the collaborative re-analysis and epidemiological studies. Among the trials, only the WHI reports include sufficient data to consider trends over the duration of use. From the epidemiological studies, only estimates among current users were included because ever use includes past use, and the collaborative re-analysis found that risk was not higher with past use regardless of the duration of use (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Risk estimates were summarized for use less than 5 years and for longer use by random effects models (Deeks *et al*., 2001). The trend for breast cancer risk according to the duration of use was estimated with the use of unweighted RR regression (Schlesselman, 1997). This estimate uses the midpoint of each defined period of use (e.g. 1.5 for 1–2 years); for periods with an undefined upper limit, the midpoint is plus 2 years (e.g. for 5 or more years, the upper limit is 5 + 2 = 7).

Duration of unopposed estrogen use and risk of invasive breast cancer

In the WHI ET, placebo and estrogen event rates were similar for 2 years; after that the cumulative rate in the estrogen group did not rise as much as the corresponding rate in the placebo group. We estimated crude RRs from the WHI event rates and persons at risk, and these are shown in Figure 3 (Anderson *et al*., 2004). Note that the estimate is based on an intention to treat analysis in which drop-outs and drop-ins total almost 50% at 5 years so that the contrast between groups was less than 100%.

As noted in the Introduction, in the collaborative re-analysis, the annual increase in breast cancer risk among users of mainly unopposed estrogen was 1.023 or 2.3% (95% CI = 1.1–3.6), which was comparable with the increase in breast cancer risk associated with each year of delayed menopause (2.8%, 95% CI = 2.1–3.4). Among women with known types of hormone use, the associated breast cancer risk was 0.99 (95% CI = 0.83–1.15) with estrogen use for less than 5 years (498 cancers among users). The associated breast cancer risk was 1.34 (95% CI = 1.16–1.52) with estrogen use 5 or more years (558 cancers among users) (Collaborative Group on Hormonal Factors in Breast Cancer, 1997).

Seven epidemiological studies not included in the collaborative re-analysis included breast cancer risk estimates by the duration of current use (Gapstur *et al*., 1999; Chen *et al*., 2002; Newcomb *et al*., 2002; Porch *et al*., 2002; Weiss *et al*., 2002; Beral and Million Women Study Collaborators, 2003). The estimates show no more than a modest rise in risk up to 5 or more years of use (Figure 3). The random effect model average breast cancer risk was 1.15 (95% CI = 0.998–1.33) with use for less than 5 years (more than 900 estrogen using cases) and 1.24 (95% CI = 1.07–1.44) with use for 5 or more years (more than 1600 estrogen using cases).

Comment: With respect to the short-term duration of unopposed estrogen use (less than 5 years), the RCT evidence with incomplete contrast indicates that breast cancer risk may decline; the collaborative re-analysis indicates that breast cancer risk is unchanged; and the recent epidemiological studies show a rise in risk that is not significant. Use for 5 or more years was associated with a non-significant decrease in risk in the WHI but carries a significantly increased risk in evidence from the epidemiological studies.

Duration of estrogen–progestin use and risk of invasive breast cancer

Breast cancer event rates in the placebo and estrogen–progestin groups of the WHI estrogen–progestin trial were similar for 4 years; after that the cumulative rate in the estrogen–progestin group was significantly higher than the corresponding rate in the placebo group (Chlebowski *et al*., 2003). Adjusted hazard rates drawn from the WHI authors' Table II are shown in Figure 3.

In the collaborative re-analysis, among women known to be using estrogen–progestin, the breast cancer risk was 1.15 (95% CI = 0.78–1.52) with use for less than 5 years (34 user cases) and 1.53 (95% CI = 0.88–2.18) with use for 5 or more years (71 user cases) (Collaborative Group on Hormonal Factors in Breast Cancer, 1997).

Six additional epidemiological studies presented breast cancer risk estimates by the duration of current use of estrogen–progestin use (Chen *et al*., 2002; Newcomb *et al*., 2002; Porch *et al*., 2002; Weiss *et al*., 2002; Beral and Million Women Study Collaborators,

Table IV. Number of cases of breast cancer according to various estimates of risk

Estrogen progestin use	Relative risk	New invasive cases per year/100 000 women	Increase in cases with use
No use (Ries *et al*., 2003)	1	300	
Randomized controlled trial estimate of risk	1.24	373	73
Women's Health Initiative estimate: adherent patients	1.49	447	147
Current-use estimate	1.70	510	210

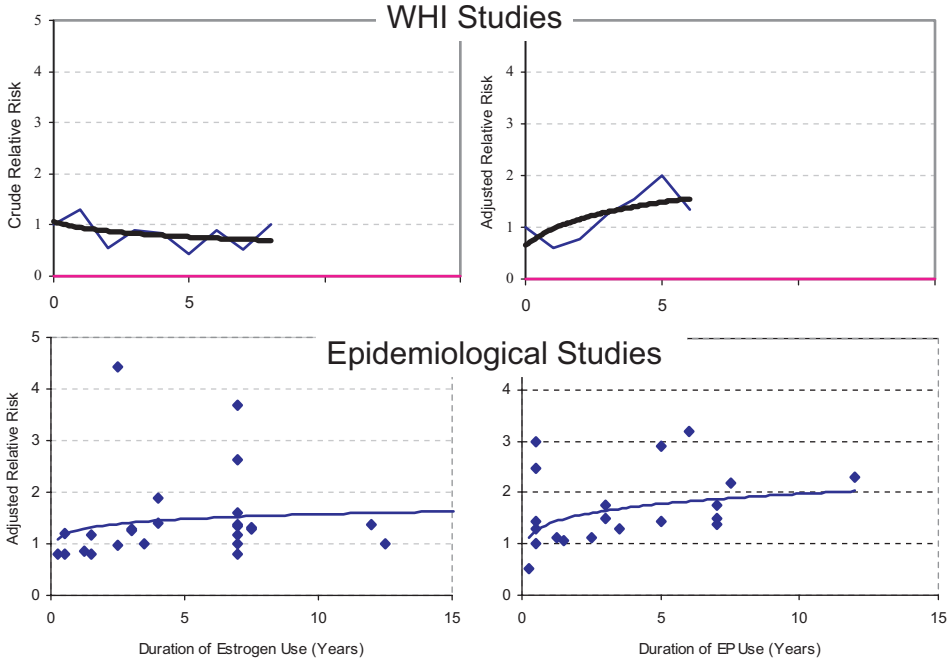

Figure 3. Duration of hormone use and breast cancer risk in the Women's Health Initiative (WHI) trials and recent epidemiological studies (see text for references). Heavy lines are unweighted logarithmic regressions.

2003; Jernstrom *et al*., 2003). The estimates show a distinct rise in risk during prolonged use (Figure 3). The random effect model average breast cancer risk was 1.34 (95% CI = 1.13–1.59) with use for less than 5 years (more than 1200 user cases) and 1.89 (95% CI = 1.54–2.31) with use for 5 or more years (more than 1700 users cases).

Comment: The RCT evidence and all sources of epidemiological evidence concur on a significantly increased risk of invasive breast cancer with use of estrogen–progestin that begins within 5 years of starting use and continues to rise after 5 years.

When does the excess breast cancer risk become normal after stopping hormone treatment?

Question: In postmenopausal women who stop using estrogen or EP, does the excess risk of invasive breast cancer decline over time?

The methods are similar to those of the previous section, with the exception that evidence from clinical trials is not yet available. The analyses examine whether recency of hormone use, that is the number of years since use was discontinued among past users, correlates with the magnitude of the RR.

The collaborative re-analysis and three epidemiological studies included adjusted RRs according to time since discontinuing hormone treatment (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Schairer *et al*., 2000; Newcomb *et al*., 2002; Beral and Million Women Study Collaborators, 2003). There was no material difference between the estimates for all hormone use (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Beral and Million Women Study Collaborators, 2003) and the separate estimates for estrogen and estrogen–progestin (Schairer *et al*., 2000; Newcomb *et al*., 2002). Data for the first 2–3 years after discontinuation of use are sparse, but one

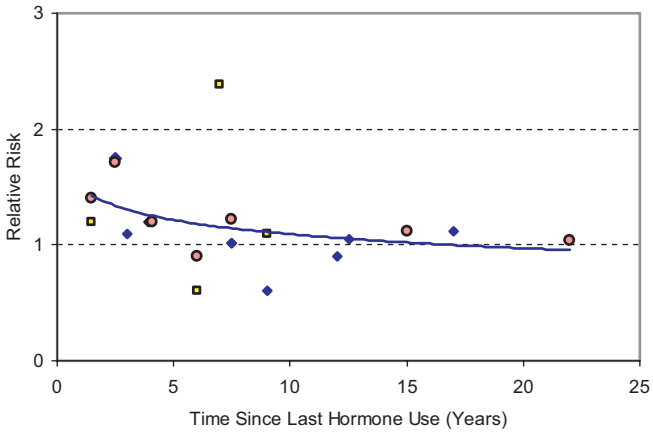

Figure 4. Breast cancer risk after cessation of hormone use in the recent epidemiological studies (see text for references). Line, unweighted logarithmic regression; circles, estrogen alone; squares, estrogen–progestin; diamonds, menopause hormones not defined.

RR estimate for discontinued use of unopposed estrogen less than 3 years in the past was significantly elevated (1.4, 95% CI = 1.1–1.8) (Schairer *et al*., 2000) (Figure 4). Although the estimates of breast cancer risk by recency did not involve significant heterogeneity, the power to assess heterogeneity was limited and random effect model results are presented. Overall, the average of all breast cancer risk estimates within 5 years after cessation was 1.14 (95% CI = 1.03–1.22). More than 5 years after cessation of use, the average breast cancer risk was 1.04 (95% CI = 0.97–1.13). Time since last use, however, explained only 18% of the variability in risk among women who discontinued hormone use (Figure 4).

Comment: The excess breast cancer risk associated with current use of hormone treatment for menopausal symptoms disappeared around 5 years after hormone use was discontinued.

Does breast cancer risk vary by hormone type, dose and route of administration?

The WHI studies involved specific types of estrogen (CEE) and progestin (MPA), and it has been suggested that the breast cancer risks might be different with other hormones types, lower dosages or non-oral routes of administration. A recent review addressed this question from evidence in RCTs and epidemiological studies published between 1987 and 2002 (Warren, 2004). That review concluded that the WHI findings on estrogen–progestin and breast cancer risk were consistent with the findings in studies that used different products, including studies from Europe where different estrogens and progestins are more common.

This section will attempt to assemble and analyse the relevant published evidence in subsections on hormone type, dosage used, progestin regimen and route of administration. No randomized studies of hormone interventions had sufficient power to distinguish among these exposure definitions with respect to breast cancer risk. Because differences among products, dosages and routes of administration are likely to be small, only risks associated with current use will be abstracted, a choice that should minimize the loss of contrast involved in past and ever use and allow for a more precise evaluation of such fine distinctions. Also, this comparison is restricted to specific exposures, and to avoid between study bias (e.g. comparing CEE in one study with estradiol in another), risks were abstracted only from those studies that provided information on each type of exposure.

Hormone type

Question: Among postmenopausal women currently using hormones, does breast cancer risk depend upon the type of estrogen or progestin product prescribed?

The inclusion criteria required studies that reported adjusted RRs of breast cancer with current use according to each type of hormone exposure.

Estrogen. For estrogen types, only the Million Women Study met the inclusion criteria (Beral and Million Women Study Collaborators, 2003). The breast cancer risks with equine estrogens and estradiol products were similar: 1.29 (95% CI = 1.16–1.43) and 1.24 (95% CI = 1.12–1.37), respectively. With more than 400 user cases in each estrogen type group and nearly 400 000 eligible nonusers in the comparison group, it is likely that this study had sufficient power to rule out a clinically meaningful difference between two estrogen types that represent the majority of use.

Progestin. For progestin types, only two studies included risks with current use for each type of hormone exposure (Beral and Million Women Study Collaborators, 2003; Stahlberg *et al*., 2004b). Although several studies included risk estimates according to ever use of different progestin types, none provided risks for use of micronized oral progesterone, injected progesterone or transvaginal progesterone. Our analysis compares MPA (C21 progestin) with C19 progestins [norethisterone, levonorgestrel (Beral and Million Women Study Collaborators, 2003) or 'testosterone like' (Stahlberg *et al*., 2004b)]. We combined separate estimates by duration from the Million Women Study and separate estimates by regimen from the Danish Nurses Cohort Study. The random effect averages of the breast cancer risks with C21 and C19 progestins were virtually the same: 2.14 (95% CI = 1.18–3.87) and 2.14 (95% CI = 1.68–2.72), respectively. With more than 1900 user cases, the lack of a clinically meaningful difference is unlikely to reflect lack of power in these studies.

Comment: In published data that were comparable and involved the most frequently used hormone types, neither the type of estrogen nor the type of progestin affected the breast cancer risk among postmenopausal women using hormone treatment.

Hormone dose

Question: Among postmenopausal women currently using hormones, does breast cancer risk depend upon the dosage of estrogen or progestin product prescribed?

The inclusion criteria required studies that reported adjusted RRs of breast cancer with current use according to each dosage of hormone. Two studies met the inclusion criteria for this question (Porch *et al*., 2002; Beral and Million Women Study Collaborators, 2003). One study reported on dosage of estrogen and progestin products (Porch *et al*., 2002) and the other on dosage of estrogen (Beral and Million Women Study Collaborators, 2003). Our analyses are based on the within-study definitions of low and high dosage.

Estrogen dosage. For estrogen dosages, all estimates of breast cancer risk in the Million Women Study involved RRs between 1.19 (>1 mg estradiol) and 1.36 (>0.625 mg equine estrogen) (Beral and Million Women Study Collaborators, 2003). Although the Women's Health Study reported a marginally significant trend from lowest (RR = 0.87 with ≤0.3 mg equine estrogen) to highest (RR = 1.43 with ≥0.9 mg) (P = 0.06), 160 of the 200 user cases were taking the intermediate dosage (0.625 mg CEE) (Porch *et al*., 2002). The random effect averages of the breast cancer risks with low and high dosages of estrogens were similar: for CEE dosages 0.625 mg or less and estradiol dosages 1 mg or less, the risk was 1.27 (95% CI = 1.11–1.45); for higher dosages, the risk was 1.25 (95% CI = 1.00–1.56), respectively.

Progestin dosage. For progestin dosages, the Women's Health Study evaluated dosages of progestin over the range from <5 to 10 mg per day (Porch *et al*., 2002). The trend from lowest to highest dose was not significant (P = 0.37). The adjusted RRs for products with <5, 5–9 and 10 mg per day, respectively, compared with no use were 1.54 (95% CI = 1.12–2.11), 1.30 (95% CI = 0.86–1.98) and 1.13 (95% CI = 0.76–1.68). The estimates involved 153 breast cancer cases among hormone users.

Comment: There is no significant dose-response effect on the breast cancer risk associated with hormone use. Among the explanations, the data may be insufficient to show trends with higher dosage, clinicians may prescribe lower dosages for apparently high-risk patients or the threshold for breast cancer risk may be lower than the clinically effective dosage. The lack of a clinically important difference is less likely to reflect lack of power in the estrogen dosage estimates.

Route of administration

Question: Among postmenopausal women currently using hormones, does breast cancer risk depend upon the route of administration of the estrogen or progestin product prescribed?

Our search found that only the Million Women Study reported the breast cancer risk according to the route of administration, and

this risk was reported only for estrogen products. The adjusted RRs were similar for oral (1.32, 95% CI = 1.21–1.45), transdermal (1.24, 95% CI = 1.11–1.39) and implanted estrogens (1.65, 95% CI = 1.26–2.16). These risks were not significantly different ($P = 0.27$) (Beral and Million Women Study Collaborators, 2003).

Comment: To recap the evidence on hormone types, dosages or routes of administration, reasonably sufficient data do not support hypotheses about variable effects on invasive breast cancer risk. Although these prescribing options may cause different clinical pharmacological responses, the effect on breast cancer appears to be a class effect that is inherent in any effective estrogen or estrogen–progestin. Potential differences among progestin types with respect to breast epithelial biology are explored further in the Discussion.

Progestin regimen

Question: Among postmenopausal women currently using estrogen–progestins, does breast cancer risk depend upon whether the progestin is prescribed in a sequential or continuous regimen?

Adjusted RRs of invasive breast cancer for all dosages and types of current estrogen and progestin use were included in this analysis, given that the above subsections found no differences among types and dosages. Data were included only for risks with current use from studies that reported breast cancer risk for both sequential and continuous regimens. The analyses included risks from individual studies by different levels of duration.

Six epidemiological studies reported breast cancer risk with current use of estrogen–progestin by sequential or continuous regimen (Chen *et al*., 2002; Porch *et al*., 2002; Weiss *et al*., 2002; Beral and Million Women Study Collaborators, 2003; Li *et al*., 2003b; Stahlberg *et al*., 2004b). The estimates for both sequential and continuous regimens were heterogeneous ($P < 0.001$). The random effect model average RRs were 1.49 (95% CI = 1.16–1.90) and 1.87 (95% CI = 1.46–2.40), respectively, for sequential and continuous regimens (P for the difference between risks = 0.13). The fixed effect model average RRs were 1.85 (95% CI = 1.72–1.99) and 1.94 (95% CI = 1.78–2.11), respectively, for sequential and continuous regimens (P for the difference between risks = 0.34). The Million Women Study accounted for 85 and 72% of the weight in the respective sequential and continuous estimates.

Comment: The continuous regimen, which is most often prescribed at present, is preferable for many women because they eventually develop amenorrhea (Archer *et al*., 1994). The trend towards a higher breast cancer risk with a continuous regimen was not significant, and it was non-trivial only in the random effect model.

The larger difference in risk for the two regimens found in the worst case random effect model may not be clinically relevant. As noted above, for women 55–60 years of age, the population incidence of breast cancer is approximately 300 per 100 000 women per annum (Ries *et al*., 2003). The 1.49-fold higher risk for the sequential regimen compared with never users would be associated with 147 excess cases [(300 × 1.49) – 300] per 100 000 women per annum. There would be 261 excess breast cancer cases, if the true risk were 1.87-fold higher with the continuous regimen. The difference between the types of regimens would involve 261–147 or 114 cases per 100 000 per annum, which is approximately 1 more case per 1000 women per annum with use of a continuous regimen. The difference in progestin exposure for sequential and continuous regimens could have public health implications, however, and merits further study.

Do hormones increase risk of lobular more than ductal breast cancers?

Background on lobular breast cancers

Ductal cancer accounts for 70–80% of invasive breast cancer cases and lobular cancer for 5–10% (Verkooijen *et al*., 2003). Lobular cancer differs in several respects from ductal cancer: it is more likely to be receptor positive and it has a better prognosis than ductal cancer. It is also more difficult to diagnose by clinical examination and by mammography because it tends to grow in sheets rather than as a discrete mass (Li *et al*., 2003a).

The incidence of lobular cancer is rising more than that of ductal cancer, and it has been suggested that menopause hormone treatment increases incidence of lobular more than ductal cancer (Levi *et al*., 2003; Li *et al*., 2003a; Verkooijen *et al*., 2003). If hormone use really does involve such a differential risk according to histology, it follows that increased use might account for the more rapid rise in the incidence of lobular cancer in recent years.

The WHI estrogen–progestin trial did not show such a differential risk: 11.2 and 10.6% of the cancers in the hormone and placebo groups, respectively, were lobular cancers, and 67.8 and 67.3% were ductal cancers (Chlebowski *et al*., 2003). Although epidemiological studies involve more hidden biases than randomized trial results, they may have more power to make distinctions at this fine level of resolution.

Methods for the lobular and ductal breast cancer analysis

Question: Among postmenopausal women currently using estrogen or estrogen–progestins, does risk of invasive lobular breast cancer differ from risk of invasive ductal breast cancer?

Data were drawn only from studies that included adjusted breast cancer risks with current use of hormones because the effect of current HRT use on breast carcinoma risk is stronger than the effect of past use. Eligible studies had to report the risks for both lobular and ductal histological types. Two studies reported these data separately from the primary study report, Daling *et al*. (2002) is the same case–control study as Weiss *et al.* (2002) and Stahlberg *et al*. (2004b) is the same cohort study as Stahlberg *et al*. (2004a). The adjusted RRs for lobular and ductal cancer were abstracted; estimates for other histological types were not abstracted. Categorical analyses evaluated the separate effects of estrogen and estrogen–progestin on lobular and ductal cancers. Given the number of analyses that have been carried out, the P values displayed should be interpreted only relative to other P values in the context of these analyses.

Current use of estrogen or estrogen–progestin and risk of lobular or ductal cancer

Seven studies included 11 corresponding estimates of lobular and ductal breast cancer risk with current use of menopause hormones (Li *et al*., 2000, 2003b; Chen *et al*., 2002; Daling *et al*., 2002; Newcomb *et al*., 2002; Newcomer *et al*., 2003; Tjonneland *et al*., 2004). All studies reported adjusted risks according to estrogen or estrogen–progestin exposure except one which reported on HRT exposure (Tjonneland *et al*., 2004). In these studies, 387 lobular cancer cases and 1582 ductal cancer cases were current hormone

users. One study estimated the differential risk between histology types as expressed by the annual risk (Newcomb *et al*., 2002). For invasive lobular breast cancer, the annual increases in risk compared with non-users for estrogen and estrogen–progestin use were 1.01 (95% CI = 1.00–1.05) and 1.04 (95% CI = 0.97–1.12), respectively. For invasive ductal breast cancer, the annual increases in risk compared with non-users for estrogen and estrogen–progestin use were 1.01 (95% CI = 1.00–1.03) and 1.03 (95% CI = 1.00–1.07), respectively.

In the remaining six studies, the average RR of invasive lobular cancer was 2.19-fold higher than the risk among non-users (95% CI = 1.61–2.99); average RR of invasive ductal cancer was not significantly higher than the risk among non-users (1.08, 95% CI = 0.84–1.39). The significant heterogeneity was not due to within-group variability ($P = 0.34$), but the variability between histology groups was highly significant ($P = 0.004$), indicating that hormone treatment increases risk of invasive lobular significantly more than invasive ductal cancer. In subgroup analyses, the lobular breast cancer risk with use of estrogen–progestin is the largest effect (Table V). The lobular cancer risk with estrogen–progestin is the only risk estimate among the subgroup analyses for which the nominal CIs do not include unity.

Comment: Epidemiological studies but not randomized trials indicate that estrogen–progestin use entails more than two-fold higher risk of invasive lobular breast cancer than invasive ductal breast cancer. The data are based on relatively few cases of lobular cancer, however, and several of the studies are from a small geographic region (Li *et al*., 2000, 2003b; Chen *et al*., 2002). The overall hormone-associated breast cancer risks for the seven studies were in the same range as the risks from the larger body of epidemiological studies, suggesting that the results may be representative.

Are the breast cancers associated with hormone use characterized by better prognostic factors?

Epidemiological studies and the collaborative re-analysis generally indicated that breast cancers associated with hormone use tended to be less advanced clinically than those in never users of hormones (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). In contrast, the WHI estrogen–progestin report on breast cancer found that tumours in the hormone group were larger and more likely to involve lymph node metastases than those in the placebo group (Chlebowski *et al*., 2003). Some epidemiological studies, however, did not find that prognostic factors were better in the hormone-associated cancers. Higher endogenous estrogen concentrations increased risk of receptor positive and negative breast cancers to an equivalent degree (Zeleniuch-Jacquotte *et al*., 1995); and use of unopposed estrogen had an adverse effect on breast cancer prognostic indices (LeBlanc *et al*., 1999). Many of the relevant epidemiological studies involved only cancer cases without cancer-free controls and thus lacked a population base for the comparative estimates. A recent systematic review of 25 studies on the influence of hormone use on prognostic factors concluded that because of their methodology, the epidemiological studies cannot negate the WHI findings (Antoine *et al*., 2004).

This section will include only studies that meet strict criteria for reporting on prognostic factors that have been published since the collaborative re-analysis. The coverage will be limited to studies that reported adjusted RRs with use of estrogen or estrogen–progestin according to the clinical stage, grade and receptor positivity of the breast cancers. An in-depth analysis is beyond the scope of this review because the topic, including the association with mortality, is broad enough for a stand-alone review.

Question: Among postmenopausal women who develop breast cancer, is a history of estrogen or estrogen–progestin use associated with different prognostic characteristics [stage, grade and estrogen receptor (ER) status] from those among non-users?

Data were included from studies that included risks of invasive breast cancer with current or ever use of hormones, provided that they reported the adjusted risks separately for E use and EP use compared with never use, according to each category of a given prognostic factor. Thus studies reporting only on E and EP use (HRT) together were not eligible, for example (Stallard *et al*., 2000; Manjer *et al*., 2001; Chen *et al*., 2002). Also, studies involving only cancer cases were not eligible because they could not include non-cancer control groups on which to base adjusted risks compared with never use, for example (Lower *et al*., 1999; Delgado and Lubian Lopez, 2001; Sacchini *et al*., 2002). One study combined stage zero and stage I in the analysis by stage (but excluded *in situ* cancers from the tumour grade and receptor analyses) (Kerlikowske *et al*., 2003). The RRs of developing stage I breast cancer for E and P users compared with non-users could be estimated from adjusted incidence rates that were presented in their data. Categorical analyses evaluated the separate effects of estrogen and estrogen–progestin. Table VI summarizes the summary risks at each level of the given prognostic factor for hormone

Table V. Hormone use and breast cancer histology

		Lobular breast cancer			Ductal breast cancer			Lobular and ductal			
	Studies	User cases	RR (95% CI)	*P* value*	User cases	RR (95% CI)	*P* value*	User cases	RR (95% CI)	*P* value*	*P* value†
Unopposed estrogen	6	164	1.44 (0.97–2.13)	0.001	795	0.90 (0.69–1.18)	0.083	959	1.07 (0.80–1.44)	0.019	0.003
Estrogen–progestin	6	182	2.82 (1.95–4.07)		629	1.15 (0.86–1.54)		811	1.65 (1.23–2.22)		<0.001
All hormones	7	387	2.19 (1.61–2.99)		1582	1.08 (0.84–1.39)		1969	1.43 (1.19–1.71)		<0.001

CI, confidence interval; RR, relative risk.
**P* values between lobular and ductal cancers.
†*P* values between estrogen and estrogen–progestin exposure.
Random effect models. Estrogen and estrogen–progestin rows do not include 41 lobular cancers and 158 ductal cancers with exposure identified only as HRT (Tjonneland *et al*., 2004).

Table VI. Associations between hormone use and breast cancer prognostic characteristics

Prognostic indicator	Studies	Estrogen		Estrogen–progestin	
		RR (95% CI)*	*P* value†	RR (95% CI)*	*P* value†
Stage‡	3		0.53		0.69
I		1.16 (0.76–1.78)		1.94 (1.03–3.66)	
II, III, IV		1.06 (0.69–1.64)		1.73 (1.05–2.84)	
Grade§	2		0.62		0.11
1 or 2		1.07 (0.66–1.74)		1.44 (1.28–1.64)	
3 or 4		0.99 (0.57–1.72)		1.29 (1.12–1.50)	
Estrogen receptor¶	4		0.06		0.0003
ER positive		1.14 (0.95–1.37)		1.98 (1.52–2.57)	
ER negative		0.92 (0.71–1.19)		1.00 (0.70–1.44)	

CI, confidence interval; RR, relative risk.
*Random effect models, except grade (inverse variance).
†*P* value for between-group heterogeneity Q comparing prognostic levels.
‡Newcomb *et al*., 2002; Kerlikowske *et al*., 2003; Stahlberg *et al*., 2004.
§Kerlikowske *et al*., 2003; Stahlberg *et al*., 2004.
¶Kerlikowske *et al*., 2003; Li *et al*., 2003b; Chen *et al*., 2004; Stahlberg *et al*., 2004a.

users compared with non-users. Given the number of analyses that have been carried out, the *P* values displayed should be interpreted only relative to other *P* values in the context of these analyses.

Stage of breast cancer

A stage I breast cancer is 2 cm or less in diameter and has not spread to the lymph nodes. Stage I tumours may be treated by local resection with or without radiation, followed by tamoxifen (Fyles *et al*., 2004). Thus, it is clinically relevant to determine whether breast cancers in women taking menopausal hormones are more likely to be Stage I or more advanced when diagnosed. Three epidemiological studies included data that addressed this issue (Newcomb *et al*., 2002; Kerlikowske *et al*., 2003; Stahlberg *et al*., 2004a) (Table VI).

There was no significant difference ($P = 0.53$) between the summary-adjusted risks for diagnosis of Stage I (1.16) or Stage II–IV disease (1.06) with use of estrogen alone.

Summary risks with use of estrogen–progestins were higher for either Stage I (1.94) or Stage II–IV disease (1.73) than corresponding risks with use of estrogens alone, consistent with findings in the above sections. The difference between the adjusted risks for EP use according to level of stage, however, was not significant ($P = 0.69$).

Breast cancer grade

The prognostic value of histological grade depends on a subjective evaluation of tubule formation, nuclear pleomorphism and mitotic count (Fyles *et al*., 2004). Histological grade correlates with overall survival, chiefly because of a strong correlation with the number of mitoses. Two epidemiological studies included data that addressed this issue (Kerlikowske *et al*., 2003; Stahlberg *et al*., 2004a). The summary risks are given for the fixed effect model; one study accounted for more than 95% of the weight (Kerlikowske *et al*., 2003), but the random effect model weighted the average towards the smaller study.

E did not significantly increase the likelihood of high-grade tumours. There was no significant difference ($P = 0.62$) between the summary-adjusted risks for diagnosis of breast cancer with histology grade 1 or 2 (1.07) or grade 3 or 4 (0.99) with use of estrogen alone (Table VI).

Summary risks with use of estrogen–progestins were again higher for grades 1 and 2 (1.44) or grades 3 and 4 (1.29) than the corresponding risks with use of estrogens alone. The difference between the average risks with EP use according to level of grade, however, was not significant ($P = 0.11$).

Presence of ERs

ER presence is an established prognostic marker in breast cancer, and it also indicates whether anti-estrogen therapy such as tamoxifen can be used (Ali and Coombes, 2000). Since the discovery of ERβ in 1996, the original ER is known as ERα. ERα is more abundant than ERβ, is expressed in epithelial cell nuclei and correlates with a better prognosis (Speirs *et al*., 2004). ERβ is expressed in both epithelial and stromal cells, but in tumour cells the levels are lower than in healthy cells, and its role in prognosis remains unclear (Speirs *et al*., 2004). Progesterone receptor (PR) serves as an indicator of functional ERα.

Four epidemiological studies included adjusted invasive breast cancer risks with estrogen alone or estrogen–progestin compared with never users according to ER presence or absence (Kerlikowske *et al*., 2003; Li *et al*., 2003b; Chen *et al*., 2004; Stahlberg *et al*., 2004a). No study specified ERα or ERβ, one study reported ER+/PR+ and ER+/PR– and both estimates were abstracted as ER+ (Li *et al*., 2003b); one study reported according to ER+ or PR+ was abstracted as ER+ (Stahlberg *et al*., 2004a).

There was no significant difference ($P = 0.06$) between the summary-adjusted risks for diagnosis of breast cancer with ER+ cancers (1.14) or ER– cancers (0.92) with use of estrogen alone (Table VI).

Summary risks with use of estrogen–progestins were higher for ER+ cancers (1.98) but not for ER– cancers (1.00) than with use of estrogens alone. The difference between the average EP-associated risks according to presence or absence of ER was very unlikely to be because of chance ($P = 0.0003$).

Comment on prognostic factors: Table VI summarizes that with one exception, the trend in epidemiological studies towards more

favourable prognostic factors is based on small differences that are not significant. In the exception, the higher risk that estrogen–progestin use would be associated with receptor positive rather than negative cancers could be an alpha error arising from the conduct of numerous statistical comparisons. Although the probability was very small, this association with estrogen–progestin use but not estrogen use lacks a manifest biological plausibility. More important to clinicians, neither estrogen alone nor EP was associated with an increase in receptor negative cancers. Overall, however, the results of this group of studies that were not included in the recent systematic review are no more convincing than the included studies with respect to a link between cancers associated with hormone use and better prognostic factors.

Discussion

This review finds that the main results of epidemiological studies and RCTs are not dissimilar with respect to the risk of invasive breast cancer associated with use of estrogen or estrogen–progestin for treatment of menopausal symptoms. The breast cancer risk is higher with use of estrogen–progestin than with use of estrogen alone; the risk rises to become significant within 5 years after initial use and the excess risk returns to normal levels within 5 years after last use. Breast cancer risk does not vary according to type of hormone, dosage or route of administration, although continuous progestin regimens may involve more risk than sequential regimens. Breast cancer risk is highest for lobular cancer types with use of estrogen–progestin combinations. Finally, there is no consistent evidence that hormone-associated cancers have better prognostic characteristics than those which develop in non-users.

Although this was not a systematic review concerning a single question, it made use of systematic methods and quantitative assessment to address the individual clinical questions. Of course, no review could capture all of the important findings of the RCTs. For example, in a detailed report of the breast cancers in the estrogen–progestin study, the WHI data suggest that women in the hormone group were more likely to require additional diagnostic studies for equivocal mammographic findings than those in the placebo group. The need to summarize briefly is an inherent weakness of any broadly based review and, in this case, it was necessary to forego commentary on some clinically important issues. The possible interaction between hormonal effects and genetic factors including those that may be manifest through a family history of breast cancer requires further study and synthesis in a review. The review also did not cover the impact of hormone use on breast cancer mortality, although it did cover prognostic factors and study of cancer prognostic factors is motivated by concern about cancer mortality. The Million Women Study indicated that breast cancer mortality was 1.22-fold higher (95% CI = 1.00–1.48) for current users at recruitment, but not for past users, compared with never users (Beral and Million Women Study Collaborators, 2003). Understanding how hormone use affects mortality will help to delineate whether the hormone effect is promotional or additive, leading to earlier diagnosis, or initiates new cancers, leading to higher incidence. There is a need for an in-depth review of prognostic factors in hormone-associated tumours and breast cancer mortality.

The risk of breast cancer with hormone use is a much-studied question. The eight RCTs involved more than 32 000 women, the collaborative re-analysis included more than 52 000 cancer cases and 108 000 controls, and the epidemiological studies in Table II included nearly two million women. The Million Women Study dominated some study questions, and the unprecedented 800 000 women eligible for that report constituted just over one third of the women in the recent epidemiological studies. The plentiful data and the broad coherence between the randomized and observational findings suggest that new studies are unlikely to alter the key findings about overall breast cancer risk. Research is needed, however, to delineate at least three attendant issues: progestin types, lobular cancer incidence and receptor presence as an indicator of prognosis.

With respect to progestin types, there is not universal agreement on the role of progestin, although this is critical to decisions about prescribing sequential or continuous regimens. Laboratory studies indicated that progestins may be associated with increased breast epithelial growth (Anderson *et al*., 1989; Lange *et al*., 1999; Pike and Ross, 2000). Mitogenic and anti-apoptotic effects may vary according to the type of progestin and type of regimen, dose levels, the duration of breast tissue exposure to progestin activity and the degree of mammary gland tissue differentiation during exposure (Druckmann, 2003) Although the progestogenic effect is common to all progestins, some biological effects differ according to progestin type. For example, progestins without androgenic action inhibit the enzymes in breast tissue that induce local synthesis of estradiol, whereas testosterone-derivative progestins are less inhibitory (Druckmann, 2003; Schindler *et al*., 2003).

Research also is needed on whether the impact of hormone use on lobular cancer is responsible in part for the increase in breast cancer risk with hormones. It remains unclear whether that influence is more important than mammography screening as a factor leading to rising lobular cancer incidence in some areas (Levi *et al*., 2003). Third in the list of issues requiring research is the need to further explore receptor presence in hormone-associated and other breast cancers, making use of the most specific techniques for characterization of the receptors for estrogen and progesterone. As understanding of receptor heterogeneity increases, it is clear that small differences in molecular structure may induce differences in receptor activity that are sufficient to alter the balance between breast cell proliferation and apoptosis (Sitruk-Ware and Plu-Bureau, 2004).

It has not been practical to estimate absolute risks for each of the above clinical questions. It may be useful, however, to provide a perspective for the estimated RRs, such as the overall 1.5- to 1.8-fold higher risk of invasive breast cancer associated with current use of estrogen–progestin. A surgical review listed as relatively modest (RR < 2), several breast cancer risk factors that have received much publicity, including hormone use, alcohol consumption, obesity and nulliparity. A prior history of neoplastic breast disease and a genetic predisposition were significantly more important factors with magnitude ranging from RR = 3 (for some women with a family history) to 200 (for premenopausal women positive for a BRCA mutation) (Singletary, 2003).

Even such modest RRs may give an individual woman an unnecessarily alarming sense of the risk. The collaborative re-analysis and the Million Women Study have estimated the actual number of breast cancer cases that can be expected according to reasonable scenarios for the average postmenopausal woman. The collaborative re-analysis estimated that for 1000 women not using

hormones, there would be 20 breast cancer cases from age 50–60 years, based on incidence rates intermediate between the United Kingdom and the United States. With 5 and 10 years of hormone use, there would be, two and six additional breast cancer cases, respectively, similar to estimates for estrogen alone in The Million Women Study (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Beral and Million Women Study Collaborators, 2003). An absolute risk of this magnitude has public health significance, but for the average woman it is probably below the level which affects decisions about hormone treatment. Estrogen–progestin use for 5 and 10 years, however, would add 6 and 19 additional breast cancer cases to the 20 cases diagnosed in non-users (Beral and Million Women Study Collaborators, 2003). The Million Women Study estimated that for every 10 cases of endometrial cancer prevented by adding a progestin to E over 10 years, there would be an additional 14 cases of breast cancer. Of course, treatment is not generally planned for such long periods, but this evidence is a compelling motivation for clinicians to explore safer ways of providing progestogen and/or safer ways of providing unopposed estrogen for women with a uterus who need treatment with hormones for menopausal symptoms.

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