Estrogen, Estrogen Plus Progestin Therapy, and Risk of Breast Cancer

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ABSTRACT

Epidemiologic evidence relating use of postmenopausal hormones to risk of breast cancer by nature relies on trends in prescribing practices. Data on the adverse effect of combination estrogen plus progestin used for long durations has only become available over the past decade. Evidence is reviewed relating estrogen alone and estrogen plus progestin to increased risk of breast cancer. Whereas current evidence indicates that longer duration of use increases risk of invasive breast cancer regardless of formulation, the rate of increase in risk is greater for combination estrogen plus progestin therapy. Although data are limited, continuous combined therapy and sequential therapy seem to have comparable impact on breast cancer risk. Combination therapy is more strongly related to lobular breast cancer than is estrogen alone. Unresolved issues remain about dose of estrogen and progestin in relation to risk, and about identification of women for whom short-term use to relieve menopausal symptoms may be safe and effective.

INTRODUCTION

Approximately 38% of postmenopausal women in the United States use hormone replacement therapy (HRT; ref. 1). In 2000, there were 46 million prescriptions for Premarin (conjugated equine estrogen), making it the second most frequently prescribed medication in the United States, and 22.3 million prescriptions for Prempro (Premarin plus progestin as a continuous combined therapy; ref. 2). Although FDA-approved indications for hormone therapy include relief of menopausal symptoms and prevention of osteoporosis, long-term use has been in vogue to prevent a range of chronic conditions, especially heart disease. Estrogen alone was the dominant hormone until the increased risk of endometrial cancer led to the addition of progestins for women with an intact uterus. Since the mid-1980s estrogen/progestin use has steadily increased (3).

In this review of evidence, I first consider formulation of postmenopausal HRT in relation to incidence of breast cancer. This is followed by a summary of evidence on hormone therapy and histologic subtypes of breast cancer.

Presented at the Fourth International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, July 21-22, 2004, Cambridge, Massachusetts.

Grant support: American Cancer Society Clinical Research Professorship.

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The relation between use of HRT and the risk of breast cancer has been reviewed many times (4, 5). Early epidemiologic evaluations considered ever use compared with never use of HRT. These data were largely driven by short-term use of unopposed estrogen for relief of menopausal symptoms. In this setting, ever use represents the average duration of use among all users, which was typically <2 years.

In 1991, Steinberg and colleagues reviewed evidence for a duration effect of HRT on risk of breast cancer (6). They concluded that the majority of studies support such a relation; longer use was related to higher risk of breast cancer. When combined quantitatively, using a dose-response slope from each study, the overall meta-analytic summary supported a clear relation of increasing risk of breast cancer with increasing duration of use of HRT. After 15 years of use, risk of breast cancer increased 30%.

To provide a summary of evidence and overcome limitations of different analytic approaches in different studies, Beral and colleagues formed the Collaborative Group on Hormonal Factors in Breast Cancer. From Oxford University they obtained data from 51 of 63 eligible studies (7). Ten of the studies could not provide original data, and one group declined to collaborate (Drug Epidemiology Unit at Boston University). The Collaborative Group then reanalyzed data using common approaches and reported in 1997 that risk of breast cancer increased significantly for each year of use of HRT (7). The primary analysis was based on 53,865 postmenopausal women with a known age at menopause, including 17,949 cases of breast cancer. The relative risk was 1.35 [95% confidence interval (CI), 1.21–1.49] for women who used HRT for 5 years or longer. The average duration of use among these women was 11 years. The analysis considered many factors that may modify the effect of HRT and concluded that only lean body mass modified the association. The adverse effect of hormone therapy was greater among lean women.

This analysis highlighted the importance of controlling for exact age at menopause when evaluating the relation between duration of use of hormones and risk of breast cancer. Early age at menopause is associated with reduced risk of breast cancer (8, 9). Thus, at any age, women with longer durations of use of HRT will, on average, have had an earlier menopause, resulting in a lower risk of breast cancer. Pike and colleagues showed that this bias will lead to an underestimate of the adverse effect of postmenopausal hormone use (10). Rockhill and colleagues (11) subsequently showed the impact of including women of unknown age at menopause in analyses. In such an analysis, the association is weaker, but more likely to be significant, because the statistical power for the analysis is increased by the inclusion of more women (11). In the Collaborative Group reanalysis, when women with missing age at menopause were included in a subanalysis, the magnitude of the association was markedly reduced.

In the primary analysis of women with known age at menopause, the collaborative reanalysis found that the major

adverse effect of HRT use was limited to women who were current or recent past users. Women who had last used hormones more than 5 years before diagnosis were not at increased risk regardless of duration of prior use of HRT (7).

Given that the majority of studies included in this combined reanalysis were published in the 1980s, most cases were diagnosed at a time when combined hormone therapy (estrogen plus progestin) had not been used for an extended period. In fact, many studies did not report on type of HRT because almost all women were using unopposed estrogen.

Whereas reviews published following this combined reanalysis differed in their conclusions about the cause-and-effect relation between use of HRT and breast cancer, Colditz pointed to a central and causal role for hormones in the etiology of breast cancer (4). Evidence from studies of blood estrogen levels among postmenopausal women show that higher levels are associated with increased risk of subsequent breast cancer; low bone density is associated with decreased risk of breast cancer; and the evidence from studies of HRT use, when viewed together, all supported a causal interpretation. Subsequent combined analysis of the prospective studies of blood estrogen levels and risk of breast cancer confirm the central role blood hormone levels play in the etiology of postmenopausal breast cancer (12).

Type of Postmenopausal Hormone Therapy and Risk of Breast Cancer

Epidemiologic studies have specifically addressed the formulation of hormone therapy used and risk of breast cancer (Table 1). Many of these more recent studies continue to have small numbers of cases among women with longer durations of use of combination estrogen plus progestin therapy.

In addition to the epidemiologic studies in Table 1, the Women's Health Initiative (WHI, ref. 13), a randomized controlled trial, was established in part to evaluate the risks and benefits of combination estrogen plus progestin therapy among postmenopausal women. The WHI was stopped early at the recommendation of the data and safety monitoring board because women receiving the active drug had an increased risk of invasive breast cancer (hazard ratio, 1.26; 95% CI, 1.00–1.59), and an overall measure of health effects suggested that the treatment was causing more harm than good (global index, 1.15; 95% CI, 1.03–1.28). The decision to stop the trial after an average follow-up of 5.2 years (planned duration, 8.5 years) was made when these results met predetermined levels of harm. Furthermore, a significant trend to increasing risk of breast cancer with increasing time on therapy was noted. These results, based on intention-to-treat random allocation to therapeutic arms, were observed despite substantial cross-over during the trial. Over the course of the trial, 42% of women allocated to estrogen plus progestin had stopped taking study medication, as had 38% of the women on placebo. In addition, some women in each group had commenced taking therapy through their own clinician: 6.2% on the estrogen plus progestin group and 10.7% on the placebo group. These compliance rates would then underestimate the true adverse effect of hormones on cancer risk among women taking therapy. Rather, the results as presented from the trial reflect the risk of a "program" administering hormone therapy to all eligible women. Subsequent analysis indicated that more women had abnormal mammograms in the estrogen plus progestin group, and the tumors in this group were more advanced (14).

The conjugated equine estrogen versus placebo component of the WHI continued until November 2003, and showed no increase in risk of breast cancer based on 218 cases (94 invasive cases in the conjugated equine estrogen arm and 124 cases in the placebo arm; ref. 15). Again, noncompliance must be considered when interpreting these data, as more than 50% of women had stopped therapy by the time of study termination.

The UK Million Women Study recruited 1,084,110 women ages 50 to 64 years attending the National Health Service Breast Screening Programme for routine mammography (16). This is the largest study of incidence published to date. Women were recruited between 1996 and 2001, and followed up using National Health Service central registers, through December 2001 for incidence and December 2002 for mortality. During follow-up, 9,364 incident breast cancer cases were identified and 637 women died due to breast cancer. Current use of estrogen alone [relative risk (RR), 1.30; 95% CI, 1.22-1.38] and estrogen plus progestin (RR, 2.00; 95% CI, 1.91-2.09) were at increased risk compared with never users after adjusting for age, time since menopause, parity and age at first birth, family history of breast cancer, body mass index, region in the United Kingdom, and socioeconomic deprivation index. Among current users, risk increased with duration of use of estrogen alone ($RR_{10\ years}$, 1.37; 1.22-1.54) and estrogen plus progestin ($RR_{10\ years}$, 2.31; 2.08-2.56). Concerning preparation of estrogen used, there was no significant difference in the risk associated with equine estrogen versus synthetic estradiol ($P_{difference} = 0.6$) or according to dose. Risk was raised significantly for users of oral, transdermal, and implanted preparations. Risk of breast cancer was significantly increased for users of medroxyprogesterone acetate, norethisterone, and norgestrel and for users of sequential and continuous regimens. Women using the combination of equine estrogen plus medroxyprogesterone acetate, comparable to that used in the WHI trial, had RRs that were 1.62 (95% CI, 1.34-1.96) for <5 years of use and 2.42 (95% CI, 2.08-2.81) for ≥5 years of use compared with never users. Of note, RRs were higher among lean women (<25 kg/m^2) than overweight and obese women using estrogen alone and for those using estrogen plus progestin. Self-reported formulation had very high agreement with physician records.

In this large prospective study mortality was also elevated during the average of ~4.1 years of follow-up breast cancer mortality was elevated significantly among women who were current users of postmenopausal hormone therapy at baseline (RR, 1.22; 95% CI, 1.05-1.41). Due to a relatively small number of deaths, the investigators did not report results separately for the different preparations of hormone therapy.

SUMMARY

The overall association between use of postmenopausal hormones and risk of breast cancer is unequivocal. Refinement of the relation for specific formulations over the past 5 years has clearly documented that estrogen increases risk of breast cancer and that adding progestin to estrogen therapy adds further to the risk. The magnitude of risk is easily underestimated, particularly in studies that do not control for age at menopause (preferably

Table 1 Studies of estrogen alone or estrogen plus progestin in relation to risk of breast cancer

Authors	Design	Dates Diagnosis	Control for age at menopause	Result	Comment
Bergkvist et al. (22)	Sweden cohort, 23,244 women ≥35 y	5.7 y of follow-up, 253 cases	Not reported	RR increased with duration of use (P = 0.0001)	Risk highest in women who used E + P
Colditz et al. (23)	Cohort	1,935 cases	Control in 2-y intervals for age at menopause, also control for type	Increased risk for current users	RR greater for older women
		930 never users		Increase for E alone, 1.32 (95% CI, 1.14-1.61)	Significant increase in death from BrCa
		270 E alone		Increase for E + P, 1.41 (95% CI, 1.15–1.74)	
		110 E + P 12 P alone 4 E + testosterone			
Stanford et al. (24)	Case-control, Seattle registry	537 cases	Age at menopause evaluated	Current E + P not related to risk, 0.9 (95% CI, 0.6–1.2)	Dose of E did not modify risk
		50–64	Analysis for duration of HRT did not control for age at menopause	Current E not related, 0.9 (95% CI, 0.7–1.3)	No association with duration of E or E + P
		1/88 to 6/90			
Persson et al. (25)	Prospective cohort ages 40–70, Uppsala, Sweden	Follow-up 1990 to June 30, 1995	No control for age at menopause	HRT, $RR_{10+\ y}$ = 2.0 (95% CI, 1.0-4.0)	Screened population
		435 cases (397; 87% invasive)		E + P, $RR_{11+\ y}$ = 2.4 (95% CI, 0.7–8.6)	E + P, 11 y based on 4 cases and 8 controls Possible stronger adverse effect after addition of progestins
Persson et al. (26)	Prospective Swedish cohort 60,298; subcohort of 11,231 prescribed HRT	Followed up from questionnaire 1987–1988 to 1993	3 strata: <50, 50–54, 55+	E, $RR_{6+\ y}$ = 1.1 (95% CI, 0.7–1.7)	
		198 cases		E + P, $RR_{6+\ y}$ = 1.7 (95% CI, 1.1–2.6) Recent use associated with higher RR than distant past use	
Magnusson et al. (27)	Case-control study Sweden	50–74 y	<45, 45-49, 50-1, 52-4, 55+	Increase per year: E, 1.03 (95% CI, 0.98-1.08); E + P, 1.07 (95% CI, 1.02–1.11)	Testosterone-derived P had stronger relation
		Dx 10/93 to 3/95	Type of menopause		Continuous combined therapy stronger relation than cyclic
		84% of cases participated 2,563 cases (42 *in situ*) 2,845 controls			
Schairer et al. (20)	BCDDP cohort, 46,355 women	2,082 cases	Used narrow categories for age at menopause	Increase in risk with E only (RR, 1.2; 95% CI, 1.0.–1.4) and E + P (RR, 1.4; 95% CI, 1.1–1.8) limited to use within previous 4 y	E + P significantly related to D

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Table 1 Studies of estrogen alone or estrogen plus progestin in relation to risk of breast cancer (cont'd)

Authors	Design	Dates Diagnosis	Control for age at menopause	Result	Comment
Schairer et al. (20)			Subanalysis excluded unknown age at menopause		Too few L to evaluate alone
Ross et al. (28)	Case-control LA county	4.5-y interval	Exclude women with hysterectomy without bilateral oophorectomy	Risk per 5 y	Risk higher with sequential HRT (1.38 per 5 y) than CCRT (1.09 per 5 y)
		1987–1989 and 1992	Age at menopause continuous	ERT, 1.06 (95% CI, 0.97–1.15)	
		1897 cases		HRT, 1.24 (95% CI, 1.07–1.45)	
		1637 controls			
Kirsh and Kreiger (29)	Case-control, Ontario, Canada	404 cases	Age at menopause, continuous variable	RR per year of use: E, 1.03 (95% CI, 0.97–1.09); E + P, 1.15 (95% CI, 1.01–1.33)	$RR_{10+\ y}$: E, 1.74 (95% CI, 0.93-3.24); E + P, 3.48 (95% CI, 1.00–12.11)
		403 controls			Results similar when restricted to invasive D or L (22 cases excluded)
		Dx 4/95 and 3/96			
Newcomb et al. (30)	Case-control, Wisconsin, New Hampshire, Massachusetts	50–79	Inferred age at menopause for women with hysterectomy. Control for age at menopause in 8 categories	Average duration: E, 10.1 y; E + P, 4.7 y	Reliability study of self-reported hormone use
		Dx 1/92 to 12/94		RR per year of use: E, 1.02 (95% CI, 1.01–1.03); E + P, 1.04 (95% CI, 1.01–1.08)	RR = 0.83 for duration of use
		5685 cases, 83% of cases available for analysis			RR diminished with time since last use for E but limited power for E + P
Li et al. (31)	Case-control, NM	1/92 through 12/94	No control for age at menopause	Risk increased with duration of ERT among both groups after control for P	Limited power
	Considers Hispanic (H) and non-Hispanic White (non-H) women	30–74 y		P use not related to risk	Duration of P, median 18 mo H, 48 mo non-H
		149 H			E, substantially longer duration of use
		217 non-H cases			
Chen et al. (32)	Case-control	Cases 7/90 to 12/95	Age at menopause did not confound results and was not ontrolled in final models	Significant increase in risk of BrCa with E, and also E + P—either sequential or continuous	CCRT few cases and trend not significant
	Group Health Cooperative	705 cases			Results stronger among leaner women
Roussouw et al. (13)	RCT	Prempro vs. placebo	RCT	HR, 1.24; $P < 0.001$	Substantial noncompliance; 42% of women stopped therapy in the E + P arm and 38% in placebo arm
		245 cases Prempro vs. 185 placebo		Significant trend with duration of use	

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Table 1 Studies of estrogen alone or estrogen plus progestin in relation to risk of breast cancer (cont'd)

Authors	Design	Dates Diagnosis	Control for age at menopause	Result	Comment
Olsson et al. (33)	Sweden cohort, 29,508 women	1990–1992 interview	Control for age at menopause	Longer CCRT, higher HR than sequential	
		Followed up through 2001		4.6 vs. 2.23	
		556 cases identified through tumor registry		Estradiol without P did not increase risk of BrCa significantly	
				48+ mo CCRT RR = 6.28 vs. sequential RR =3.11	
Million Women Study collaborators (16)	UK cohort	Recruited 1996 to 2001	For hysterectomy assume postmenopausal from age 53 and assume age at menopause comparable to others of same age	Current use:	Risk increased regardless of pattern of P use, risk increased with duration of use of hormones, mortality increased significant for current users, but not broken out for type of hormone used
	1,084,110 women, ages 50-64 y	Followed up for incidence and mortality		E only, RR 1.30 (95% CI, 1.21–1.40)	
		9,364 incident BrCa		E + P, RR 2.00 (95% CI, 1.88–2.12)	
		637 BrCa deaths		E only, $RR_{10+\ y}$ 1.37 (95% CI, 1.22–1.54)	
				E + P, $RR_{10+\ y}$ 2.31 (95% CI, 2.08–2.56)	
Anderson et al. (15)	Women's Health Initiative	Premarin vs. placebo	Women with prior hysterectomy ages 50–79 y	HR 0.77 (95% CI, 0.59–1.01)	By termination of study more than 50% of women were not taking study medications
	RCT		94 cases in Premarin and 124 in placebo		

Abbreviations: *E,* estrogen alone; *P,* progestin; *BrCa,* breast cancer; *Dx,* diagnosis; *BCDDP,* Breast Cancer Detection Demonstration Project; *D,* ductal carcinoma; *L,* lobular carcinoma; *CCRT,* continuous combined replacement therapy; *ERT,* estrogen replacement therapy; *RCT,* randomized controlled trial; *HR,* hazard ratio.

exact age in single years). The better the statistical control for age at menopause, the stronger the association between duration of use of hormone therapy and risk of breast cancer. Refinement of our understanding of the relation between days per month of use of progestin and risk is ongoing. The randomized controlled WHI trial clearly shows that continuous combined therapy significantly increases risk of breast cancer. Several studies also suggest that sequential use of estrogen plus progestin also increases risk. The largest study to date, the UK Million Women Study with over 9,000 cases of breast cancer, reports no difference in risk among women using estrogen plus progestin based on the number of days per month that the progestin is used.

When Is an Increase in Risk a Cause of Cancer?

In synthesizing evidence to evaluate a cause-and-effect relation, one considers a range of issues including the strength of the study design, the consistency of the findings, and the temporal relation (exposure before diagnosis of disease), among others. Applying these considerations to the evidence for hormones and breast cancer, one can conclude that use of postmenopausal hormones causes breast cancer. Use of estrogen plus progestin causes more cancers than estrogen alone for any given duration of use. Further evidence supporting a causal role for estrogens in breast cancer etiology comes from the prevention trials of selective estrogen receptor modulators. The antiestrogen effects of tamoxifen and raloxifene have both reduced the incidence of breast cancer in healthy women (17, 18).

Breast Cancer Subtypes

The relation between hormone therapy and the histologic subtype of breast cancer has recently gained attention. Li and colleagues analyzed data available through the U.S. Surveillance, Epidemiology, and End Results (SEER) program to evaluate trends in breast cancer incidence from 1987 through

1999 (19). Adjusting for age and stage at diagnosis, they note a 4% increase in breast cancer diagnosed over this 13-year period. In absolute terms, the increase was 1.5 additional cases of ductal carcinoma per 100,000 women and 6.2 additional cases of lobular carcinoma per 100,000 women. They note a concurrent increase in the use of combined HRT over this same period, raising the hypothesis that the two trends may be related.

Several methodologic challenges must be addressed when evaluating risk in relation to a subset of cases. This is particularly so when the subset of potential interest comprises only ≤10% of the total disease burden. First is the challenge of adequate statistical power and the need for large studies to overcome chance findings. Second is the potential for changing diagnostic criteria or the rigor of their application by pathologists. Finally, analytic approaches may vary. Among studies reporting on postmenopausal hormone therapy and histologic subtypes of breast cancer, there has been considerable variation in analytic approaches and findings reported. Table 2 provides a summary of the major studies, their findings and methodologies.

INTERPRETATION

There is a strong suggestion that estrogen plus progestin therapy is related to risk of lobular cancer. Given the clear causal relation between estrogen plus progestin therapy and breast cancer overall, the stronger relation with lobular breast cancer further refines our understanding of this cause-and-effect relation. With the large and growing evidence on the role of combination estrogen plus progestin on risk of breast cancer, we cannot rule out a causal relation with ductal carcinoma also, although it will be a smaller relative risk as noted by Li et al. The prospective data from the Breast Cancer Detection Demonstration Project cohort (20) support this significant increase in risk for ductal cancer in addition to the risk for lobular breast cancer. Notably, the largest case-control studies by Newcomb and colleagues show that combination estrogen plus progestin is related to increased risk of both ductal and lobular carcinoma, a finding that is likely necessary to explain the consistent overall elevation in risk observed for total breast cancer incidence.

Limitations that must be considered when interpreting these data include the design of studies addressing histologic subtypes. To date, most of these studies have used a case-control design, which has the potential for more bias in estimating relative risks associated with hormone use. However, one would not expect such bias to operate differentially according to histology subtypes of breast cancer. Importantly, the approach to statistical analysis in which age at menopause is either excluded or poorly controlled could also bias the result, as described earlier. Mammography has been considered as one factor in the increase in reported breast cancers over the past 15 or more years. However, studies show that mammography is not particularly effective as a means to identify lobular breast cancer; hence, this is unlikely to account for the findings. Furthermore, the contribution of mammography as a source of bias has been evaluated and determined to have minimal impact in an environment in which the majority of women in their 50s and 60s undergo routine screening (21). The UK study, conducted within the context of the national mammography screening program, further reduces these sources of potential bias. Whereas the evidence from the randomized controlled WHI trial would be deemed to be least biased based on study design, the number of incident breast cancers was small and hence the statistical power to differentiate between the magnitude of relative risks for lobular and ductal cancer was limited.

Throughout the studies reporting on use of hormone therapies and risk of breast cancer, risk is limited to recent and current users. The typical definition of recent use in the literature is within 5 years of diagnosis, although some studies shorten this interval to within 2 years of diagnosis. Data remain sparse to evaluate risk among women who used combination therapy for long durations, say >10 years, and then stopped therapy.

In conclusion, these data support a causal role for estrogen plus progestin in relation to the risk of breast cancer. The increase in risk of breast cancer per year of use is greater for the combination therapy than for use of estrogen alone. Estrogen alone, however, is also related to an increase in risk of breast cancer. Combination therapy increases risk of lobular cancer more than it increases risk of ductal breast cancer.

OPEN DISCUSSION

Dr. James Ingle: As I remember, in the published report of the WHI study of estrogen alone versus placebo, there was a reduction in invasive breast cancer in the treatment arm of about 23%. Could you comment on that?

Dr. Graham Colditz: That is in the context of a lot of noncompliance; it is not significant. If we look at the standard epidemiologic study, women who are started on estrogen at menopause either had more symptoms or had lower bone density as an indication for estrogen treatment. Those factors suggest a woman is at lower risk of breast cancer to begin with. So some of the epidemiologic data that might show a lower risk in the first few years of use of unopposed estrogen compared with a never user could in fact be related to the indication for use. Now, a randomized trial should get rid of that issue, and yet it doesn't seem to. So I am left with no perfect explanation as to why a relatively short-term use of estrogen in current and past users produces a suggestion of lower risk. However, it is just 200 cases.

Dr. Richard Santen: When I made rough calculations regarding the power of the study, it didn't seem to me that the WHI study was powered sufficiently to demonstrate an increased risk of breast cancer from estrogen alone. If the relative risk increases by 2% a year, then at 5 years the relative risk is increased by 10%. If you calculate the incidence in the population and multiply this by a 10% increased risk, the numbers of excess breast cancers would seem to be too low to be statistically significant. Am I correct about that?

Dr. Colditz: Right. If you look at the sorts of risks that are coming out of the other estrogen alone studies, it would have been underpowered to find an independent adverse effect there.

Dr. Santen: One of the interesting things about the estrogen plus progestin WHI study was that the increased risk in breast cancer with E + P was only seen in the individuals who had previously been on hormone therapy and then stopped before they went on E + P. That would tend to suggest that perhaps it is

Table 2 Type of hormone replacement therapy and the risk of breast cancer according to cell type of cancer

Authors	Design	Dates of diagnosis	Analysis	Results	Comment
Gapstur et al. (34)	Prospective Iowa Women's Health Study 37,105 women	11-y follow-up, 1986 to 1996; 1520 cases BrCa	SEER tumor classification Age at menopause "classified into logical categories"	175 *in situ*, 82 favorable histology, 1164 D and or L	No relation ever use HRT and *in situ* or invasive D or L among women with ≥5 y of use HRT, RR invasive BrCa favorable significantly greater than RR for invasive D/L
Manjer et al. (35)	Malmo prevention clinic. Cohort 5865 postmenopausal women Exam 83 to 92 Dx through 4/97	141 cases no control for age at menopause	D → BrCa: 99 L → BrCa: 16 HRT yes/no	RR (95% CI): D,1.25 (0.76–2.07); L,: 4.38 (1.60–12.0)	
Li et al. (36)	Cancer control, King County	20 cases L 185 cases 258 controls		RR (95% CI): L, 2.6 (1.1–5.8); D, 0.7 (0.5–1.1)	HRT related to L and not D
Chen et al. (32)	Case-control, Group Health Cooperative	Cases 7/90 to 12/95 705 cases	Long term use 57+ mo	RR (95% CI): L, 3.07 (2.05–7.44); non-L, 1.52 (1.01–2.29)	Results appear stronger in l but trend significant in both L and D
Newcomer et al. (37)	Case-control, Wisconsin, New Hampshire, Massachusetts, and Maine	1988-1991 219 L 2,172 D 242 D subtypes		L associated with recent E or E + P use E 1.8 (1.0–3.4) E + P 3.6 (1.807.6)	No association with D. Controls for age and type of menopause but does not address duration of therapy
Daling et al. (38)	Multicenter case-control study	Dx 7/94 through 4/98	Age at menopause imputed	$RR_{>5\text{-y use}}$	Analysis among women with known age at menopause substantially increased RR for D. Researchers' conclusions: data from this study suggest that neither E nor CCRT substantially increase risk of D among women <65
	Cases <65 Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle	263 L 1386 D 100 other	Results adjusted for age, race, study site, and type of menopause Subanalysis limited to women with known age at menopause	E 0.7 (D)-251; 1.3 (L)-57 E + P, 1.0 (D)-222; 2.0 (L)-64 Sequential E + P 1.0, 1.5; CCRT 1.2, 2.5	
Li et al. (39)	Case-control, Western Washington state 65–79	Dx 4/97 through 5/99 196 L 656 D 114 other histology	Control for type of menopause and age at menopause in 5-y categories		

a multiple-hit process. How would you respond to that interpretation?

Dr. Colditz: Well, certainly in the context of WHI; in the context of the Million Women study, most in the validation study of 66% plus were taking the same medication for the full duration of the experience of taking a postmenopausal hormone. So, not quite comparable. I think the bottom line, though, is consistent with multiple hits being required. In fact, adding the progestin presumably is keeping the cell cycle going more so than in the nonuser or the unopposed estrogen, and therefore facilitating the accumulation of more hits. We know that mammographic breast density goes up, on average, when a woman starts taking hormones, so there are markers of increasing activity in the breast.

Dr. Kent Osborne: I don't know much about the statistical design of WHI, but one would have thought that the statisticians would have anticipated a fairly high dropout rate.

Dr. Colditz: They actually did, but the dropout rate exceeded the design features. It went to 50% in both arms, estrogen alone and the estrogen plus progestin. The noncompliance was at a point that the trial was about to become uninformative with further follow-up.

Dr. Donald McDonnell: It is my recollection that there was no real increase in DCIS or noninvasive breast cancer in WHI. Is it not strange that they were able to pick up an increase in invasive breast cancer without picking up increases in the precancerous lesions?

Dr. Colditz: The challenge with estrogen plus progestin is that it makes the mammogram denser, when then makes it harder to detect lobular lesions and maybe some of the DCIS.

Dr. C. Kent Osborne: The reverse of that phenomenon is in the P1 prevention trial in that there is still relatively short follow-up of exposure, so that the first batch of cancers are the preexisting ones that have been stimulated to become clinically evident. So, conceivably, the hormones are stimulating them to progress out of DCIS and into the invasive stage.

Dr. Colditz: So if you can contrast the two situations, 5 years of follow-up is enough to get this significant increase in cancers. And if you compare the P1 or raloxifene studies, in the same amount of time you can get a significant decrease in cancers.

Dr. Osborne: And in both situations, the agents may both be acting on preexisting subclinical cancers.

Dr. Santen: When investigators in Europe comment upon the Women's Health Initiative Study, they commonly state that the estrogen used is Premarin, which is derived from horse urine and contains a large amount of estrone sulfate. The progestin used is medroxyprogesterone acetate, which may not be representative of all progestins as a class. Reading the Million Women Study, I became reasonably convinced that the findings observed represented a class effect of estrogen plus progestin and not Premarin and MPA. Do you generally ascribe to that conclusion?

Dr. Colditz: Coming in, I would not have thought so, but that is my read of the Million Women Study. They had hundreds of cases with subdermal use, and we always thought subdermal would be different.

Dr. Carlos Arteaga: You are doing some prospective studies that require biopsies in women at risk. How do you deal with the fact that, according to some studies, just a biopsy itself may increase the risk of breast cancer? Has that come up with reviewers and how have you dealt with it, because it has been an occasional problem in some of our presurgical studies in women with invasive cancer.

Dr. Colditz: In part because of the recent *JNCI* piece [J Natl Cancer Inst 2004;96:616–20], we've gone back to try and estimate what really is the risk in women who have had a biopsy that has no proliferative or atypia changes, what we would call sort of normal, no proliferative disease. In the Vanderbilt studies and in all our studies, that group is used as the reference, which is fine when you are looking at the benign markers, but when you go back to then look in the broader population all the other studies just have a history of biopsy for benign lesion, that gives you a 50% increase in risk. So how do you explain that? We met with our statisticians last week to plan that.

REFERENCES

1. Keating N, Cleary P, Rossi A, Zaslavsky A, Ayanian J. Use of hormone replacement therapy by postmenopausal women in the United States. Ann Intern Med 1999;130:545–53.

2. Kreling D, Mott D, Wiederholt J, Lundy J, Levitt L. Prescription drug trends. In: A chartbook update. Menlo Park (CA): Kaiser Family Foundation; 2001. p. 1–72.

3. Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992. Obstet Gynecol 1995;85:6–10.

4. Colditz GA. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. J Natl Cancer Inst 1998;90: 814–23.

5. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276–85.

6. Steinberg KK, Thacker SB, Smith SJ, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991;265:1985–90.

7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiologic studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350: 1047–59.

8. Lilienfeld AM. The relationship of cancer of the female breast to artificial menopause and marital status. Cancer 1956;9:927–34.

9. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. J Natl Cancer Inst 1972;48:605–13.

10. Pike M, Ross R, Spicer D. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. Am J Epidemiol 1998;147:718–21.

11. Rockhill B, Colditz G, Rosner B. Bias in breast cancer analyses due to error in age at menopause. Am J Epidemiol 2000;151:404–8.

12. The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.

13. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.

14. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. JAMA 2003;289:3243–53.

15. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701–12.

16. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.

17. Fisher B, Costantino J, Wickerham D, et al, other National Surgical Adjuvant Breast and Bowel Project Investigators. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90:1371–88.

18. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. JAMA 1999; 281:2189–97.

19. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. JAMA 2003;289: 1421–4.

20. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton LA, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;283:485–91.

21. Joffe MM, Byrne C, Colditz GA. Postmenopausal hormone use, screening, and breast cancer: characterization and control of a bias. Epidemiology 2001;12:429–38.

22. Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989;321:293–7.

23. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589–93.

24. Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995;274:137–42.

25. Persson I, Thurfjell E, Bergstrom R, Holmberg L. Hormone replacement therapy and the risk of breast cancer. Nested case-control study in a cohort of Swedish women attending mammography screening. Int J Cancer 1997;72:758–61.

26. Persson I, Weiderpass E, Bergkvist L, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and progestin replacement. Cancer Causes Control 1999;10:253–60.

27. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy.Int J Cancer 1999;81:339–44.

28. Ross RK, Paganini-Hill A, Wan P, Pike M. Effect of hormone replacement therapy on breast cancer: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328–32.

29. Kirsh V, Kreiger N. Estrogen and estrogen-progestin replacement therapy and risk of postmenopausal breast cancer in Canada. Cancer Causes Control 2002;13:583–90.

30. Newcomb PA, Titus-Ernstoff L, Egan K, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:593–600.

31. Li R, Gilliland FD, Baumgartner K, Samet J. Hormone replacement therapy and breast carcinoma risk in Hispanic and non-Hispanic women. Cancer 2002;95:960–8.

32. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734–41.

33. Olsson HL, Ingvar C, Bladstrom A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. Cancer 2003;97:1387–92.

34. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. JAMA 1999;281:2091–7.

35. Manjer J, Malina J, Berglund G, Bondeson L, Garne JP, Janzon L. Increased incidence of small and well-differentiated breast tumours in post-menopausal women following hormone-replacement therapy. Int J Cancer 2001;92:919–22.

36. Li CI, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570–7.

37. Newcomer LM, Newcomb PA, Potter JD, et al. Postmenopausal hormone therapy and risk of breast cancer by histologic type (United States). Cancer Causes Control 2003;14:225–33.

38. Daling JR, Malone KE, Doody DR, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer 2002; 95:2455–64.

39. Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 2003;289:3254–63.