Hormone Replacement Therapy and Breast Cancer: A Qualitative Review

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OBJECTIVE: To assess whether recent epidemiologic evidence supports an association between use of estrogen replacement therapy or hormone replacement therapy and risk of breast cancer.

DATA SOURCES: The keywords "estrogen," "estrogen replacement therapy," or "hormone replacement therapy," and "breast cancer" or "breast neoplasm," were used to search for articles published from 1975–2000 in MEDLINE and Dialogweb. Only articles published in peer-reviewed journals and containing original data were included in this review.

METHODS: Unadjusted or age-adjusted risk estimates for breast cancer among ever users of estrogen therapy compared with never users were abstracted from published articles or calculated using the data provided in the published reports.

TABULATION, INTEGRATION, AND RESULTS: We found little consistency among studies that estimated the risk of breast cancer in hormone users compared with nonusers and in studies assessing the risk by duration of use. However, there was consistently a lower risk of death from breast cancer in hormone users compared with nonusers.

CONCLUSION: The evidence did not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen only. Additional observational studies are unlikely to alter this conclusion. Although a small increase in breast cancer risk with hormone therapy or an increased risk with long duration of use (15 years or more) cannot be ruled out, the likelihood of this must be small, given the large number of studies conducted to date. (Obstet Gynecol 2001;98:498–508. © 2001 by the American College of Obstetricians and Gynecologists.)

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Over 25 years ago, epidemiologic studies identified and subsequently confirmed that unopposed estrogen replacement therapy was associated with increased risk of endometrial carcinoma.[1–20] Despite the absence of data from clinical trials, this association has been acknowledged as causal by the medical community, in large part because it is consistent among studies, relatively strong, and more apparent at increased doses and longer durations of use. The association of menopausal estrogen therapy with breast cancer risk, however, remains controversial, despite the publication of over 50 epidemiologic studies and at least six meta-analyses during the past 25 years.[21–81]

This topic is of significant public health concern, given the fear of breast cancer and the relatively prevalent use of estrogen therapy. Currently, the prevailing opinion appears to be that estrogen replacement therapy (ERT, unopposed estrogen therapy) modestly increases the risk of breast cancer, and hormone replacement therapy (HRT, combined estrogen and progestin therapy) increases the risk more than ERT.[50,63,64] Recent publications that have garnered considerable media attention appear to support this opinion.[63,64]

A pooled reanalysis of over 90% of the world's data on breast cancer and hormone replacement therapy published in 1997[80] likely had considerable influence on the formation of that opinion. Although some investigators reason that the summation of observational data, either by pooled reanalysis or traditional meta-analysis, produces precise and definitive answers, others have raised serious concerns about the integrity and validity of these summary risk estimates.[82,83] Furthermore, meta-analysis can distance the reader from the original data (Smith GD, Egger M. Meta-analyses of observational data should be done with due care. BMJ 1999;318:56 [letter]), thus potentially obscuring the overall pattern of results from the entire body of research.

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Another appropriate approach is to assess qualitatively whether the body of observational epidemiologic evidence supports a causal association between use of hormone therapy (defined here as either ERT or HRT) and risk of breast cancer. If each study on hormone therapy and breast cancer samples the "ultimate" truth about the association, then the risk estimates for the association should have a distribution, with most estimates clustered around the "ultimate" truth and progressively fewer estimates at the extremes of the range. Among the criteria for inferring a causal association from observational studies are a consistency in the findings, a strong association, and biologic plausibility.[84] In this review, we examined the distribution of risk estimates obtained from studies of the association between hormone therapy and breast cancer, focusing on the overall pattern of results, the consistency of the results, and the strength of the associations. Specifically, we focused on the following key questions: (1) What is the risk of being diagnosed with breast cancer among postmenopausal women who ever received any form of ERT or HRT compared with those who never received such therapy? (2) What is the risk of death from disease among patients with breast cancer who have used ERT or HRT compared with patients who never used that therapy?

METHODS

We identified a list of publications of observational epidemiologic studies that included original data on ERT and breast cancer risk, HRT and breast cancer risk, and hormone therapy and breast cancer mortality.

DATA SOURCES

The keywords "estrogen," "estrogen replacement therapy" or "hormone replacement therapy," and "breast cancer" or "breast neoplasm," were used to search for articles published from 1975–2000 in MEDLINE and Dialogweb. Each coauthor performed searches using several combination terms, such as "estrogen plus breast cancer and/or breast neoplasm," "estrogen replacement therapy plus breast cancer and/or breast neoplasm," "hormone replacement therapy plus breast cancer and/or breast neoplasm." Additionally, reference lists from identified original articles, previous reviews, and meta-analyses were searched by each coauthor to enhance completeness. We then compared our searches to obtain a complete list of articles on ERT or HRT and breast cancer risk and mortality rates. All articles were included in this list if they contained original data and were published in peer-reviewed journals. There were no discrepancies between the coauthors regarding which papers should be included because we agreed to include all published papers with original data, regardless of study characteristics, reliability, or quality. We did not assess the reliability or quality of each study because the purpose of this review is to present the results from all published studies on the association between ERT or HRT and breast cancer risk. Thus, we did not make subjective judgments about the reliability or quality of individual studies and instead included all studies. The major characteristics of each included study are listed in Table 1.

Unadjusted or age-adjusted risk estimates for breast cancer incidence and mortality rate among ever users of estrogen compared with never users was abstracted from the published article or calculated by the authors from information provided in the publication. We elected to present unadjusted or age-adjusted risk estimates so that reasonable comparisons could be made across the studies that adjusted for a variety of different factors. For case-control studies, the risk estimate was the odds ratio (OR), and for cohort studies, the estimate was the relative risk (RR). These risk estimates and their 95% confidence intervals (CI) were plotted in chronological order on a logarithmic scale.

Additionally, all cohort studies were reviewed to assess whether the investigators had presented risk estimates for breast cancer by duration of hormone use. If so, the published results were extracted or calculated from information available in the publication and are presented graphically.

In situations where there are multiple publications from one study population, only one risk estimate is included (eg, there are three publications from the Iowa Women's Health Study). This estimate was from the most recent publication from that population unless that article included only subgroup analyses.[85,86] In that case, the risk estimate from the most recent publication that assessed information on the entire population was used. Other than this exclusion criterion, all other publications were included in this review.

RESULTS

We identified 45 publications that assessed the association between ERT and breast cancer risk (Figure 1).[21–65] Twenty studies assessed the association between HRT and breast cancer risk (Figure 2),[31,40,44,45,47,51,53–57,60,61,63–69] five assessed the risk of hormone therapy and death from breast cancer (Figure 3),[69,71–74] and six assessed the risk of hormone therapy and breast cancer survival (Figure 3).[70,75,88–91] The data presented in Figures 1 and 2 show an overall lack of consistency and only modest increases or decreases in risk of breast cancer for estrogen users. Of the

Table 1. Design and Population of Published Studies on the Association Between Estrogen or Hormone Replacement Therapy and Breast Cancer Risk

Type of study	Study	Study population
Population-based case-control	Mack et al, 1975[21]	99 cases/396 controls
	Casagrande et al, 1976[23]	90 cases/83 controls
	Ross et al, 1980[26]	124 cases/281 controls
	McDonald et al, 1986[37]	183 cases/531 controls
	Wingo et al, 1987[38]	1369 cases/1645 controls
	Ewertz, 1988[40]	1486 cases/1334 controls
	Rohan et al, 1988[41]	451 cases/451 controls
	Palmer et al, 1991[45]	607 cases/1214 controls
	Yang et al, 1992[47]	685 controls/699 cases
	Weinstein et al, 1993[48]	837 cases/860 controls
	Newcomb et al, 1995[53]	3130 cases/3698 controls
	Stanford et al, 1995[54]	537 cases/492 controls
	Brinton et al, 1998[56]	919 controls/1031 cases
	Magnusson et al, 1999[60]	3345 cases/3454 controls
	Ross et al, 2000[64]	2653 cases/2429 controls
	Moorman et al, 2000[65]	397 cases/425 controls
	Ng et al, 1997[68]	882 controls/204 cases
	Bergkvist et al, 1989[70]	261 cases with breast cancer & estrogen use/6627 controls with breast cancer
Hospital-based case-control	Wynder et al, 1978[24]	785 cases/2231 controls
	Jick et al, 1980[25]	77 cases/139 controls
	Kelsey et al, 1981[28]	332 cases/1353 controls
	Sherman et al, 1983[32]	113 cases/113 controls
	Kaufman et al, 1984[33]	1610 cases/1606 controls
	Horwitz and Stewart, 1984[34]	257 cases/664 controls
	Kaufman et al, 1991[44]	1686 cases/2077 controls
	Harris et al, 1992[46]	604 cases/520 controls
	La Vecchia et al, 1995[51]	2569 cases/2588 controls
	Lipworth et al, 1995[52]	820 cases/1548 controls
	Levi et al, 1996[67]	64 cases with estrogen use/113 controls with estrogen use
Population/hospital-based case-control	Nomura et al, 1986[36]	161 white cases; 183 Japanese cases 159 white controls; 181 Japanese controls
Hospital/community-based case-control	Hulka et al, 1982[30]	199 cases/451 hospital controls; 82 community controls
Health plan-based case-control	Hiatt et al, 1984[35]	119 cases/119 controls
	Hoover et al, 1981[27]	345 cases/611 controls
Screening/clinic-based case-control	Persson et al, 1997[55]*	435 cases/1740 controls
	Henrich et al, 1998[57]	109 cases/545 controls
Prospective cohort	Grodstein et al, 1997[74]	3637 cases (ie, deaths), 425 from breast cancer, 34,625 provided info regarding estrogen use
	Schairer et al, 1999[75]	2614 PMW with BC
	Hoover et al, 1976[22]	49 cases/1891 estrogen users
	Thomas et al, 1982[29]	Cohort: 1439
	Gambrell et al, 1983[31]	Cohort: 5563/53 cases
	Mills et al, 1989[42]	Population: 20,341/215 cases
	Bergkvist et al, 1989[43]	Cohort: 23,244/253 cases
	Colditz et al, 1995[50]	1935 cases
	Persson et al, 1999[61]	Cohort: 10,472 at risk for BC
	Lando et al, 1999[62]	Cohort: 5761/219 cases
	Schuurman et al, 1995[66]	Cohort: 62,573/471 cases
	Sellers et al, 1997[69]	Cohort: 35,919/1085 cases
	Henderson et al, 1991[72]	Cohort: 8853 with info on estrogen use
	Willis et al, 1996[73]	Cohort: 422,373/1469 cases (deaths from BC)
Retrospective cohort	Dupont et al, 1999[59]	Cohort: 5813 with follow-up data through menopause and without premature BC
Prospective/retrospective cohort	Hunt et al, 1990[71]	Cohort: 4544
	Hunt et al, 1987[39]	Cohort: 4544
Community-based cohort study	Sourander et al, 1998[58]	Participants: 7944; 988 current estrogen users, 757 former users
Follow-up cohort	Schairer et al, 2000[63]	Cohort: 46,355 with 2082 cases available for analysis
Record-linkage cohort	Risch and Howe, 1994[49]	Cohort: 32,790 742 cases

BC = breast cancer; PMW = postmenopausal women.
* Nested.

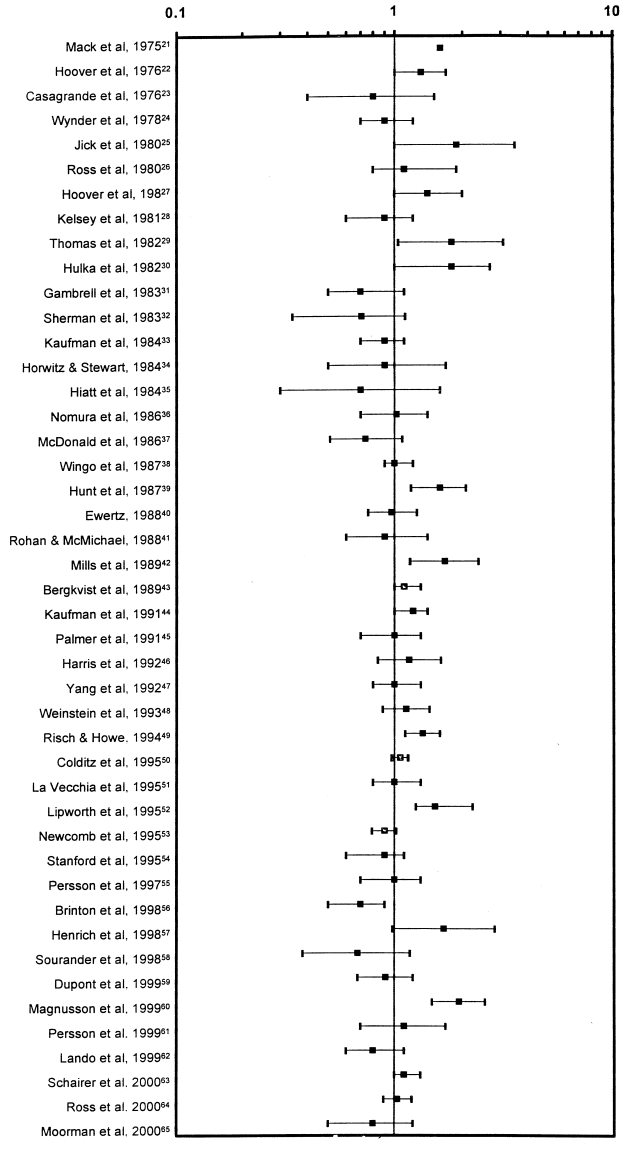

Figure 1. Risk estimates for incident breast cancer: ever users compared with never users of estrogen replacement therapy (unopposed estrogen).

Bush. Estrogen and Breast Cancer. Obstet Gynecol 2001.

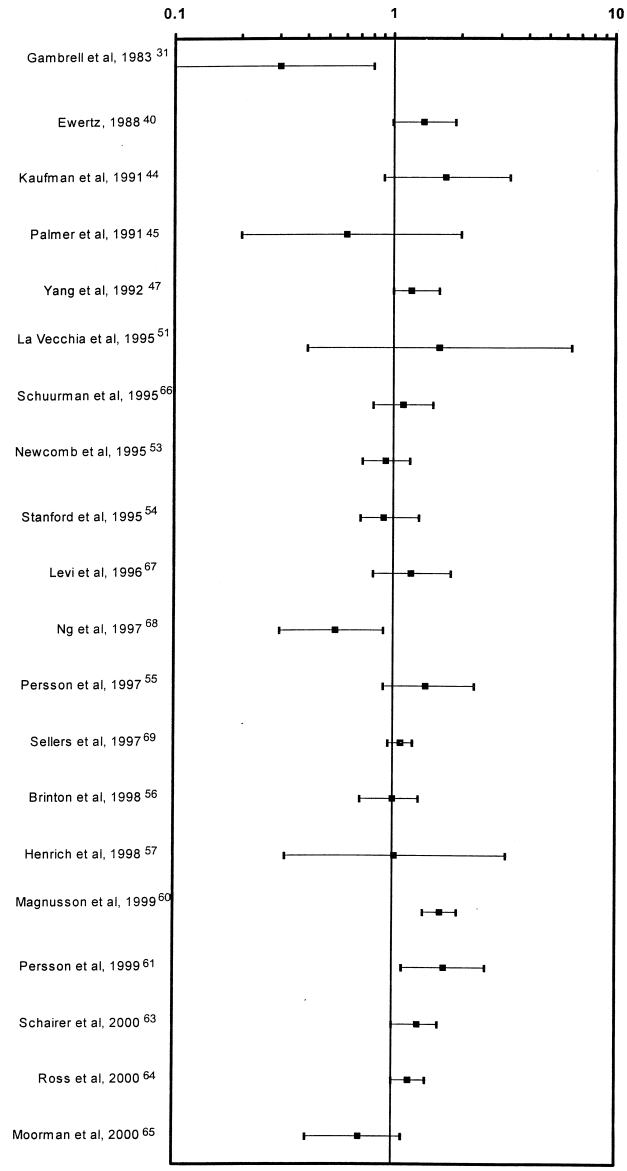

Figure 2. Risk estimates for incident breast cancer: ever users compared with never users of hormone replacement therapy (estrogen plus progestin).

Bush. Estrogen and Breast Cancer. Obstet Gynecol 2001.

studies in Figure 1, 20% reported risk estimates less than 0.9,[23,31,32,35,37,56,58,62,65] 33% reported risk estimates greater than 1.1,[21,22,25,27,29,30,39,42,44,46,49,50,52,57,60] and 47% reported risk estimates between 0.9 and 1.1.[24,26,28,33,34,36,38,40,41,43,45,47,48,51,53–55,59,61,63,64] None of those studies reported risk estimates greater than 2.0.

The studies on HRT use reported in Figure 2 also show inconsistent results. Only four of these observational studies reported statistically significant findings: two showed a significant higher risk of breast cancer with HRT use,[60,61] and two found a significant protective effect of HRT on breast cancer risk.[31,68] Additionally, one small clinical trial of HRT use found no increase in breast cancer among women taking combined therapy for up to 22 years.[87]

Figure 3 presents the data from studies of breast cancer mortality rates (top half of figure) and survival after diagnosis of breast cancer (bottom half of figure). Although there is a lack of consistency regarding the risk of breast cancer with hormone therapy, there is consistency regarding hormone use and both mortality rates

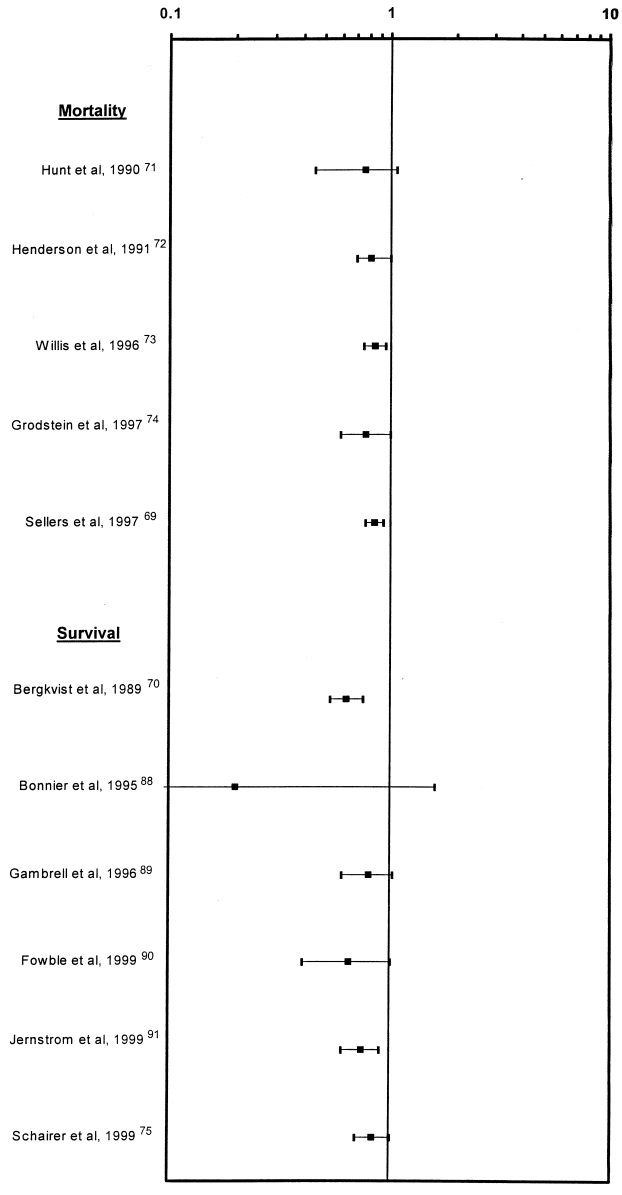

Figure 3. Risk estimates for death from breast cancer and breast cancer survival: ever users compared with never users of hormone replacement therapy (estrogen plus progestin).

Bush. Estrogen and Breast Cancer. Obstet Gynecol 2001.

from breast cancer[69,71–74] and breast cancer survival.[70,75,88–91] The risk estimates for death from breast cancer in hormone users compared with nonusers in all five studies are less than 1.0, and several of those estimates are statistically significant.[69,73] Similarly, all of the risk estimates for breast cancer survival in hormone users versus nonusers are less than 1.0; two are statistically significant.[70,91]

Figure 4 presents the risk estimates for breast cancer by duration of hormone use for all cohort studies which evaluated the risk by duration.[42,43,50,59,61,62,92,93] Most studies included in Figure 4 presented estimates for any hormone use or all hormone use, while three[43,61,92] provided separate estimates for estrogen only (ERT) and estrogen combined with progestin (HRT). Each study reported risk estimates based on different durations of use, making direct comparisons for specific durations between studies somewhat difficult. However, we can generally assess the consistency of risk estimates between studies for those women using hormone therapy for the longest durations, which ranged from over 5 years[59,93] to over 20 years.[92] Again, there is a lack of consistency in the results between studies. Women using hormone therapy for the longest durations compared with nonusers had: 1) a significantly elevated risk of breast cancer in three studies (in one for ERT[43], one for any hormone therapy,[50] and one for HRT[61]), 2) a nonsignificantly elevated risk of breast cancer in five studies (three for any hormone therapy,[42,92,93] one for HRT,[43] and one for ERT[61]), and 3) no increase in risk in two studies for any hormone therapy.[59,62]

There is also a lack of consistency in the results for a duration effect within studies. For example, in three studies[43,50,61] and in Schairer et al's[92] ERT cohort, there was a generally consistent increasing risk with longer durations of use. However, three other studies[59,62,93] found no evidence of an increase in risk with longer durations of use, while Mills et al[42] and Schairer et al for HRT[92] found inconsistent results by duration of use.

CONCLUSION

Over 25 years ago, epidemiologic studies showed that ERT was associated with an increased risk of endometrial cancer, and that association was consistent among studies, relatively strong, and increased with increasing duration of use. In contrast, the relatively large body of literature on the association between estrogen and breast cancer is inconsistent, and the distribution of risk estimates is what would be expected if there were no association. That is, most of the estimates of risk converge around 1.0, and the range of the estimates is limited. Therefore, we conclude that the body of literature does not support an association between ERT or HRT use and breast cancer. In light of the overall pattern seen during the past 25 years, additional observational studies are unlikely to alter this conclusion. Conversely, consistent data suggest that estrogen users are less likely to die from breast cancer than nonusers, a finding that has received relatively little attention.

An association between estrogen and risk of breast cancer is thought to be biologically plausible for several

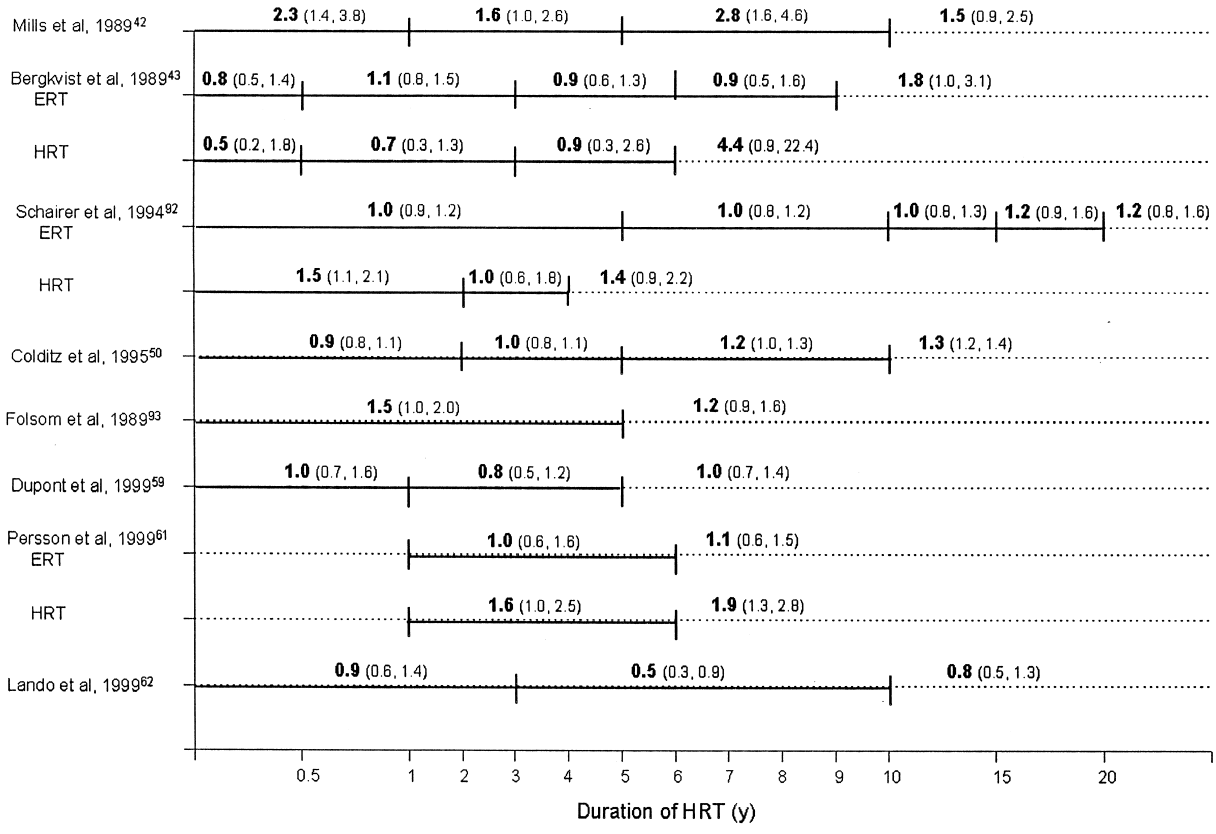

Figure 4. Relative risk estimates (95% CI) for incident breast cancer: ever users compared with never users of hormone replacement therapy by duration of use reported in cohort studies. ERT = unopposed estrogen replacement therapy. HRT = estrogen plus progestin.

Bush. Estrogen and Breast Cancer. Obstet Gynecol 2001.

reasons, including the finding that many risk factors for breast cancer (eg, early age at menarche, late age at first birth, nulliparity, late age at menopause) are thought to be related to estrogen; the discovery that removal of the ovaries can induce tumor regression in breast cancer patients[94]; and the finding that early oophorectomy protects against breast cancer.[95] However, risk factors such as those are not direct measures of estrogen but reflect ovarian functioning. The ovary produces many compounds in addition to estrogens, including progesterone, inhibin A, inhibin B, dehydroepiandrosterone (DHEA), and androgens. In light of the lack of direct evidence supporting an estrogen-breast cancer association and that these risk factors reflect ovarian functioning, an ovarian product other than estrogen might be associated with breast cancer pathogenesis.

The observation that breast cancer can be treated successfully with anti-estrogens (tamoxifen)[96] has also been used as an argument to support a biologically plausible association between hormone therapy and breast cancer. Tamoxifen was designated as an anti-estrogen because it was shown to bind to the estrogen receptor and therefore was thought to block the action of estrogen in the breast. We now know that tamoxifen not only binds to the estrogen receptor, but also configures the receptor in a way similar (but not identical) to that of estrogen. Thus, it could be argued that tamoxifen is not an anti-estrogen but a partial estrogen that turns on some (but not all) of the genes that estrogen does, and probably turns on others that estrogen does not.

A major question this analysis presents is "Why do the findings presented here differ from the current opinion that ERT modestly increases the risk of breast cancer and that HRT increases the risk more than ERT?" One reason is because the data are inconsistent, and that inconsistency in the overall pattern of results means that alternative hypotheses can be supported readily with some data. In other words, causality can be in the eye of the beholder, particularly when results are ambiguous. Our findings might differ because the data presented here are from the entire study populations, whereas other investigators might report an association only in

selected subgroups, hypothesizing that certain women might be more vulnerable to estrogen's adverse effects (eg, current compared with past users, thin women compared with heavy women, or women with a family history of cancer).[63,85,86] Although subgroup analysis might be used to identify particularly susceptible groups of individuals, it is inherently problematic. If 40 different subgroups were investigated, the findings from two (5%) of those subgroups would be expected to be statistically significant by chance alone. Investigators rarely inform their readers of the number of subgroups considered, so the likelihood of a spurious association cannot be assessed. Therefore, a statistically significant finding found only in a subgroup and not in the entire study population should be viewed with caution.

The current belief that women using HRT have a higher risk of breast cancer than women using ERT could be a function of the recency of several publications[60,61,63,64] as well as failure of those studies to take ovarian status of the participants into account. In other words, women using HRT are much more likely to have their uterus and ovaries than women using ERT or no therapy. Because oophorectomy is protective against breast cancer and women taking ERT are more likely to have had an oophorectomy than women taking HRT, one can hypothesize that women taking ERT would have a lower risk of breast cancer than women taking HRT. Thus, a higher rate of breast cancer in HRT users would be expected because the other groups (ERT users, nonusers) are at lower risk because they include oophorectomized (lower-risk) women.

Two findings in this review were consistent across studies. One is that hormone users are less likely to die from breast cancer than nonusers. This finding makes the body of literature appear even more inconsistent; ie, the data suggest no effect on the incidence of breast cancer but suggest protection from death from breast cancer. It is difficult, but not impossible, to explain these two different findings. It would be difficult to explain an increase in breast cancer incidence together with a reduction in breast cancer mortality with hormone use. In other words, it is difficult to argue that hormone use causes breast cancer in women but then prevents them from dying from it, unless all previous studies suffer from both healthy estrogen user bias and surveillance bias.

Biologically, there are at least two reasons that hormone therapy could be associated with a real reduction in breast cancer mortality. First, it is possible that women taking hormone therapy are more likely to be screened for cancer than nonusers and thus are more likely to have their breast tumors diagnosed at an earlier and more curable stage. Many (but not all) studies found that women taking HRT were more likely to have smaller, lower grade tumors at diagnosis, and this is thought to occur because the breast cancers are more likely to be detected by screening mammography.[88,97] Thus, a survival benefit might be seen in users because of increased screening in that group. However, it is also possible that breast tumors growing in the presence of estrogen are biologically better tumors, ie, lower grade, well differentiated, and slower to proliferate. Some studies that control for screening modality report that breast tumors in hormone users are more likely to be ER+, grade 1, well differentiated, low S-phase, and node-negative than those in nonusers.[98–100] This situation could be analogous to that seen in estrogen-associated endometrial tumors, which are less aggressive and invasive than endometrial tumors occurring spontaneously.

The second consistent finding is that the lack of agreement between studies persisted throughout the entire 25-year period. We believe that results of additional observational studies are unlikely to vary from this pattern and therefore also unlikely to provide additional support for any hypothesis regarding the estrogen-breast cancer association. It is possible that randomized clinical trials could clarify the association between ERT or HRT and breast cancer. Currently, the Women's Health Initiative is assessing the association between ERT or HRT and breast cancer risk, and we hope that this large randomized trial will shed some new light on the association.

Although the data presented here do not support an association between ERT or HRT and breast cancer risk, this review has some potential limitations. Although we made every attempt to find all published articles on the association between ERT or HRT and breast cancer, it is possible that we failed to include some studies. Although publication bias seems unlikely because other studies indicate that studies reporting a positive association (ie, studies that reported an association between HRT or ERT and breast cancer) are more likely to be published than those reporting a null association (ie, those that reported no association between HRT or ERT and breast cancer), we can not rule out that possibility. Finally, we chose to include all published studies without evaluating their quality and reliability. Thus, it is possible that some of the studies analyzed in this review are limited by confounders such as oophorectomy status, menopausal status, race or ethnicity, and socioeconomic factors.

Nonetheless, the evidence from the body of literature over the past 25 years does not support the hypothesis that estrogen use increases the risk of breast cancer or that combined hormone therapy increases the risk more than estrogen only. Although a small increase in breast

cancer risk with hormone therapy or an increased risk with long duration of use (>15 years) cannot be ruled out, the likelihood of this must be small, given the many studies conducted to date.

REFERENCES

1. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293:1164–7.
2. Persson I. The risk of endometrial and breast cancer after estrogen treatment. A review of epidemiological studies. Acta Obstet Gynecol Scand 1985;130(Suppl):59–66.
3. Gambrell RD Jr, Bagnell CA, Greenblatt RB. Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review. Am J Obstet Gynecol 1983;146:696–707.
4. Mack TM, Pike MC, Henderson BE, Pfeffer RI, Gerkins VR, Arthur M, et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976;294: 1262–7.
5. Smith DC, Prentice RL, Bauermeister DE. Endometrial carcinoma: Histopathology, survival, and exogenous estrogens. Gynecol Obstet Invest 1981;12:169–79.
6. Vakil DV, Morgan RW, Halliday M. Exogenous estrogens and development of breast and endometrial cancer. Cancer Detect Prev 1983;6:415–24.
7. Fowler WC Jr. Estrogens and endometrial cancer: Fact or fiction? Ala J Med Sci 1982;19:38–45.
8. Elwood JM. Estrogens and endometrial cancer: Some answers and some further questions. Can Med Assoc J 1981;124:1129–31.
9. Hulka BS, Fowler WC Jr, Kaufman DG, Grimson RC, Greenberg BG, Hogue CJ, et al. Estrogen and endometrial cancer: Cases and two control groups from North Carolina. Am J Obstet Gynecol 1980;137:92–101.
10. Brinton LA. The relationship of exogenous estrogens to cancer risk. Cancer Detect Prev 1984;7:159–71.
11. Potischman N, Hoover RN, Brinton LA, Siiteri P, Dorgan JF, Swanson CA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 1996;88:1127–35.
12. McPherson CP, Sellers TA, Potter JD, Bostick RM, Folsom AR. Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. Am J Epidemiol 1996;143:1195–202.
13. Hammond CB, Jelovsek FR, Lee KL, Creasman WT, Parker RT. Effects of long-term estrogen replacement therapy II. Neoplasia. Am J Obstet Gynecol 1979;133: 537–47.
14. Weiss NS, Szekely DR, Austin DF. Increasing incidence of endometrial cancer in the United States. N Engl J Med 1976;294:1259–76.
15. Berger GS, Fowler WC Jr. Exogenous estrogens and endometrial carcinoma: Review and comments for the clinician. J Reprod Med 1977;18:177–80.
16. Dril VA. Relationship of estrogens and oral contraceptives to endometrial cancer in animals and women. J Reprod Med 1980;24:5–13.
17. Hulka BS, Kaufman DG, Fowler WC Jr, Grimson RC, Greenberg BG. Predominance of early endometrial cancers after long-term estrogen use. JAMA 1980;244: 2419–22.
18. Cushing KL, Weiss NS, Voigt LF, McKnight B, Beresford SAA. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. Obstet Gynecol 1998; 91:35–9.
19. Brinton LA, Hoover RN. Estrogen replacement therapy and endometrial cancer risk: Unresolved issues. Obstet Gynecol 1993;81:265–71.
20. Buring JE, Bain CJ, Ehrmann RL. Conjugated estrogen use and risk of endometrial cancer. Am J Epidemiol 1986;434–41.
21. Mack TM, Henderson BE, Gerkins VR, Arthur M, Baptista J, Pike MC. Reserpine and breast cancer in a retirement community. N Engl J Med 1975;26:1366–71.
22. Hoover R, Gray LAJ Sr, Cole P, MacMahon B. Menopausal estrogens and breast cancer. N Engl J Med 1976; 295:401–5.
23. Casagrande J, Gerkins V, Henderson BE, Mack T, Pike MC. Brief communication: Exogenous estrogens and breast cancer in women with natural menopause. J Natl Cancer Inst 1976;56:839–41.
24. Wynder EL, MacCornack FA, Stellman SD. The epidemiology of breast cancer in 785 United States caucasian women. Cancer 1978;41:2341–54.
25. Jick H, Walker AM, Watkins RN, D'ewart DC, Hunter JR, Danford A, et al. Replacement estrogens and breast cancer. Am J Epidemiol 1980;112:586–94.
26. Ross RK, Paganini-Hill A, Gerkins VR, Mack TM, Pfeffer R, Arthur M, et al. A case-control study of menopausal estrogen therapy and breast cancer. JAMA 1980; 243:1635–9.
27. Hoover R, Glass A, Finkle WD, Azevedo D, Milne K. Conjugated estrogens and breast cancer risk in women. J Natl Cancer Inst 1981;67:815–20.
28. Kelsey JL, Fischer DB, Holford TR, LiVoisi VA, Mostow ED, Goldenberg IS, et al. Exogenous estrogens and other factors in the epidemiology of breast cancer. J Natl Cancer Inst 1981;67:327–33.
29. Thomas DB, Persing JP, Hutchinson WB. Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. J Natl Cancer Inst 1982;69:1017–25.
30. Hulka BS, Chambless LE, Deubner DC, Wilkinson WE. Breast cancer and estrogen replacement therapy. Am J Obstet Gynecol 1982;143:638–44.
31. Gambrell RD Jr, Maier RC, Sanders BI. Decreased inci-

dence of breast cancer in postmenopausal estrogen-progestogen users. Obstet Gynecol 1983;62:435–43.

32. Sherman B, Wallace R, Bean J. Estrogen use and breast cancer. Interaction with body mass. Cancer 1983;51: 1527–31.
33. Kaufman DW, Miller DR, Rosenberg L, Helmrich SP, Stolley P, Schottenfeld D, et al. Noncontraceptive estrogen use and the risk of breast cancer. JAMA 1984;252: 63–7.
34. Horwitz RI, Stewart KR. Effect of clinical features on the association of estrogens and breast cancer. Am J Med 1984;76:192–8.
35. Hiatt RA, Bawol R, Friedman GD, Hoover R. Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer 1984;54:139–44.
36. Nomura AMY, Kolonel LN, Hirohata T, Lee J. The association of replacement estrogens with breast cancer. Int J Cancer 1986;37:49–53.
37. McDonald JA, Weiss NS, Daling JR, Francis AM, Polissar L. Menopausal estrogen use and the risk of breast cancer. Breast Cancer Res Treat 1986;7:193–9.
38. Wingo PA, Layde PM, Lee NC, Rubin G, Ory HW. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. JAMA 1987;257: 209–15.
39. Hunt K, Vessey M, McPherson K, Coleman M. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Br J Obstet Gynaecol 1987;94:620–35.
40. Ewertz M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. Int J Cancer 1988;42:832–8.
41. Rohan TE, McMichael AJ. Non-contraceptive exogenous oestrogen therapy and breast cancer. Med J Aust 1988;148:217–21.
42. Mills PK, Beeson WL, Phillips RL, Fraser GE. Prospective study of exogenous hormone use and breast cancer in seventh-day adventists. Cancer 1989;64:591–7.
43. 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.
44. Kaufman DW, Palmer JR, de Mouzon J, Rosenberg L, Stolley PD, Warshauer ME, et al. Estrogen replacement therapy and the risk of breast cancer: Results from the Case-Control Surveillance Study. Am J Epidemiol 1991; 134:1375–85.
45. Palmer JR, Rosenberg L, Clarke EA, Miller DR, Shapiro S. Breast cancer risk after estrogen replacement therapy: Results from the Toronto Breast Cancer Study. Am J Epidemiol 1991;134:1386–95.
46. Harris RE, Namboodiri KK, Wynder EL. Breast cancer risk: Effects of estrogen replacement therapy and body mass. J Natl Cancer Inst 1992;84:1575–82.
47. Yang CP, Daling JR, Band PR, Gallagher RP, White E, Weiss NS. Noncontraceptive hormone use and risk of breast cancer. Cancer Causes Control 1992;3:475–9.
48. Weinstein AL, Mahoney MC, Nasca PC, Hanson RL, Leske MC, Varma AO. Oestrogen replacement therapy and breast cancer risk: A case control study. Int J Epidemiol 1993;22:781–9.
49. Risch HA, Howe GR. Menopausal hormone usage and breast cancer in Saskatchewan: A record-linkage cohort study. Am J Epidemiol 1994;139:670–83.
50. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, 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.
51. La Vecchia C, Negri E, Franceschi S, Favero A, Nanni O, Filiberti R, et al. Hormone replacement treatment and breast cancer risk: Cooperative Italian study. Br J Cancer 1995;72:244–8.
52. Lipworth L, Katsouyanni K, Stuver S, Samoli E, Hankinson SE, Trichopoulos D. Oral contraceptives, menopausal estrogens, and the risk of breast cancer: A case-control study in Greece. Int J Cancer 1995;62:548–51.
53. Newcomb PA, Longnecker MP, Storer BE, Mittendorf R, Baron J, Clapp RW, et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. Am J Epidemiol 1995;142:788–95.
54. 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.
55. 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.
56. Brinton LA, Brogan DR, Coates RJ, Swanson CA, Potischman N, Stanford JL. Breast cancer risk among women under 55 years of age by joint effects of usage of oral contraceptives and hormone replacement therapy. Menopause 1998;5:145–51.
57. Henrich JB, Kornguth PJ, Viscoli CM, Horwitz RI. Postmenopausal estrogen use and invasive versus in situ breast cancer risk. J Clin Epidemiol 1998;51:1277–83.
58. Sourander L, Rajala T, Raihi I, Makinen J, Erkkola R, Helenius H. Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy (ERT). Lancet 1998;352:1965–9.
59. Dupont WD, Page DL, Parl FF, Iummer WD Jr, Schuyler PA, Kasami M, et al. Estrogen replacement therapy in women with a history of proliferative breast disease. Cancer 1999;85:1277–83.
60. Magnusson C, Baron JA, Correia N, Berger GS, Dami HO, Persson I. Breast cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int J Cancer 1999;81:339–44.

61. Persson I, Weiderpass E, Bergkvist L, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. Cancer Causes Control 1999;10:253–60.
62. Lando JF, Heck KE, Brett KM. Hormone replacement therapy and breast cancer risk in a nationally representative cohort. Am J Prev Med 1999;17:176–80.
63. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000; 283:485–91.
64. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328–32.
65. Moorman PG, Kuwabara H, Millikan RC, Newman B. Menopausal hormones and breast cancer in a biracial population. Am J Pubic Health 2000;90:966–71.
66. Schuurman AG, van den Brandt PA, Goldbohm RA. Exogenous hormone use and the risk of postmenopausal breast cancer: Results from the Netherlands Cohort Study. Cancer Causes Control 1995;6:416–24.
67. Levi F, Lucchini F, Pasche C, La Vecchia C. Oral contraceptives, menopausal hormone replacement therapy and breast cancer risk. Eur J Cancer Prev 1996;5: 259–66.
68. Ng EH, Gao F, Ji CY, Ho GH, Soo KC. Risk factors for breast carcinoma in Singaporean Chinese women: The role of central obesity. Cancer 1997;80:725–31.
69. Sellers TA, Mink PJ, Cerhan JR, Zheng W, Anderson K, Kushi LH, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. Ann Intern Med 1997;127:973–80.
70. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. Am J Epidemiol 1989;130:221–8.
71. Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: An updated analysis. Br J Obstet Gynaecol 1990;97:1080–6.
72. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991;151:75–8.
73. Willis DB, Calle EE, Miracle-McMahill HL, Heath CW Jr. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. Cancer Causes Control 1996;7: 449–57.
74. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;336:1769–75.
75. Schairer C, Gail M, Byrne C, Rosenberg PS, Sturgeon SR, Brinton LA, et al. Estrogen replacement therapy and breast cancer survival in a large screening study. J Natl Cancer Inst 1999;91:264–70.
76. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. Arch Intern Med 1991; 151:67–72.
77. Colditz GA, Egan KM, Stampfer MJ. Hormone replacement therapy and risk of breast cancer: Results from epidemiologic studies. Am J Obstet Gynecol 1993;168: 1473–80.
78. Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders WD, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991;265:1985–90.
79. Steinberg KK, Smith DC, Thacker SB, Stroup DF. Breast cancer risk and duration of estrogen use: The role of study design in meta-analysis. Epidemiology 1994;5: 415–21.
80. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet 1997;350: 1047–59.
81. Sillero-Arenas M, Delgado-Rodriguez M, Rodigues-Canteras R, Bueno-Cavanillas A, Galvez-Vargas R. Menopausal hormone replacement therapy and breast cancer: A meta-analysis. Obstet Gynecol 1992;79:286–94.
82. Shapiro S. Point/counterpoint: Meta-analysis of observational studies. Meta-analysis/Shmeta-analysis. Am J Epidemiol 1994;140:771–8.
83. Egger M, Schneider M, Smith GD. Spurious precision? Meta-analysis of observational studies. BMJ 1998;316: 140–4.
84. Hill AB. Principles of medical statistics. 9th ed. London: Lancet Ltd, 1971.
85. 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.
86. 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.
87. Nachtigall MJ, Smilen SW, Nachtigall RD, Nachtigall RH, Nachtigall LE. Incidence of breast cancer in a 22-year study of women receiving estrogen-progestin replacement therapy. Obstet Gynecol 1992;80:827–30.
88. Bonnier P, Romain S, Giacalone PL, Laffargue F, Martin PM, Piana L. Clinical and biological prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. Obstet Gynecol 1995;85: 11–7.
89. Gambrell RD Jr. Hormone replacement therapy and breast cancer risk. Arch Fam Med 1996;5:341–8.
90. Fowble B, Hanlon A, Freedman G, Patchefsky A, Kessler

H, Nicolaou N, et al. Postmenopausal hormone replacement therapy: Effect on diagnosis and outcome in early-stage invasive breast cancer treated with conservative surgery and radiation. J Clin Oncol 1999;17:1680–8.

91. Jernstrom H, Frenander J, Ferno M, Olsson H. Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. Br J Cancer 1999;80:1453–8.
92. Schairer C, Byrne C, Keyl PM, Brinton LA, Sturgeon SR, Hoover RN. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). Cancer Causes Control 1994;5:491–500.
93. Folsom AR, Mink PJ, Sellers TA, Hong CP, Zheng W, Potter JD. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am J Public Health 1995;85:1128–32.
94. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment, with illustrative cases. Lancet 1896;July 11: 104–7.
95. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
96. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the Nurse's Health Study. Am J Epidemiol 2000;152: 950–64.
97. Gajdos C, Tartter PI, Babinszki A. Breast cancer diagnosed during hormone replacement therapy. Obstet Gynecol 2000;95:513–18.
98. Harding C, Knox WF, Faragher EB, Baildam A, Bundred NJ. Hormone replacement therapy and tumour grade in breast cancer: Prospective study in screening unit. BMJ 1996;312:1646–7.
99. Salmon RJ, Ansquer Y, Asselain B, Languille O, Lesec G, Remvikos Y. Clinical and biological characteristics of breast cancers in post-menopausal women receiving hormone replacement therapy for menopause. Oncol Rep 1999;6:699–703.
100. Lower EE, Blau R, Gazder P, Stahl DL. The effect of estrogen usage on the subsequent hormone receptor status of primary breast cancer. Breast Cancer Res Treat 1999;58:205–11.

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