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Systematic Evidence Review
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Hormone Replacement Therapy and Breast Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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* The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Objective: To evaluate and update the prior review evaluating the risk of breast cancer and breast cancer (BCA) death associated with the use of postmenopausal hormone replacement therapy (HRT) by reviewing the medical literature which has been published since the last US Preventive Services Task Force update.

Data Source: All English language studies identified in the MEDLINE database from 1992-2000 and all previously published meta-analyses. In addition, reference lists of key articles, letters, and editorials were reviewed for all related studies, including those pre-dating the database search.

Study Selection: All studies that evaluated breast cancer incidence or mortality as a primary or secondary outcome in association with hormone replacement therapy published between 1992-2000. Studies evaluating the effect of hormone replacement therapy on breast density were also reviewed.

Data Extraction: The following studies met inclusion criteria: 8 meta-analyses from the years 1988-1997, 1 nested case-control study, 14 case-control studies, and 15 cohort studies all evaluating breast cancer incidence, mortality, or both. Of the 15 cohort studies, 10 represented unique cohorts and of the 14 case control studies, 2 involved updates of the same case set. Data from each study were abstracted to prepared forms. When more than one study from the same population was reported, data from the most recent publication were reviewed. If data from the same population were analyzed by cohort and by case-control analysis, both results were reported if they evaluated different outcomes. In addition, several studies evaluating breast density and HRT were reviewed, and the best studies summarized.

Data Synthesis: For ever or short-term use of estrogen, 7 of the 8 meta-analyses, 8 of the 11 case-control studies, and 6 of the 7 cohort studies evaluating incidence showed no increase in breast cancer with hormone replacement therapy. Of the original studies reviewed evaluating incidence, 12 of 19 showed no increased risk of breast cancer with long duration ERT or HRT use. However, 5 of the meta-analyses showed increased risk with duration over 5 years and 2 important cohort studies showed increased risk with longer duration use. Eleven original studies evaluated combined estrogen and progestin, and one showed increased risk of BCA with short-term use; 3 of the 5 evaluating duration with combined therapy showed increased risk that was statistically significant. Current use of ERT was associated with significantly increased risk of breast cancer in two of the best cohort studies; use of combined therapy was associated with increased risk in 3 studies. Six recent cohort studies (1992-2000) evaluated breast cancer mortality in association with hormone use: 1 showed increased risk of death, 4 showed decreased risk of death, and one showed no association. Several recent studies show that post-menopausal estrogen therapy is associated with increased breast density by mammography and that adding progesterone to estrogen results in even greater increases in breast density. Finally, there is evidence suggesting an important interaction between HRT and alcohol use and HRT and lower body weight.

Conclusions: The association of short-term hormone replacement therapy with the development of breast cancer is uncertain based on multiple studies with inconsistent findings. Among studies indicating increased risk, the risk is largely confined to current and long-term use (>5-10 years), and the risk is relatively small (RR 1.2-1.5). Reduced mortality is a fairly consistent finding among the studies evaluating breast cancer

mortality and HRT use. The addition of progesterone to estrogen and current, as well as long-term, use may be associated with breast cancer risk above that of estrogen itself. Although the biological plausibility of an association between postmenopausal hormone use and breast cancer is high, the studies showing risk or benefit from the use of post-menopausal hormones are limited by the observational nature of the epidemiologic data existing to date. Data from randomized controlled trials are needed to validly evaluate the relationship.

Contents

Chapter 1. Introduction

In this systematic evidence review, we evaluate data on the relationship between the use of postmenopausal hormone replacement therapy (HRT) and the risk of breast cancer (BCA). This report is an update of the second US Preventive Services Task Force report, and therefore primarily reviews literature from the last 8 years to update the results of prior analyses evaluating this relationship, as well as the role of postmenopausal progesterone, in breast cancer development and mortality. The context of this review is in the overall evaluation of postmenopausal hormone replacement therapy as chemoprophylaxis for chronic conditions. The results from this report will be used as part of an overall report on the risks and benefits of hormone replacement therapy for postmenopausal women.

Background

Hormone replacement therapy is used in the United States and worldwide to treat symptoms of menopause and to prevent chronic conditions such as osteoporosis. It is one of the most commonly prescribed drugs in the United States; a recent survey in the United States of postmenopausal women ages 50 to 75 showed that nearly 38% of women were currently using estrogen or hormone replacement therapy (58.7% of those with prior hysterectomy and 19.6% without hysterectomy).[1] A major and as yet unanswered clinical question is whether hormone replacement therapy increases a woman's risk of breast cancer. This issue is a critical one because the use of HRT is prevalent and because breast cancer is a relatively common disease, so that even a small increase in breast cancer in association with hormone use could significantly influence public health.

The importance of endogenous estrogen in the development of breast cancer has been evaluated and confirmed in multiple studies of differing methodologies. Studies in animals have shown that breast cancer can be induced by the administration of estrogen.[2] Among humans, some studies have shown that women with increased levels of circulating estrogen are at higher risk for the subsequent development of breast cancer.[3-6] Other studies have had conflicting findings,[7] and some have shown this relationship in postmenopausal women only.[8]

Reproductive events are important risk factors for breast cancer. Those shown to increase risk include early menarche[9] and late menopause,[10] both of which prolong exposure to higher levels of estrogen as well as other reproductive hormones. Other reproductive experiences, such as late age at first pregnancy and nulliparity, increase breast cancer risk.[11] Oopherectomy among premenopausal women is protective against breast cancer,[12] possibly because of reduced exposure to estrogen. Other risk factors also suggest an important role for estrogen in BCA development. In postmenopausal women, obesity, which correlates with increased estrogen levels, is also associated with an increased risk of BCA.[12] Recent studies have also shown that increased bone density, possibly a reflection of lifetime estrogen exposure, is associated with increased rates of breast cancer.[13] Finally, age-adjusted rates of increase in breast cancer incidence slow at menopause when estrogen levels fall.[12]

Also supporting the role of estrogen in the development of breast cancer are convincing data showing that tamoxifen, an estrogen receptor modulator that has antagonistic effects in the breast, reduces recurrence rates of breast cancer among women who have had breast cancer.[14] In addition, one large US study has shown that tamoxifen reduced the

development of incident breast cancer among women at higher than average risk for its development.[15]

In association with reproductive events, significant changes in progesterone levels (as well as other hormones) occur and may also influence breast cancer development. Progesterone alone or acting synergistically with estrogen regulates breast epithelial cell proliferation during the normal menstrual cycle,[16] and hormone therapy that includes progesterone may increase the risk of breast cancer more than estrogen alone.[17] In addition, when BCA does occur, the presence or absence of progesterone receptors on breast tumors is associated with prognosis.[18, 19] These observations and concepts, as well as earlier epidemiologic data,[17, 20] raise concerns that progesterone may also be important in the development of breast cancer. However, exposure to endogenous and/or exogenous progesterone has been less frequently evaluated in epidemiologic, serologic, and clinical studies.

The clinical and observational data suggesting a relationship between endogenous estrogen exposure and the development and etiology of breast cancer have led to concerns about the use of exogenous noncontraceptive estrogen and breast cancer risk. A number of studies have evaluated this relationship, and the findings have been mixed. An important limitation of many past studies is that few have addressed the role of combination estrogen and progesterone therapy in the development of breast cancer. The current standard of practice is for progesterone to be prescribed with estrogen for all women with an intact uterus to prevent the development of endometrial hyperplasia and/or malignancy. However, because use of progesterone in association with estrogen is a relatively recent practice, few epidemiologic studies have evaluated the relationship of

progesterone and/or the combination of estrogen and progestins to breast cancer risk. Several studies suggest elevated risks associated with progesterone, but these often have wide confidence intervals and lack statistical significance.[17, 20] Fortunately, recent studies have evaluated risks associated with combination therapy, and these will be reviewed in this report.[21, 22]

Several important questions regarding hormone replacement therapy and breast cancer risk among postmenopausal women have not yet been answered in the medical literature. These questions primarily relate to risks associated with current, short-term and long-term hormone use, as well as risks associated with combination therapy involving estrogen and progesterone. These questions are outlined in detail below, and this report systematically reviews the recent literature evaluating these risks.

Recommendations of Second Task Force

In the 1996 edition of the US Preventive Services Task Force *Guide to Clinical Preventive Services*,[23] the association of hormone replacement therapy and breast cancer was summarized after evaluating data from more than 40 observational studies and 6 meta-analyses. Broadly, the summary findings found that, compared to the risk for women who have never taken hormones, the risk of breast cancer among current users and women who had used estrogen long-term was increased by approximately 20-50%. The USPSTF also found little evidence that adding progestins to estrogen influenced the risk of breast cancer associated with hormone replacement therapy.[23] Since 1995, several important studies with data from large cohorts have provided particularly important information about this association.

Analytic Framework and Key Questions

The analytic frameworks in Figures 1 and 2 show the target population, interventions, and health outcome measures we examined for the overall question of the benefits and risks of postmenopausal HRT. Arrows 1 and 2 in Figure 2, and the analytic framework in Figure 3, correspond to issues of HRT and breast cancer specifically covered in this report. The key questions outlined in Figure 4 correspond to the numbered arrows in the analytic framework, and guided our literature review. We were concerned with HRT as chemoprophylaxis for chronic conditions rather than as a treatment for menopausal symptoms, and therefore focused on the use of either estrogen alone or estrogen combined with progesterone in healthy, postmenopausal women.

There are several critical key questions to consider when evaluating the research describing the role of exogenous estrogen or estrogen/progesterone in breast cancer development and prognosis. First, is either estrogen alone or estrogen with progesterone associated with a change in breast cancer mortality? Second, does short-term estrogen use increase the risk of breast cancer? The third question, which is most relevant to the use of estrogen to prevent chronic conditions, is whether long-term estrogen increases breast cancer risk. The fourth question, which reflects the current standard of practice, is whether the combination of estrogen and progesterone, either short-term or long-term, increases the risk of breast cancer. Fifth, is current use of estrogen or hormone replacement therapy associated with increased risk of breast cancer? Sixth, are there sub-populations of women who might be at increased risk of breast cancer when using HRT? Finally, because increased breast mammographic density is independently associated with

an increase in breast cancer risk,[24] as well as with decreased accuracy of mammography,[25] does estrogen or estrogen/progestins change breast density?

Chapter 2. Methods

Literature Search Strategy

The topic of hormone replacement therapy and breast cancer was searched in the MEDLINE database from 1992 to January 2000. Full search strings are listed in Appendix 1. Since this review is an update, we did not review all prior studies but did want to overlap with some of the literature previously reviewed by the second Task Force. We also thought that the more recent studies would provide the most valid and reliable evaluation of HRT use and breast cancer risk, given changes in clinical practice, and improved knowledge of important BCA risk factors and potential confounders of the relationship between HRT and BCA. Criteria for inclusion in the systematic review were that the study was conducted in postmenopausal women and that it was in the English language or in a key non-English journal. We included meta-analyses, randomized controlled trials, observational cohort studies, and case-control studies published between 1992 and 2000, if they reported incidence, mortality, pathology, stage, or mammography pattern. MEDLINE updates were conducted monthly, and all abstracts were reviewed by 2 investigators to identify papers for full-text review. Editorials, letters, and reviews were also evaluated to ensure that no key papers were missed in the original MEDLINE search. Appendix 2 summarizes the results of the literature review.

Literature Synthesis and Preparation of Systematic Evidence Review

Study data were abstracted onto data collection forms that were prepared at the beginning of the review. A difficulty in interpreting this literature is that analyses and results are reported differently among the studies. Most studies report point estimates

comparing "ever" to "never" or non-use of HRT. However, some report their findings only as current use or after a specific duration of use. These are important differences to note, since some studies have identified elevated risks only in association with current use (as opposed to ever use). Also, ever use and current use may reflect a broad range of duration, from days to years. When possible, we differentiate these findings on the tables and in the text of this report. Hormone use was classified in each study as unopposed estrogen (ERT) or estrogen plus progesterone (CHRT) when it was specified. When the type of estrogen or progestin therapy was not specified, or the data were analyzed or reported together, exposure was categorized as HRT.

The most appropriate method of evaluating the relationship between HRT and BCA is a randomized, controlled trial. However, only 1 trial has been conducted. This trial[26] is older, involved high dose estrogen therapy, and is limited in size (168) and generalizability, and thus contributes little to the evidence and will not be discussed in this review. Therefore, this review almost entirely involves observational studies, which are limited by lack of randomization among women taking or not taking HRT.

Among the observational studies evaluating the relationship between HRT and breast cancer, cohort studies are methodologically stronger since they assess exposure prior to the onset of disease, and are not as dependent on the recall of hormone use as case-control studies. In addition, although there are 2 case-control studies of good quality, case-control studies are limited because some patients with disease refuse to participate, and because of the frequent inability to evaluate patients with severe disease or those who have died. Women who have died of BCA or who have metastatic disease may have had different HRT exposures, which might bias the results of the study. In

addition, case-control studies are prone toward recall bias, where cases remember or report exposures differently than controls. In this review, therefore, we assign more importance to the results from cohort studies. In ranking the quality of both cohort and case-control studies, we give significant weight to adequate control of potential breast cancer risk factors because of known differences among HRT and non-HRT users that might influence breast cancer risk independent of HRT use. The methods of evaluating study quality were created by the current US Preventive Services Task Force[27] and are described in Appendix 3. Meta-analyses dating from 1988 were all reviewed and the data are displayed in Table 1.

Chapter 3. Results

The findings in the Results section will be presented for each key question by study type. Most emphasis will be given to findings from studies of good quality, utilizing a "best evidence" approach to the literature.[28] Each of the original studies was rated in quality according to standardized criteria developed by the USPSTF[27] (described in Appendix 3). Each study is described in detail in Appendix 4, which is organized by study type. Only meta-analyses from 1992 on are described in Appendix 4, although 2 earlier ones are listed in Table 1.

Does short-term use of exogenous postmenopausal estrogen increase the risk of breast cancer?

In most published studies, short-term use of estrogen has been variably defined but almost always analyzed as "ever" use and compared to "never" use. Generally, the average duration of use of ERT is not reported, and it can range significantly from weeks to years. Not all studies evaluate the relationship by duration of use. Also, many of the studies rely on the use of pharmacy records, so that "ever" use is defined by filling a prescription, though nothing is known about compliance in this setting. Therefore, the analytic category of "ever" use of ERT represents a broad category of duration of use. We have chosen to include the results from studies that evaluated only "hormone use" or in which the type of hormone use was not specified (HRT) in the results section describing estrogen (ERT) use because we believe that the majority of patients would have had the greatest exposure to estrogen alone, rather than CHRT, based on the study dates. We recognize this may result in some misclassification of type of exposure, but wanted to include this information in this review. All of the original studies that included

a description of "short" duration in their paper are displayed in Table 4. Notably "short" duration varies among the studies.

Meta-analyses

Among the 8 meta-analyses evaluating this association,[12, 29-35] only the most recent study by the Collaborative Group on Hormonal Factors in Breast Cancer, which included data from 51 case-control studies involving 52,705 breast cancer patients,[12] showed an elevated risk of BCA associated with ever use of HRT (OR 1.14, $p < 0.001$). Seven other meta-analyses have not identified increased risk associated with ever use. The discrepancy between the most recent study and the prior meta-analyses may reflect differences in surveillance among users and nonusers, since mammography has become more commonly used. This is supported by the finding that the most recent study found the excess risk of breast cancer to be largely due to localized disease, with an associated deficit in advanced disease during the first 5 years of HRT use. Another explanation of why the Collaborative Study results may differ from the other 7 meta-analyses is that it incorporated data from more recent studies in which CHRT use has become more common, and CHRT may be associated with greater breast cancer risk than ERT alone. This is supported by the finding in this study of an elevated RR of 1.15 (SE 0.19) for the use of CHRT or progestin alone among users with duration under 5 years and a relative risk of 0.99 (SE 0.08) for ERT alone.

Since the risk factors for breast cancer in women who take HRT differ in many ways from those of women who do not, the most useful information from meta-analyses may come from a study that pooled data from several randomized controlled trials of HRT for outcomes other than BCA, where BCA rates were evaluated among women

randomized to HRT or placebo.[35] This study identified no increase in BCA risk associated with short-term ERT exposure (RR 0.85; 95% CI, 0.38-1.89), but the analysis involves fewer than 2000 women and few cases of BCA, and has limited power to evaluate the relationship.

Cohort Studies

Since 1992, 8 cohorts studies have evaluated the relationship between short-term or "ever" use of ERT or HRT, and BCA incidence. The most recent results from these cohorts are summarized here and in Table 2. All studies are described in Appendix 4. Six of the 7 cohort studies showed no overall increase in risk of breast cancer associated with ever use of ERT or HRT where the formulation was not specifically evaluated.[21, 36-40] These studies included the Iowa Women's Health Study (IWHS),[36] the NHANES I follow-up study,[39] and the Breast Cancer Detection Demonstration Project (BCDDP) study,[21] all good quality studies, as well as 1 study of fair quality[37] and 2 of poor quality.[38, 40] These studies are described in detail in Section 4 in the Appendix and in Evidence Table 1. The only cohort study showing an increased risk of breast cancer among ever-users was the Saskatchewan cohort study.[41] This study is of poor quality because there was no assessment of important breast cancer risk factors in the study and the women were between ages 43-49—not representative of a postmenopausal cohort. Thus, it contributes little to the evaluation of short-term ERT use and breast cancer, and the best evidence from cohort studies indicates that short-term use of estrogen is not associated with an increased incidence of BCA. However, although the IWHS did not show an overall increased risk of BCA with ever use of less than 5 years (RR 1.07), increased risk of favorable histology BCA among ever users of 5 or fewer years (RR

1.81) was shown and statistically significant.[36] When only studies with a defined length of short-term ever use were reviewed, none of the studies showed increased risk (Table 4).

Case-control Studies

Fourteen case-control studies[22, 42-54] published since 1992 evaluated breast cancer risk (incidence) in association with short-term ERT (see Evidence Table 1). Eight studies, including 2 good population-based studies from the United States,[47, 48] have shown no increase in breast cancer risk associated with ever use of estrogen. Two of the 14 recent case-control studies evaluating incidence,[52, 53] each rated of fair quality, have shown elevated risks associated with ever use of ERT. One study of poor quality, in which the hormone composition was unspecified but presumably mostly estrogen because the authors state that little CHRT was used at the time, also showed an increase in risk associated with ever use (Tables 3 and 4).[49]

Summary

- Seven of 8 meta-analyses have shown no increase in risk of breast cancer associated with ever use of postmenopausal HRT. The most recent meta-analysis involving observational studies showed a statistically significant elevated risk of 1.14 for short-term use, which was attributed to an excess risk of localized disease and a deficit in advanced disease, suggesting increased surveillance among users.
- A meta-analysis using pooled data from 9 small randomized controlled trials of estrogen therapy and reporting breast cancer incidence as a complication of

short-term therapy showed no increase in risk of breast cancer among short-term ERT users.[35]

- The majority (7 of 8) of cohort studies, including the 2 best-quality studies,[20, 21, 36-40] show no overall increase in breast cancer risk with short-term postmenopausal ERT or HRT use, though the IWHS suggested increased risk of favorable histology BCA among short-term users.
- The majority of case-control studies, including the best quality studies, show no association between short-term use of ERT or HRT and breast cancer.

Does long-term use of postmenopausal estrogen increase the risk of breast cancer?

Many of the recent studies evaluating postmenopausal estrogen use have evaluated risk by duration of use of ERT and HRT. The issue has been analyzed in a variety of ways, as can be seen in the tables (Tables 2 and 3 and Evidence Tables 1 and 2). For example, duration may be evaluated only among current users in some studies, or among ever users in other studies, making comparison of studies difficult. Also, duration has been evaluated in past users by time since quitting or by time since beginning ERT.

Meta-analyses

Among the 8 meta-analyses reviewed, 5 evaluated risk of breast cancer by duration of use and all identified increased risk with longer duration of use.[12, 29, 31, 32, 34] The relative risks are remarkably similar and range from 1.23 to 1.51 for periods of use from 5 to 20 years. The use of estrogen only (ERT) is not specifically analyzed, though it likely represents the vast majority of formulations, based on the dates of the studies pooled for the meta-analyses. Several of these meta-analyses are very well done.

However, they are all limited by several factors, including limitations of the design and methodology of the pooled studies, heterogeneity among the studies, and changes in practice patterns such that including older data may be irrelevant to current practice. Even in the most recent meta-analyses, the mean year of diagnosis of BCA was 1985, when doses of estrogen tended to be higher and little progesterone was used. A problem in all of the observational studies, and compounded in the meta-analyses that pool studies, is lack of control for important confounders. This problem significantly limits interpretation of the meta-analyses results. Epidemiologists have also argued that combining data from observational studies in meta-analyses does not provide useful information.[55]

Cohort Studies

Four of the 7 recent cohort studies that evaluated breast cancer risk by duration of ERT showed no increase in rates of breast cancer (of any histology) with increased duration of ERT use. Studies showing no overall increase in risk include the IWHS[36] and the NHANES I study,[39] which are both good quality studies, a cohort study from Finland,[38] and one from the Netherlands.[37] However, the IWHS investigators also evaluated incidence rates by histological type of breast cancer. Although there was no overall increase in risk of breast cancer with increasing duration of ERT or HRT in the IWHS, there was an increased risk of invasive breast cancer of favorable histology with increased duration (RR $\leq$ 5 years 1.81; RR > 5 years 2.65) of HRT use, which was statistically significant, although based on only 82 cases. Unfortunately, the formulation of the HRT in this study is not specified, though it is likely that much of it was ERT.

Two cohort studies showing increased breast cancer risk with increasing duration specifically evaluated risk associated with ERT. One is the Saskatchewan cohort study,[41] which showed a relative risk of 1.50 for more than 3 years of ERT use. However, the study failed to assess confounding variables and relied on population comparisons to determine risk which limits the validity of the finding.

Another study of good quality evaluating risk among women enrolled in the Breast Cancer Detection Demonstration Project (BCDDP)[21] showed an increase in BCA risk with increasing duration of ERT use, but only among lean women, for whom the relative risk was 1.6 (95% CI, 1.2-2.2) for 4 or more years of use. The relative risk among non-lean women using ERT for more than 8 years was 1.0. Interestingly, as will be discussed below, this interaction was also shown among CHRT users in this study. This effect modification with ERT and body weight has also been observed in other studies, including the recent Collaborative Study meta-analyses.[12] Whether this finding reflects biological differences, unassessed confounding among leaner women, or detection bias (with improved breast cancer detection in leaner women) is uncertain and will be discussed below.

The Nurses Health Study[20, 56] is an important study showing an increase in risk of breast cancer with long duration of HRT use. Among all current users, the risk of breast cancer was not increased until after 10 years of use (RR 1.46; 95% CI, 1.20-1.76). There was no gradation in risk or dose-response relationship by duration among current users. There was no association between duration of ERT use and risk of BCA among past users. When duration was evaluated by age categories, current users ages 55-64 had significantly increased risk of breast cancer after 5 years of use (RR 1.54-1.70). Women

ages 55-59 who were current users also had an elevated risk of breast cancer with less than 5 years use (RR 1.37).

The reasons for different findings in overall BCA rates by duration between the NHS and the other good quality studies, particularly the IWHS, are unclear. Each involved large numbers of postmenopausal women, had study designs that were similar in implementation, and evaluated confounding variables very well. Because the IWHS began more recently than the NHS, the ERT/HRT formulations may differ, although little information is given in either study about formulations or doses of estrogen or HRT. The NHS study has longer follow-up, however (>10 years), which may partially explain the different findings between these good-quality cohort studies. Another consideration is that women in the IWHS are older and nearly 100% postmenopausal, which may be associated with different BCA risks in association with ERT/HRT than a cohort of younger postmenopausal women such as those enrolled in the NHS. However, the increase in rate of favorable histology BCA in the IWHS is consistent with the NHS findings.

Case-control Studies

Fourteen case-control studies have been published since 1992 evaluating the relationship between duration of postmenopausal ERT and risk of breast cancer.[22, 42-54] Twelve studies have been published evaluating duration of HRT use, where the formulation is not characterized, and BCA risk.[9, 22, 45-53, 57, 58] As above, we have chosen to evaluate unspecified HRT in the estrogen category. Three of the studies involve the same cases, so only the most recent publication is reviewed. Eight of the 12 studies evaluating duration of ERT or HRT have shown no statistically significant increase in

risk in association with duration. Among the 12 case-control studies, the two studies of best quality[47, 48] showed no association between duration of ERT or HRT use and BCA risk. In fact, the Stanford study[48] shows statistically significant reduced risk of breast cancer among users of 8-15 years duration (OR 0.5).

It is interesting to compare the estimates from studies specifically indicating that the patient took ERT with studies where the components of the HRT were not specifically characterized; the point estimates for HRT generally tend to be higher than those for ERT, although most are not statistically significant. Of the 4 case-control studies specifically evaluating ERT duration and BCA risk, 2 showed statistically increased risk with long duration of use. The Yang study,[42] of fair quality, showed no increase in risk until 10 or more years (OR 1.6; 95% CI, 1.1-2.5). The Magnusson study[53] showed a dose-response relationship with increasing duration of use with an odds ratio of 2.7 for more than 10 years of use (95% CI, 1.47-4.96). The Magnusson study, however, is of poor quality because of lack of control for important confounders and possible misclassification of estrogen use, so its results must be viewed with caution. The best-quality case-control study evaluating ERT use by duration and the risk of BCA was the Stanford study,[48] which showed statistically significant reduced risks of BCA with 8-15 years of ERT use (OR 0.5).

Of the 12 case-control studies evaluating HRT of unknown formulation, but presumed to be largely estrogen based on the dates of case diagnoses, 3 have shown statistically significant increases in breast cancer with increased duration of use.[22, 46, 53] One of these 3 studies includes the fair-quality Swedish study by Persson,[46] which identified an odds ratio of 2.1 (95% CI, 1.1-4.0) after 11 years of HRT use. The most

recently published case-control study[22] did not show a statistically significant increased risk of BCA associated with long duration ERT use (OR 1.24 for over 15 years use), but did find an increase in risk of 10% for each 5 years of use of HRT (OR 1.10; 95% CI, 1.02-1.18), though some of these cases likely used progesterone. Finally, the Swedish study by Magnuson,[53] which showed increasing risk with increasing duration of ERT use, also evaluated risk by duration in association with HRT, where the composition was not specified, and found a dose-response relationship between duration of use of HRT and breast cancer with odds ratios ranging from 1.29 for fewer than 2 years of use to 2.43 for over 10 years, all statistically significant. For the reasons discussed above, this study is of poor quality and its results should be interpreted with caution. The good quality population-based case-control study by Newcomb[47] showed no increase in BCA risk with increasing duration of HRT.

Nine of the recent case-control studies evaluated breast cancer incidence by time since last use.[42-44, 47, 48, 50-53] The findings were variable, with no consistent pattern among the studies. Six of the 15 case-control studies evaluated time since starting hormone replacement therapy and duration of use and breast cancer risk.[43, 44, 48, 50-52] Of these, 3 showed no significant findings,[43, 50, 52] 2 showed a statistically increased risk with shorter time since beginning HRT,[44, 51] and a good-quality US study showed a statistically reduced risk of breast cancer associated with greater time since first use and greater duration of use.[48]

Two of the recent case-control studies evaluated hormone replacement therapy and breast cancer by type of estrogen (conjugated versus non-conjugated).[50, 52] Only one study indicated a higher odds ratio associated with non-conjugated estrogen use (OR

1.89) than with conjugated (OR 1.49), although the findings were not statistically significant.[52]

Summary

- All 5 of the meta-analyses evaluating breast cancer risk and duration of HRT (formulations unspecified) show increased risk with "long-term" (>5 years) HRT use (RR 1.23-1.51). No analysis specifically evaluated ERT use.
- The findings of the cohort studies evaluating risk of BCA by duration of ERT or HRT use are inconsistent. Four of the 7 recent cohort studies evaluating duration have shown no statistically significant increase in overall risk of breast cancer in association with longer duration of therapy. One of these 4, however, did show significantly increased risk of favorable histology BCA. Of the 4, 2 specifically evaluated ERT use and 2 did not specify formulation.
- Of the cohort studies suggesting increased risk with increased duration, one is of poor quality and its results are therefore of questionable validity. One is of good quality and showed increased risk of BCA only in association with long duration ERT in lean women (RR 1.5) after 8 years of use. The NHS, which is of good quality, showed increased risk (RR 1.46) with duration of 10 or more years, which was statistically significant, and increased risk of BCA after 5 years use of ERT in women ages 55-64. Finally, the IWHS showed an increased risk of favorable histology BCA with increasing duration of use.
- Eight of the 12 recent case-control studies evaluating duration of ERT or HRT, including the 2 of best quality, showed no increase in risk of breast cancer with increased duration of use.

- None of the studies shows any consistent relationship with past use of any duration.

Is combination therapy with estrogen and progesterone (CHRT) associated with increased risk of breast cancer?

The issue of combination therapy and its association with breast cancer risk is an important one to address, since it is now the standard of care to use CHRT in women with an intact uterus to prevent endometrial hyperplasia and cancer. However, this is a relatively recent practice, and the research in this area is more limited and largely confined to studies conducted in the last 10 years. The second USPSTF found little evidence that adding progestins to estrogen influenced the risk of breast cancer associated with CHRT.

Although there are no trials, useful information on short-term use of CHRT comes from 2 recent randomized controlled trials: one evaluating the role of CHRT in the secondary prevention of coronary artery disease and the other its association with lipids. In the Postmenopausal Estrogen/Progestin Interventions (PEPI trial), which evaluated CHRT use and lipids, 3 women among the 174 (1.72%) randomized to placebo and 5 among the 701 (0.71%) randomized to treatment with CHRT developed breast cancer over the 3-year study period.[59] In the HERS trial, 32 out of 1,380 (2.32%) women randomized to CHRT and 25 of the women randomized to placebo (1.81%) developed BCA after 4 years of study.[60]

Meta-analyses

None of the meta-analyses conducted to date has specifically evaluated CHRT use and breast cancer risk.

Cohort Studies

Three of the recent cohort studies have specifically evaluated the relationship between breast cancer and CHRT. These include the NHS,[20] the BCDDP screening cohort study,[21] and the Saskatchewan cohort.[41] The NHS showed a statistically significant elevated relative risk of 1.41 (95% CI, 1.15-1.74) for current use of CHRT and a relative risk of 2.24 for current use of progesterone alone, but did not specifically evaluate ever or long-term CHRT use. The study from the BCDDP[21] is an important one for its subgroup analysis. For ever use of CHRT, the relative risk was 1.3, but not statistically significant. Current use of CHRT was associated with a relative risk of 1.4 (95% CI, 1.1-1.9). When risk was evaluated by duration of 4 or more years, an increase in risk was shown only among lean women (RR 2.0, 95% CI, 1.3-3.0). Non-lean women had a relative risk of 1.3 associated with CHRT, which was not statistically significant. Risk was not evaluated by dose schedule of progesterone (continuous or cyclic) in this study. Finally, the large cohort study from Saskatchewan[41] reported on CHRT of $\geq$1 years duration and found no increase in risk, but its results should be interpreted cautiously because the relative risk is only adjusted for age.

Case-control Studies

Eight of the 14 recent case-control studies evaluating incidence specifically evaluated the association between breast cancer and CHRT.[22, 42, 43, 47, 48, 50, 52, 53] See Table 3 for summary findings. Of these 8, only the Magnusson study showed a statistically significant increase in risk of BCA with ever use of CHRT (RR 1.63; 95% CI, 1.37-1.94).[53] Seven of the case-control studies showed no association between ever use

of CHRT and breast cancer risk, with odds ratios ranging from 0.9-1.6 and not statistically significant. It is notable that the case-control studies of highest quality had point estimates of relative risk of 0.9-1.01.[47, 48]

Three of the case-control studies evaluated risk of BCA by duration of CHRT. The good-quality study by Stanford[48] showed no association between duration of CHRT and BCA. The Magnusson study[53] showed increased risk with increasing duration of CHRT therapy, with relative risks ranging from 1.4 (95% CI, 1.01-1.94) for 2-5 years' use, to 2.95 (95% CI, 1.84-4.72) for more than 10 years use of CHRT, as well as a dose-response relationship. When the types of progesterone were evaluated, there was a suggestion that testosterone-derived progesterone was associated with increased risk when compared with regimens containing non-testosterone-derived progesterone. This study, however, is limited by poor control of BCA risk factors, as well as by possible misclassification of estrogen exposure.

The other case-control study showing increased risk of BCA with increasing duration of CHRT use was the Ross study, published in 2000,[22] which identified an odds ratio of 1.24 (95% CI, 1.07-1.45) for each 5 years of CHRT use. Risk also increased from an odds ratio of 1.11 for < 5years use to 1.51 for over 5 years use; the statistical significance is not reported. The majority of women taking CHRT in this study were using medroxyprogesterone sequentially. The study is important because it also evaluated risk associated with different dose schedules for progesterone, and found that the increased risk of BCA associated with combination therapy was primarily due to an increase in risk associated with cyclic use of progesterone in CHRT (OR 1.38, 95% CI, 1.13-1.68) for each 5 years of use. The risk associated with continuous combined therapy

was OR 1.09 (95% CI, 0.88-1.35) per 5 years of use. This is the first published study to evaluate risk of BCA associated with combination therapy by dosing schedule. Increasing duration of sequential CHRT was also associated with increasing risk of breast cancer, with OR ranging from 1.19 for fewer than 5 years use to 1.79 for more than 10 years use. Among women using continuous CHRT, even of long duration, there was no increase in risk of BCA (OR 1.23).

Summary

- The addition of progesterone to estrogen therapy for women with an intact uterus is a relatively recent practice and the current standard of care. Consequently, fewer studies evaluate this practice, and studies have less power to evaluate the relationship.
- No randomized trials have specifically evaluated CHRT, although data from 2 trials of CHRT in other outcomes does not indicate increased risk.
- No meta-analyses have specifically evaluated combination therapy.
- Among the 3 cohort studies evaluating CHRT use, none showed statistically significant increases in risk associated with ever or short-term use of CHRT, though 2 had elevated point estimates (RR 1.3-1.41).
- Two cohort studies evaluated duration of CHRT use and breast cancer risk; only one showed statistically increased risk (RR 2.0) for duration over 4 years and only among lean women.
- Seven of the 8 case-control studies evaluating risk of BCA and CHRT use, including the study of highest quality, showed no increase in risk with ever or short-term use of CHRT.

- Two of the 3 case-control studies evaluating risk of breast cancer by duration of CHRT showed increased risk with increasing duration. One of these 2 studies showed a greater risk of BCA with the use of sequential progesterone CHRT compared to continuous progesterone CHRT use. The best quality study showed no association between long-term CHRT and BCA.

Does current ERT or CHRT increase the risk of Breast Cancer?

Meta-analyses

Among the 8 meta-analyses conducted to date, 3 have evaluated current use of estrogen,[12, 29, 31] and all have shown statistically significant increases in risk (RR 1.21-1.40) of BCA with current use. The Collaborative Study meta-analysis[12] is unique in this area because it defined current use as use within the last 12 months. The other 2 meta-analyses reported current use based on studies that reported use at the time the study evaluated exposure, which could reflect any duration of use. Data on current HRT/ERT/CHRT use and BCA are displayed in Table 5.

Cohort Studies

Four of the recent cohort studies evaluated BCA risk in association with current use of ERT or CHRT. Three good quality studies[20, 21, 36] show elevations in risk associated with current use. The NHS divided current use by type of HRT and found increased risks of 1.32, 1.41 and 2.24 associated with ERT, CHRT and progesterone alone, respectively, all statistically significant. In the NHS, however, current use could be of any duration and overall, no significantly increased risk was observed until after 10 or

more years of use (RR 1.46; 95% CI, 1.20-1.76). However, current use of less or greater than 5 years duration was associated with a statistically significant increased risk among women aged 55-59 (RR 1.37-1.54). In the IWHS, only current use of 5 or fewer years was evaluated and the risk of both favorable histology and invasive ductal or lobular cancer was significantly increased with relative risks of 4.42 and 1.38, respectively. The BCDDP study also showed increased risk, but only with current CHRT (RR 1.4; 95% CI, 1.1-1.9). A study of poor quality found no association.

Case-control Studies

Four case-control studies evaluated BCA risk among current users. The best study[48] showed relative risks of 0.9 for both ERT and CHRT. A fair-quality study from the New Haven area[52] showed a non-statistically-significant relative risk of 1.52 for current use and any type of cancer, and 1.87 for current use and invasive cancer only. Two poor quality studies also evaluated current HRT use; one suggested increased risk (RR 1.5)[51] and one suggested decreased risk,[50] although neither was statistically significant. These data are displayed in Table 5.

Summary

- Current use of HRT reflects a broad duration of use.
- All 3 meta-analyses evaluating risk of BCA among current users of HRT have shown statistically significant increases in risk (RR 1.21-1.40).
- Three good quality cohort studies have shown elevated risk in association with current HRT, ERT, and CHRT use.
- The findings were inconsistent among the 4 case-control studies evaluating current HRT use. The best study showed no association.

Does exogenous estrogen and/or estrogen plus progesterone increase the risk of fatal breast cancer?

Cohort Studies

Six recent observational cohort studies evaluated mortality as an outcome, but none identified the components of the hormone replacement therapy in their analyses (see Table 6). The NHS showed an elevated incidence of breast cancer among hormone replacement therapy users, but there was not a statistically significant increased risk of death among current or past users of hormone replacement therapy.[20] However, among ever users of 5 or more years duration, the relative risk of death from breast cancer was elevated at 1.45 (95% CI, 1.01-2.09). Case-control analysis of data from this cohort published in 1997 had point estimates for risk of death from breast cancer of 0.76 among current users.[61] The Kaiser cohort study[62] did show an elevated relative risk of death among long-term HRT users but it was not statistically significant. However, the study is of poor quality and contributes little to the evidence.

Four cohort studies report reduced mortality rates among estrogen users.[63-66] The large cohort study from Sweden involving 22,579 women identified a significant decrease in standardized mortality ratio of 0.5 (95% CI, 0.4-0.6) among HRT users, though this is a poor quality study because of the use of external controls and no adjustment for confounding.[64]

The Iowa Women's Health Study,[65] which found no overall association with hormone replacement therapy and incident breast cancer, found significant reductions in breast cancer mortality in women using HRT. Among women without a family history of

breast cancer, past users of hormone replacement therapy for fewer than 5 years had a reduced risk of death (RR 0.86; 95% CI, 0.76-0.97). Among women with a family history of breast cancer, current versus never use of hormone replacement therapy for 5 or fewer years was associated with a relative risk for breast cancer death of 0.24 (95% CI, 0.06-0.97), and past versus never use for 5 or fewer years use was associated with a relative risk of 0.71 (95% CI, 0.51-0.98).

A cohort study by Willis[63] evaluated deaths among a cohort of women enrolled in a cancer-prevention study. This study enrolled 422,373 post-menopausal women in 1982 and followed them until December 1991. Breast cancer risk factors, co-morbidity, and hormone use were evaluated at entry with a self-administered mailed questionnaire. Hormone use was characterized as ever, current, or former use, and by duration of use, age at first use, and years since last use. Vital status was determined by phone queries using volunteers and by consulting the National Death Index. Breast cancer deaths were defined as those with breast cancer as the underlying diagnosis. Within this cohort, the overall risk of breast cancer among ever versus never users was reduced, with a relative risk of 0.84 (95% CI, 0.75-0.94). Past versus never use also had reduced risk, with relative risk of 0.78 (95% CI, 0.68-0.89). When duration and risk of death were evaluated, there was not a significant duration effect.

In the large BCDDP trial,[66] women with node-positive breast cancer who were current users for 4 or fewer years had a statistically significant decrease in risk of death of 0.5 (95% CI, 0.3-0.8). Point estimates of relative risk of death among current users (node-negative or node-positive) of more than 12 years duration were elevated at 1.9-2.2, but were not statistically significant. A statistically significant increase in risk of death

associated with hormone replacement therapy use was observed among lymph node-positive women with more than 12 years of past use (RR 4.4; 95% CI, 1.7-11.8)).

Case-control Studies

Of the 15 case control studies, only the large Nurses Health Study evaluated risk of death from breast cancer among women using hormone replacement therapy. In this nested case control study, 3,637 women died and were randomly matched to 10 controls each by age at menopause and 2-year period near the case patient's death. The multivariate-adjusted relative risk of death associated with current versus never hormone replacement therapy use was 0.76 (0.56-1.02), and past hormone replacement therapy use versus never (RR 0.83; 95% CI, 0.63-1.09).[61] Risk of death by duration of use was not evaluated.

Summary

- No mortality studies specifically evaluated risk of death by composition of HRT.
- Four of the 6 studies published since 1992 show statistically significant reduced mortality among "ever" users of HRT.
- For long-term HRT users, only the NHS showed an increase in risk of death from BCA for $\geq$5 years use (RR 1.45; 95% CI 1.01-2.09).

Are there subpopulations of women at higher risk of breast cancer in association with hormone replacement therapy?

Family History

Women with a family history of breast cancer have an elevated baseline risk of breast cancer. The interaction of family history and hormone replacement therapy has been evaluated in several studies. In the Iowa Women's Health Study,[65] no differences in

risk of developing breast cancer or dying from breast cancer were identified among individuals with or without a family history of breast cancer. A meta-analysis did not identify increased breast cancer risk among users of hormone replacement therapy in women with a family history of breast cancer.[29] In contrast, another meta-analysis reported a significantly elevated risk of breast cancer among women using hormone replacement therapy who had a family history of breast cancer (RR 3.4) compared to women using hormone replacement therapy without such a family history (RR 1.5).[32] The most recent meta-analysis, using data from 52,705 women worldwide with breast cancer, identified no significant difference in breast cancer risk among women using HRT with a family history of breast cancer.[12]

Body Mass Index

An important interaction identified in some studies is an increased risk of breast cancer among thinner women who use hormone replacement therapy.[12, 21, 45, 48, 53] Among premenopausal women, lower body mass index (BMI) is associated with a higher risk of breast cancer.[65] However, in postmenopausal women, higher BMI is associated with increased rates of breast cancer.[12] Thus, epidemiologic data suggest an important relationship or interaction between body mass index and BCA independent of HRT, which makes evaluation of the HRT/BMI interaction more difficult. Whether BMI is causally related to breast cancer or represents confounding by another factor is unclear. The identified interaction of HRT with lower BMI identified in some studies may be related to increased detection rates among thinner women, particularly given that current or recent use has the strongest association.

Benign Breast Disease

Because certain types of benign breast disease are associated with breast cancer either as part of the pathologic pathway or etiologically, the interaction of hormone replacement therapy and benign breast disease is of interest and concern. This relationship was evaluated in 3 meta-analyses, and no relationship was identified.[29, 30, 32]

Alcohol

Although each study evaluated the role of estrogen in different ways, 2 studies suggested an important interaction of estrogen with alcohol use. The observation that hormone replacement therapy use in women who drink alcohol increases risk of breast cancer has been made in the Nurses Health Study and the Iowa Women's Study, both good-quality, well-conducted cohort studies from the United States involving large groups of women.[56, 67] The interaction was also suggested in a Greek case-control study, but was not statistically significant.[68] The interaction was initially described in a 1990 report from the Nurses Health Study. In this study, women who did not consume alcohol had no increase in breast cancer risk with use of hormone replacement therapy (RR 0.99; 95% CI 0.62-1.60), and women who drank alcohol and were current hormone replacement therapy users had an elevated risk of breast cancer (RR 1.56; 95% CI 1.2-2.0). Similarly, the IWHS showed an elevated relative risk of breast cancer associated with HRT only among women who drank alcohol.

Summary

- There is no current evidence of an important interaction between HRT and benign breast disease.

- There is good evidence from 2 well-conducted cohort studies of an interaction between HRT and alcohol, resulting in higher risk among women who drink alcohol and use HRT than among women using HRT who do not drink alcohol.
- The data evaluating HRT risk and interaction among women with a family history of breast cancer are inconsistent.
- Five studies using different methodologies have suggested increased risk of developing BCA among lean women taking HRT.

Does hormone replacement therapy change breast density on mammograms?

In several studies, mammographic density has been shown to be a strong, independent risk factor for the development of breast cancer.[24, 69-71] Several studies of mammographic breast density and use of hormone replacement therapy have had conflicting results. The most recent and important will be briefly reviewed.

Mammograms of 41 postmenopausal women enrolled in a clinical trial of hormone replacement therapy were blindly evaluated before they began estrogen replacement therapy and continuous progesterone of 2.5 to 5 mg per day and one year following the commencement of hormone replacement therapy. In this study, mammographic density increased significantly from baseline in 73% of the women randomized to hormone replacement therapy.[72]

A second study performed subset analyses on 307 women involved in the Postmenopausal Estrogen/Progestin Interventions trial.[73] Participants were those who had a baseline mammogram and at least one follow-up mammogram, were compliant with therapy, had not used estrogen in the 5 years prior to the baseline mammogram, and

did not have breast implants. Treatments included placebo, conjugated equine estrogens (0.625 mg/day), conjugated equine estrogen plus cyclic medroxyprogesterone, conjugated equine estrogen plus continuous medroxyprogesterone acetate, or conjugated equine estrogen plus cyclic micronized progesterone. Overall, 12.2% of the 295 women who were not at the highest baseline breast density had increases in breast density. Over the 3 years of follow-up, this increase in density was more prominent among those using CHRT, with increases ranging between 19 and 24%. In addition, CHRT was associated with the greatest density increase (5- to 7-fold increase among CHRT compared to ERT). In the logistic regression, the relative odds of an increase in density for CHRT was 13.1 for conjugated equine estrogen plus cyclic medroxyprogesterone acetate, 9.0 for conjugated equine estrogen plus daily medroxyprogesterone acetate, and 7.2 for conjugated equine estrogen plus cyclic micronized progesterone. In the logistic regression, age and alcohol had important effects on changes in mammographic density. For each 5-year increase in age, the odds of increasing mammographic density were 2 times greater. Women who drank alcohol were 3.6-fold more likely to have an increase in density than those who did not drink in association with use of HRT.

A hospital-based study[74] evaluated 81 postmenopausal women in a screening program before and after beginning hormone replacement therapy. In this study, 31% of patients treated with CHRT showed increased density compared to 8.7% in women treated with ERT.

Summary

- Well-conducted studies have shown that HRT increases mammographic breast density.

- Compared to ERT, CHRT causes greater and more frequent increases in breast density. Evidence suggests that the increase in density associated with CHRT is greater when progesterone is administered cyclically (compared to continuously).
- One study shows that the increase in breast density among women using HRT is significantly higher among women who drink alcohol.

Does hormone replacement therapy influence prognostic characteristics?

A number of studies have evaluated the prognostic characteristics of breast cancer detected in women taking hormone replacement therapy. Characteristics evaluated have included stage at diagnosis, presence or absence of estrogen and/or progesterone receptors, cathepsin D, histology, and cell kinetics. In general, HRT has been associated with increased rates of estrogen receptor positive, early stage, and more favorable histology tumors,[75-81] although this has not been shown in all studies.[82-85] Because mortality data are available from 4 well-conducted cohort studies, these factors were not extensively reviewed.

Chapter 4. Discussion

The biological plausibility that the use of either ERT or CHRT might increase the incidence of breast cancer is strong and supported by experimental, clinical, and epidemiologic studies. However, the studies evaluating the relationship between postmenopausal ERT or CHRT and BCA risk have had inconsistent findings. In general, the findings are as follows:

1. The vast majority of recent studies, including several of good quality, show no increase in risk of BCA in association with short-term use of ERT.
2. Current use of ERT has been shown to be associated with an increase in risk of BCA in several studies and 3 meta-analyses with relative risks in the range of 1.2 to 1.5.
3. The results of studies evaluating the long-term use of ERT are mixed. With the exception of the NHS and a subset from the IWHS, the strongest studies show no statistically significant association. Many studies of good to poor quality have had slightly elevated, though non-statistically significant point estimates, so that when studies are combined in meta-analyses, all suggest increased risks of 20-50% with 5-20 years duration of HRT.
4. Fewer studies have evaluated the use of postmenopausal CHRT, particularly long-term use. The majority show no statistically significant increase in risk with ever use.

5. Long-term use of CHRT is associated with elevated risks of BCA in 3 of the 5 studies evaluating its use. The risk appears to be disproportionately increased among lean CHRT users and/or women using progesterone sequentially.
6. Recent data support an important interaction with HRT and CHRT among women who are lean. Whether this is due to a biological effect, confounding, selection bias, or detection bias in leaner women, is unclear.
7. HRT use may increase the risk of BCA more among women who use alcohol than among those who do not use alcohol.
8. Increased breast density is a risk factor for BCA, and ERT is associated with significant increases in mammographic breast density. CHRT seems to result in even greater increases in breast density than ERT.
9. The majority of studies show decreased BCA mortality among women who use HRT, although this finding may reflect selection bias among HRT users.
10. Past use of HRT is not associated with increased risk of BCA.

Most recent evidence shows no increase in BCA risk associated with short-term HRT/ERT/CHRT use. In evaluating this finding it is important to consider potential flaws in the data. The most prominent of these is the possibility of selection bias in the use of ERT or CHRT. Do women at higher or lower risk of BCA differentially use short-term HRT? Many studies support the contention that women who take HRT are different from those who do not in ways that affect BCA risk. For example, women who use HRT tend to be wealthier, to have fewer children, to be more educated, and to use more alcohol, all epidemiologically associated with increased rates of BCA. On the other hand,

particularly in Europe, women often use HRT for the relief of menopausal symptoms, and women with more menopausal symptoms often have physical characteristics associated with a lower risk of breast cancer, such as lower body mass index. Also, very often HRT is used for symptoms in women who undergo surgical menopause, which, if performed prior to natural menopause, is associated with lower risk of breast cancer. Both of these situations may artificially result in biases toward less measured effect of estrogen on breast cancer than might truly be the case.

Another concern in evaluating negative results among studies is that inclusion of women with simple hysterectomy in analyses may have led to a systematic underestimate in risk of BCA associated with HRT. This concern was initially raised in a study by Pike,[86] who suggested that because age at menopause is strongly negatively correlated with use of ERT, and younger age at menopause decreases risk of BCA, including women with simple hysterectomy with an estimated age of menopause may systematically result in relative risk estimates which are artificially low. This issue was evaluated in the Nurses Health Cohort by comparing relative risk estimates among the full cohort with relative risk estimates when women with a simple hysterectomy were excluded. In this analysis, relative risk was 1.05 (95% CI, 1.03-1.07) for each year of estrogen use when women with simple hysterectomy were excluded and 1.04 (95% CI, 1.02-1.06) when all women were included and age at menopause was calculated as the time when 90% of women would have achieved menopause. Only a randomized controlled trial can eliminate selection bias in the use of HRT and validly evaluate the HRT and BCA relationship.

Of the studies showing increased risk of breast cancer associated with hormone replacement therapy, several show it with current use,[12, 20, 29, 31, 53] and few show increased risk with past use. This finding may be explained by estrogen acting as a promoter or co-carcinogen of breast cancer rather than an initiator, and fits with hypothesized models of carcinogenesis. In this model, estrogen may acutely raise breast cancer risk, which then decreases when estrogen is stopped. Pregnancy and its association with short-term increased breast cancer risk is a natural model that fits the conceptualization of risk associated with current HRT use. After a full-term pregnancy, women have increased rates of breast cancer, which persist for 1 to 2 years and then return to baseline, suggesting a late-stage promoting effect of pregnancy. However, the association of current hormone replacement therapy use and BCA might also be explained by other factors, such as surveillance bias, increased cancer detection in an unscreened population becoming screened, and, more recently, if progesterone truly is associated with increased risk (above that of estrogen alone), the addition of progesterone to more current hormone regimens.

The results of the meta-analyses reviewed and point-estimates from some of the case-control studies and cohort studies suggest that long-term ERT or CHRT use may be associated with an increase in BCA risk of 20-50% after 5 or more years of use. Very few of the studies have shown a graded risk with duration of use, which argues against a dose-response relationship, though several studies have shown increased risk after at least 5 years of use, suggesting a threshhold effect. Newcomb has raised the issue that users of long-duration estrogen are more likely to be current users, and that the increased risk identified with increased duration actually reflects recency of use.[47] The lack of

association of breast cancer with past use of HRT, even of long duration, is suggestive of explanations other than a dose-response relationship. As discussed above, this may reflect that estrogen acts as a promoter or co-carcinogen rather than an initiator of BCA. In addition, although some of the studies have attempted to evaluate levels of screening, women on HRT may have more opportunity for the diagnosis of BCA because of increased surveillance. This increase in surveillance among hormone replacement therapy users has been documented in a number of studies, including the Nurses Health Study[56] and the Iowa Women's Health Study.[36]

In evaluating the observational data, it becomes evident that many of the studies that show an increased risk of breast cancer associated with HRT show it only among recent or current users and not among past users, even of long duration. This may reflect surveillance bias among current users or, alternatively, may reflect estrogen's postulated role as a promoter in the etiology of breast cancer. There has been a marked increase in the diagnosis of ductal carcinoma *in situ* since mammography use has become more widespread. This suggests a pool of prevalent breast cancer that can be diagnosed with mammography, and increased surveillance among hormone replacement therapy users may artificially elevate breast cancer incidence rates. Increased surveillance is supported by data from some of the observational studies showing that women taking hormone replacement therapy have an increased incidence of *in situ* carcinoma and/or earlier stage tumors.[12, 87]

Further supporting the observation that HRT use and its association in some studies with increased incidence of breast cancer may reflect surveillance or over-diagnosis bias, are data from 4 of the 6 recent cohort studies evaluating mortality from

breast cancer among hormone replacement therapy users. These data show that breast cancer mortality rates are reduced among women who were taking hormone replacement therapy at the time of diagnosis. Alternatively, it has been postulated that the observed decrease in BCA mortality among HRT users may be due to the promoting effects of estrogen on estrogen-sensitive tumors, which have a better prognosis than non-estrogen-sensitive tumors. This possibility is supported by studies showing that even after adjustment for the stage and size of breast tumors, women on HRT had a prognosis as good or better than women not taking estrogen.[17, 88] However, these studies can also be interpreted to suggest that women who take estrogen differ from those who do not in characteristics that influence prognosis. Lower mortality from breast cancer in the setting of increased incidence rates may also reflect the propensity of hormone replacement therapy users to undergo more intense surveillance and screening for breast cancer with increased detection of early stage and/or *in situ* breast cancers of good prognosis.

Until recently, there have been few data on progesterone use. As the addition of progestational agents to estrogen use has become the standard of care among women with an intact uterus, more data have accumulated regarding risks associated with estrogen combined with progestins and/or with progestins alone. The issue is an important one, since clinical evidence among premenopausal women shows that rates of mitoses in breast epithelial tissue are highest when endogenous progesterone levels are highest.[89] Also, when progesterone is applied to breast tissue from postmenopausal women *in vitro*, rates of mitoses in breast epithelial tissue are increased. This suggests that progesterone may have an important etiologic role in breast cancer.[89]

However, studying the risk of breast cancer associated with progestational agents is even more difficult than evaluating the risks associated with estrogen alone, for several reasons. First, the type of progestational agent varies among studies. The most commonly studied formulation has been medroxyprogesterone acetate. Second, the dose varies among studies. Finally, progestins have been given in varying schedules, though typically either continuously or sequentially, which may affect the risk of breast cancer associated with them. Two of the recent cohort studies and 2 of the recent case-control studies suggest significant increases in risk of BCA above that of ERT/HRT, associated with the addition of progesterone to estrogen. One study reports that this risk was increased only among women using sequential progesterone (versus continuous).[22] Some experimental evidence suggests that continuous progesterone may inhibit breast epithelial cell proliferation but that sequential progesterone may stimulate it in association with estrogen.[90, 91] Finally, some studies evaluating the role of HRT and changes in breast density indicate that while estrogen alone increases breast density, the combination of estrogen and progesterone leads to greater increases.[73, 74] Because increased breast density has been shown to be a risk factor for breast cancer independent of other risk factors, this is a concern.

Three studies suggest an increased risk of breast cancer among women who use alcohol and hormone replacement therapy that is higher than that among women who do not drink alcohol and use HRT.[56, 67, 68] In addition, the study of mammographic density changes using data from the PEPI trial showed significantly greater increases in breast density in association with HRT among women who drank alcohol than among those who did not.[73] A biological mechanism is suggested by the finding that blood estradiol levels

are elevated in women taking hormone replacement therapy and increase markedly (to preovulatory levels) in women who take estrogen and drink alcohol.[92] In women who do not use hormone replacement therapy, baseline estradiol levels are lower and unchanged by using alcohol.[92] Other data suggesting increased exposure to estrogen among women who use alcohol come from the osteoporosis literature, where moderate alcohol use has been shown to decrease fracture risk, and fractures and osteoporosis have been thought to be markers for prior estrogen exposure. Not all studies have shown this interaction.[93]

A finding reported in a number of studies[12, 21, 45, 48, 53] is an increase in BCA risk among lean women who use HRT, but not among heavier women using HRT. In one study, which stratified by type of HRT,[21] CHRT seemed to confer more risk than ERT in lean women. The reason for this interaction is unclear. The issue is complicated by the already complex interaction between weight and BCA risk, where premenopausal women who are lean have higher risks of BCA than heavier women, and where postmenopausal women who are heavier have higher rates of BCA than leaner women.[12] Thus, a biological explanation is plausible. One suggestion has been that overweight postmenopausal women already have relatively high endogenous estrogen levels and that adding exogenous estrogen does little to change risk, whereas adding exogenous estrogen to women with lower endogenous estrogen levels results in a substantial increase in risk relative to heavier women. This theory fits with a threshold-type effect of ERT and/or CHRT. Methodologic explanations for the increased risk of BCA observed in leaner women using HRT include confounding by other breast cancer risk factors, inclusion of

premenopausal women (whose risk of BCA is increased if lean) in analyses, and/or increased detection of BCA in leaner women.

In the absence of controlled trials, evaluating a causal role for estrogen and/or progestational agents in the development of breast cancer is fraught with problems. Observational studies are subject to significant biases. Most prominent of these biases in the area of HRT is that almost all studies have shown that women who use estrogen are different from those who do not.[20, 56, 94] Longitudinal data among women who are premenopausal and followed into menopause also show that women who take estrogen postmenopausally are different in significant ways from those who do not prior to menopause. Women who take estrogen on average are better educated, drink more alcohol, have fewer children and later pregnancies, are leaner, exercise more, and have less co-morbidity,[95] and several of these characteristics have been shown to be epidemiologically linked to increased rates of breast cancer. It has also been suggested that physicians may prescribe HRT to women at lower risk of BCA, which could result in underestimates of BCA risk associated with HRT. This may have been particularly true during the years of many of these studies when the significant risk of endometrial cancer in association with unopposed estrogen was identified.

Thus, the role of estrogen in breast cancer may be confounded by its relationship with these other important known risk factors for breast cancer. These factors can be adjusted for analytically when they are measured. What cannot be adjusted for statistically, however, are lifestyle and/or environmental exposures and/or genetic characteristics that are not measured or may not yet be identified as risk factors for breast cancer. A very good example of the limitations of observational studies comes from the

HERS trial. To date, most epidemiologic studies evaluating the relationship between HRT and coronary disease incidence have shown significantly reduced risks among women using HRT. However, in the HERS study of secondary prevention of CHD with CHRT, women randomized to CHRT actually had increased rates of CHD events in the first 2 years of the study.[60] These findings were surprising and contradictory to a significant body of observational studies showing reduced risk of CHD among women with known CHD who used HRT. [96-98] This example illustrates the importance of randomized controlled trials.

Breast cancer is a multietiologic disease and most BCA occurs in women without known major risk factors. Studies have shown that only a relatively small proportion of breast cancer is explained by known risk factors. This indicates that other important risk factors might work alone or in aggregate with others that are as yet unknown, and emphasizes the important metholdologic problem in observational studies of BCA and HRT in which not all risk factors can be adjusted for. It is plausible, and even likely, that risk of BCA is influenced by childhood and adolescent exposures, such as diet, exercise, body weight or other environmental exposures, and little attention has been given to premenopausal exposures that might be associated with HRT and BCA risk.

Clarifying the role of exogenous estrogen and/or progesterone in the development of breast cancer will require randomized controlled trials so that potential confounders that may be associated with breast cancer risk are randomly distributed among users and non-users. The Women's Health Initiative is a randomized controlled trial of HRT involving approximately 27,000 women that began in 1992 and has several goals, one of which was to evaluate HRT and breast cancer risk. Data were to be published from this

study in approximately 2005. However, it was recently reported in the lay press that women using hormone replacement therapy had elevated rates of myocardial infarction, stroke, and blood clots. Although the study was not stopped, this finding may affect compliance and may limit the ability of the study to evaluate the association of hormone replacement therapy and breast cancer. As the life expectancy of women continues to increase, and the "baby boom" generation enters menopause, valid answers to the questions posed above are critical, given the relatively high incidence of BCA and the common use of HRT. We are hopeful that the Women's Health initiative will provide answers to these difficult questions.

Chapter 5. Research Priorities

1. Use data from ongoing randomized controlled trials of estrogen and estrogen-progesterone use to further evaluate the risk of breast cancer associated with hormone use.

2. Further evaluate the role of exogenous progesterone by type and by dosing schedule in breast cancer development in epidemiologic studies, as well as in basic science research. Attempt to clarify subpopulations of women who might be at increased risk of developing breast cancer in association with hormone use, particularly considering genetic risk factors, alcohol use, body mass index, and age.

3. Given the large number of women needed for a clinical trial or cohort study, and the relatively urgent need for information, utilize multicenter prospective, current case-control studies, especially in HMO settings, where drug records are available to further evaluate the association.

4. Use epidemiologic methods to evaluate whether HRT has different effects in women with BRCA 1 and/or BRCA 2 tumor suppressor gene mutations. Are women with these mutations at any higher risk of BCA if they use HRT?

5. Further evaluate the association of estrogen and progesterone with BCA tumors at the basic science level, particularly its effect/relationship with the BRCA tumor- suppressor genes.

6. Evaluate childhood and adolescent exposures and their association with breast cancer. Large databases such as NHANEs might be useful in this evaluation.

ADDENDUM

This report was completed in December 2001. On May 31, 2002 after approximately 5.2 years of follow-up, the Women's Health Initiative (WHI) randomized controlled trial was stopped on the recommendation of the data safety and monitoring board because the test statistic for invasive breast cancer exceeded the stopping boundary for this outcome. At the time the study was stopped, the hazard ratio for invasive breast cancer associated with the use of estrogen 0.625mg and medroxyprogesterone acetate 2.5mg per day in 1 tablet was 1.26 (95% nominal CI; 1.00-1.59). When the confidence interval was adjusted for multiple analyses over time it was 0.83-1.92. No significant difference for *in situ* breast cancer was shown. Three breast cancer deaths occurred in the combined therapy group (n=8506) and 2 in the placebo group (n=8102). Subgroup analyses indicated that women reporting prior postmenopausal hormone use had higher hazard ratios for breast cancer associated with CHRT use in the trial than women who had not previously used hormones (HR 1.06 [95% CI; 0.81-1.38]). When duration of prior hormone use was evaluated, women with less than 5 years of prior use had increased risk (HR 2.13 [95% CI; 1.15-3.94]). Prior use of 5-10 years among those randomized to CHRT showed a hazard ratio of 4.61 (95% CI; 1.01-21.02) and greater than 10 years of prior use was associated with a hazard ratio of 1.81 (95% CI; 0.60-5.43) among women randomized to CHRT use in the trial. No interactions were identified with known breast cancer risk factors.

A separate arm of the WHI evaluating whether oral estrogen prevents cardiovascular disease among women with prior hysterectomy (n=10,739) was not terminated so the association between ERT and breast cancer in this trial remains uncertain, with results expected in 2005.

These findings are consistent with some, but not all, of the observational studies which specifically evaluated CHRT use and are reported in our evidence review. In addition, they are consistent with prior meta-analyses of observational studies which have evaluated the HRT - breast cancer relationship, though have not specifically evaluated CHRT use. The findings from the WHI trial evaluating estrogen use alone will help clarify whether the increase in breast cancer risk is associated with the estrogen or progesterone components of the therapy, or both.

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Appendix 1. Search Strategy

The topic of HRT and breast cancer was searched in the Medline database including 1994 to January 2000.

1 exp hormone replacement therapy
estrogen replacement therapy

2 hormone replacement.tw. (text word taken from title and abstract of article)

3 estrogen replacement.tw.

4 exp estrogens/ ad,tu (ad = administration & doseage; tu = therapeutic use)

equilenin	estrogens, catechol
equilin	estrognes, conjugated
estradiol	estrogens, non-steroidal
estriol	estrone

5 exp estrogens, synthetic/ ad,tu

estrogens, non-steroidal	epimestrol
chlorotrainisene	ethinyl estradiol
coumestrol	mestranol
dienestrol	quinestrol
diethylstilbstrol	hexestrol
zearalenone	zeranol

6 1 **or** 2 **or** 3 **or** 4 **or** 5

7 breast neoplasms

8 breast neoplasms, male

9 7 **or** 8

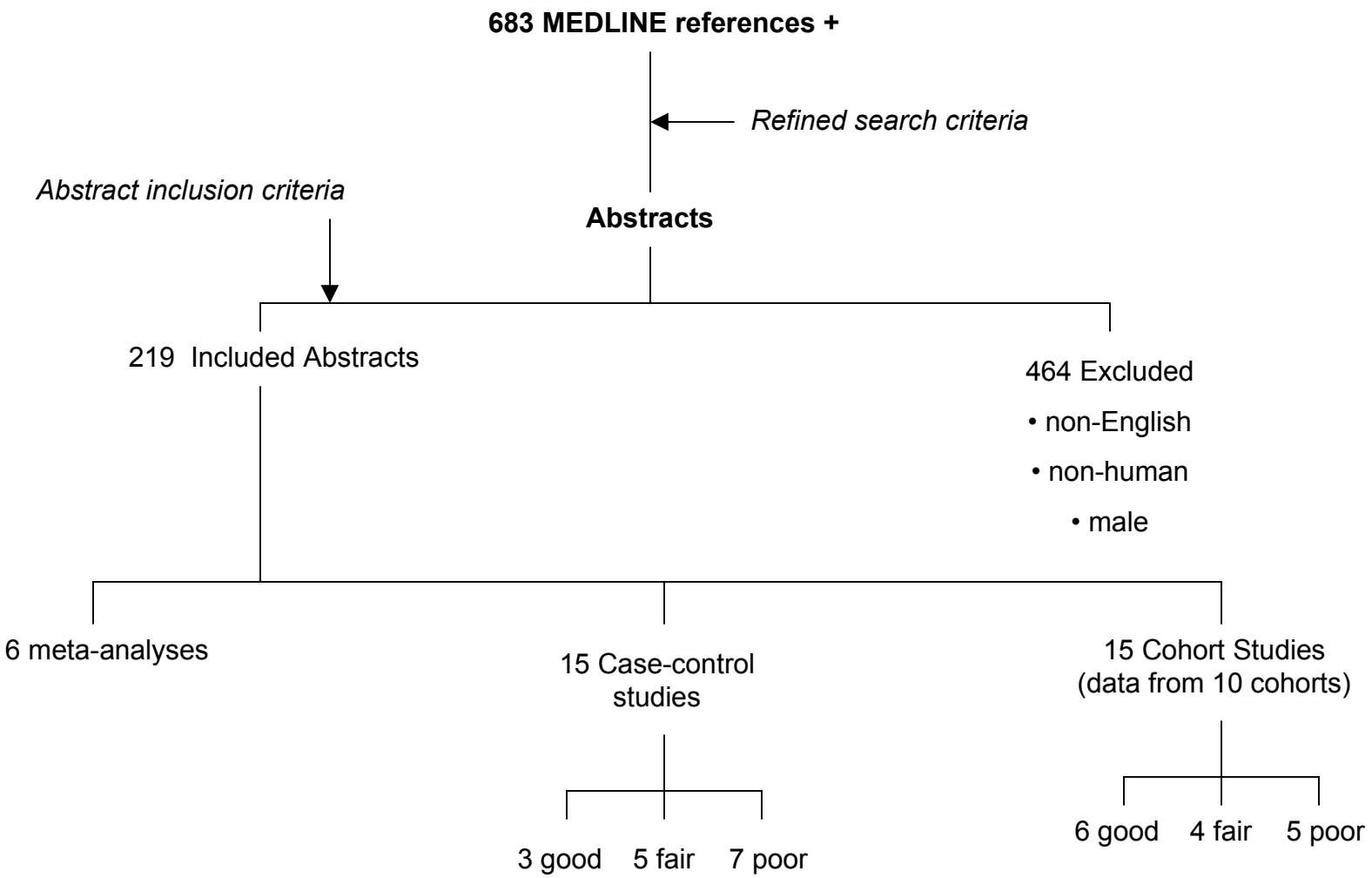
10 6 **and** 9

11 **limit** 10 to human

12 **limit** 11 to english language

13 *looked at english abstracts of foreign articles*

Appendix 2. Search Results



Appendix 3: Criteria for Grading the Internal Validity of Individual Studies

Design-Specific Criteria and Quality Category Definitions

Presented below is a set of minimal criteria for each study design and then a general definition of three categories-- "good," "fair," and "poor" --based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known important limitations. "Poor" studies have at least one important limitation.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Appendix 3: Criteria for Grading the Internal Validity of Individual Studies (continued)

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
  -for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTS.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

Appendix 4: Study Summaries

Meta-analyses

More than 50 observational studies have evaluated the relationship between hormone replacement therapy (HRT) and breast cancer (BCA) incidence or mortality, and the majority have shown no statistically significant association, although several have had point estimates in either direction. This suggests that an association, if it does exist, is likely to be small, and that very large sample sizes may be needed to detect a small but potentially important association. In an effort to increase sample sizes (and thus power), 7 meta-analyses have evaluated the relationship between ever use of hormone replacement therapy and breast cancer using data derived from observational studies. Summary data from the 7 meta-analyses are displayed in Table 1, but only the six meta-analyses published between 1992-2000 are described in detail below. In addition, one meta-analysis combining data from 9 randomized controlled trials of estrogen replacement therapy (ERT) or combined hormone replacement therapy (CHRT) evaluated the risk of BCA associated with HRT. It is very difficult to interpret the results of meta-analyses combining data from observational studies because it is difficult to be certain of the quality of the data that were pooled in the meta-analyses. If the studies do not adequately control for confounding or use inappropriate controls, the summary estimates will be biased. After reviewing much of the literature pertaining to HRT and BCA risk, we found very few studies to be of high quality. Consequently, the results of meta-analyses combining studies of less than high quality should be interpreted cautiously.

Sillero-Arenas 1992[31]**:** Twenty-seven published studies dating from 1971 through June 1990 were blindly reviewed for quality by 2 independent reviewers. Ever-use of HRT was associated with a summary relative risk of 1.06 (95% CI, 1.0-1.12). When only case-control studies were evaluated, the summary relative risk for ever use was 1.01 (95% CI, 0.95-1.08); for cohort studies it was 1.16 (95% CI,1.05-1.28). When duration was evaluated, there was no overall increase in BCA risk until after 12 years (RR 1.23; 95% CI, 1.07-1.42), and no dose-response relationship was identified.

Grady 1992[34]**:** This analysis reviewed literature from 1970 through 1990 that evaluated the risk of BCA associated with HRT use and included 39 studies. The summary relative risk for ever use of HRT was 1.01 (95% CI, 0.97-1.05). The study identified no association with BCA risk and dose of HRT. To evaluate the risk associated with long-term use, the authors combined data from studies reporting 8 or more years of HRT use and calculated a summary relative risk of 1.3 (95% CI, 1.2-1.6). Because there were very few studies, there was no calculation of a summary risk for CHRT.

Colditz 1993[29]: This study evaluated data from 31 studies and calculated a relative risk of 1.02 (95% CI, 0.93-1.12) for ever use. Current use was associated with increased risk of 40% (RR 1.40; 95% CI, 1.08-1.40). Combining data from 17 studies, Colditz observed no relation or trend between years of ERT and BCA risk. However, use for $\geq$10 years was associated with relative risk of 1.23 (95% CI, 1.08-1.40).

The overall relative risk associated with CHRT, based on 4 studies, was 1.13 (95% CI, 0.78-1.64). The risk associated with HRT use was also evaluated in women with a history of benign breast disease, and no relationship was identified. An interesting analysis also evaluated studies by geographic location and found that the summary

relative risk of BCA from European studies was 1.34 (95% CI, 1.09-1.65) and from other countries 1.04 (95% CI,.98-1.09). The reason for different findings between the European and non-European studies is unclear. One possibility is that in Europe, synthetic estrogen is the predominant form of HRT and it is associated with higher circulating estrogen levels.[29] In other regions, natural conjugated estrogens are more commonly used. Another consideration is that European studies are often less well adjusted for known BCA confounders, which may result in higher risk estimates.

Steinberg 1994[32]: This analysis used data from 16 case-control studies dating from 1976-1989. The summary relative risk was 1.0 for ever use of ERT. For women with any type of menopause, the risk associated with HRT did not increase until after 5 years, whereafter each year greater than 5 years increased the relative risk by 0.015 (95% CI, 0.004-0.021). Fifteen years of use was associated with increased risk of 30% (RR 1.3; 95% CI 1.2-1.6). This study also identified an interaction of HRT and positive family history (RR for HRT 3.4 among women with a positive family history, RR 1.5 among women without family history).

Collaborative Group on Hormonal Factors in Breast Cancer 1997[12]**:** In 1997 the Collaborative Group reanalyzed approximately 90% of the worldwide epidemiologic evidence describing the relationship between HRT use and breast cancer. Of the 63 eligible studies, original data were contributed by 51 studies (49 published, 2 unpublished). Data were evaluated in a case-control format. Cases were defined as women with invasive breast cancer; controls were women without breast cancer. Information on tumor spread was available from 21 studies. Current use was defined as use at the time of BCA diagnosis or within one year.

There were many important epidemiologic findings in this study, and many known BCA risk factors were reaffirmed. One finding was that menopausal status was an important determinant of BCA risk, since postmenopausal women had a lower risk of BCA than premenopausal women of the same age and child-bearing pattern. Therefore, if menopausal status and age at menopause are not adequately evaluated in epidemiologic studies, there can be substantial confounding by these variables, since they are also associated with HRT use.

To deal with this issue, the main analyses of this study involved only postmenopausal women with known age at menopause and included 53,865 postmenopausal women (17,949 cases and 35,916 controls). The median age at diagnosis was 60 and the median year of diagnosis 1985. Thirty percent of the cases and 34% of the controls had used HRT at some time. For all studies combined, the odds ratio (OR) was 1.14 for ever use (p=0.00001). Among ever-users of HRT, there was increasing risk of BCA with increasing duration of use (p=0.003). The relative risk of BCA was 1.35 (95% CI, 1.21-1.49) for $\geq$ 5 years' use. In addition, the relative risk of BCA was elevated significantly among current users (RR 1.21), but not among past users.

The interaction between HRT use and several other risk factors was examined, and lower body mass index (BMI) and weight were shown to be associated with elevated risks among HRT users of $\geq$5 years duration. There was no increase in BCA risk in association with HRT among women $\geq$65 kg or with BMI $\geq$25.0 kg/m^z. Tumor spread was reported in 54% of cases and ever-users were much more likely to have localized disease. Among current or recent users of HRT, the excess risk of BCA was confined to

localized disease. Approximately 80% used preparations, mostly containing estrogen, and 12% used CHRT. No association was noted between type of HRT and BCA.

Hemminki 1997[35]: This analysis used pooled data from 22 randomized controlled trials of estrogen therapy in studies evaluating outcomes such as bone density or lipids. It reported on breast cancer incidence among those randomized to receive HRT compared to those randomized to placebo. Of the 22 trials reviewed, 9 reported on rates of breast cancer among women randomized to hormone replacement therapy or placebo. Although these studies involved both ERT and CHRT, the data were combined and the estimated relative risk of incident breast cancer was 0.85 (95% CI, 0.38-1.89) comparing users to non-users. This study has several limitations, including a small number of women and events, relatively short-term HRT use, probable selection of women at lower than average risk of BCA for inclusion in HRT trials, and no evaluation for duration.

Cohort Studies

We reviewed 16 cohort study reports from 10 cohorts and rated them in quality as good, fair, or poor, based on the following criteria: size and representativeness of the cohort, adequate assessment of HRT use, adequate assessment of potential breast cancer risk factors, and duration and completeness of follow-up.

The Nurses Health Study (NHS) 1995[20]: The NHS is a cohort study of good quality involving nearly 70,000 postmenopausal nurses in the United States who were enrolled in 1976. Each woman initially completed a mailed questionnaire describing known or suspected risk factors for breast cancer with mail follow-up every 2 years. After 725,550 person-years of follow-up, 1,935 cases of newly diagnosed invasive BCA were identified. Follow-up of the cohort is 95% complete, and control for confounding

factors fairly good, though no adjustment was made for alcohol use or body mass index in the multivariable analyses. The NHS is the only cohort study published in the last 5 years showing increased breast cancer incidence among current users of ERT (RR 1.36; 95% CI, 1.14-1.54), CHRT (RR 1.41; 95% CI, 1.15-1.74), and progesterone only (RR 2.24; 95% CI, 1.26-3.98). When this increased risk among current users was evaluated by duration of use, the study showed that the risk was increased after 5 years of use in women ages 55 to 64 (RR 1.54-1.7) and among all women after 10 or more years (RR 1.46 95% CI, 1.20-1.76). Past use of any duration was not associated with an increased risk of breast cancer. A prior evaluation of this cohort, published in 1990, indicated an interaction of hormone replacement therapy with alcohol use.[57] In the earlier report, the age-adjusted relative risk of breast cancer was 0.99 among women who did not drink alcohol and used HRT, and increased among current alcohol and HRT users (RR 1.56, 95% CI, 1.2-2.0). The authors did not report this association fully adjusted for other risk factors, and the association was not reviewed in their 1995 publication.

The Iowa Women's Health Study (IWHS)1999, 1997, 1995[36,65,94]: This prospective cohort study of good quality was initiated in 1985. Women ages 55-69 with valid Iowa licenses were identified at random from the 1985 Iowa Department of Motor Vehicles registry. A 16-page questionnaire was sent to members of this population and returned by 41,386, who then became the cohort. The 16-page questionnaire was designed to address important risk factors for cardiovascular disease and cancer. The most recent publication from this cohort evaluating the risk of breast cancer associated with hormone replacement therapy[36] involves a mean follow-up time of 11 years and 371,471 person-years. A total of 1,520 incident breast malignancies were identified from

follow-up questionnaires, the SEER Network Cancer Registry and the National Death Index. Overall, there was no association between ever use of hormone replacement therapy and breast cancer risk (RR use ≤ 5 years 1.07). However, when the findings were evaluated by type of breast cancer, favorable histology BCA accounted for 82 of the incident cancers and the relative risk was significantly elevated among those with ≤ 5 years of ever use (RR 1.81) and ≥ 5 years of ever use (RR 2.65). For favorable histology, current use of estrogen for fewer than 5 years was associated with a RR of 4.42 (95% CI, 2.0-9.76) and for more than 5 years with a RR of 2.63 (95% CI, 1.18-5.89). Current use of 5 or fewer years was also associated with a relative risk of invasive ductal or lobular carcinoma of 1.38 (95% CI, 1.03-1.85). The relative risks of invasive breast cancer with unfavorable prognosis and/or *in situ* breast cancer associated with ever use of estrogen or ever use of long-term estrogen were not increased. A limitation of this cohort study (or the publications to date) is that there is no analysis by type of hormone replacement therapy (CHRT versus ERT). A prior report from this cohort evaluated risk of breast cancer among women with and without a family history of breast cancer. The overall adjusted relative risk of breast cancer was 1.34 for current use of estrogen for 5 or fewer years (95% CI, 0.98-1.8). The risk of BCA in association with HRT was not increased among women with a family history of BCA..[65] Another finding from this cohort was an elevated relative risk of breast cancer among women using hormone replacement therapy who used more than 5 grams of alcohol per day on average (RR ≥1.8).[67] No association was shown between HRT and breast cancer among women who were not using alcohol, suggesting biological effect modification.

National Health and Nutrition Examination Survey I (NHANES I) 1999[40]: Between 1971 and 1974, 5,761 postmenopausal women representing various regions of the United States were interviewed and underwent a baseline examination. Every 4 years they received follow-up phone interviews. Hormone use was evaluated as ever/never use, with attempts to evaluate duration. Potential risk factors and confounders were well characterized except for alcohol use and benign breast disease. Breast cancer cases were identified by self-report and medical records, and pathology was reviewed at the National Cancer Institute. After an average of 12.7 years of follow-up (72,253 person years), 219 cases of breast cancer had occurred. The adjusted relative risk of ever versus never use of hormone replacement therapy was 0.8 (95% CI, 0.6-1.1). The adjusted relative risk for fewer than 3 years of use was 0.9 (95% CI, 0.6-1.4), for 3 to 6 years of use 0.5 (95% CI, 0.3-0.9), and for more than 10 years 0.8 (95% CI, 0.5-1.3). This is a good quality study; it is a nationally representative cohort with good assessment of confounding factors and good follow-up. Limitations are its relatively small size and lack of information on hormone composition.

Breast Cancer Detection Demonstration Project (BCDDP)2000, 1994 [21, 66, 87]: This was a large breast cancer detection screening trial performed in the United States. It included 46,355 postmenopausal women who were enrolled between 1973 and 1980, and followed for incident breast cancer for a median duration of 12.3 years (437,687 person-years). During follow-up, 2,082 cases of breast cancer were reported. Hormone use was characterized within the study by telephone interviews and mailed questionnaires. Ever use of ERT, CHRT, or estrogen and CHRT was not associated with an increased relative risk of breast cancer. Current use of ERT was associated with a relative risk of 1.1 (95%

CI, 1.0-1.3), and current CHRT use with a relative risk of 1.4 (95% CI, 1.1-1.9). For both ERT and CHRT, the relative risk of breast cancer associated with hormones was elevated only among thinner women with body mass index of ≤ 24.4 kg/m2. Among lean women using ERT, the risk of breast cancer was elevated at 8-16 years and more than 16 years, with relative risks of 1.5 and 1.6, respectively, and positive for trend. There was no increase in BCA risk with use of ERT of any duration in women with BMI > 24.4 kg 1m^{z}. Among CHRT users, the relative risk of breast cancer was elevated at 4 or more years of use at 2.0 (95% CI, 1.3-3.0); point estimates for CHRT use among heavier women were also evaluated (RR 1.3-1.5), but not statistically significant. The relative risk of breast cancer with ERT increased 0.03 (0.01-0.06) per year and for CHRT 0.12 (0.02-0.25) per year of use. This study is of good quality. It is an important study because it is one of the first studies to show a statistically significant increase in BCA in association with CHRT above that of ERT alone, though there have been elevated point estimates in other studies. This study is of good quality. Its results may be less generalizable than others because the women in the BCDDP were a higher BCA risk population.

A prior report[87] from this cohort indicated significant increases in *in situ* BCA in this cohort associated with ever use of both ERT (RR 1.4; 95% CI, 1.0-2.0) and CHRT (RR 2.3; 95% CI, 1.3-3.9). However, in the more recent publication, increased duration of ERT use in lean women increased the risk of both early-stage and late-stage invasive disease. Also, in the more recent report, there was no significant increase in risk of *in situ* cancer associated with either regimen.

Finally, a 1999 publication from this cohort reported mortality rates by duration of use among past and current HRT users.[66] Mortality was reduced among current users of < 12 years duration for both node-positive and node-negative BCA. Mortality was increased among node-negative (RR 1.8; 95% CI, 0.8-4.3) and node-positive (RR 4.4; 95% CI, 1.7-11.8) past users with $\geq$ 145 months duration of use.[66]

Netherlands 1995[37]: A prospective study of 62,573 women ages 55 to 69 was conducted in the Netherlands. The cohort was assembled in September 1986, and information on exogenous hormone use and other risk factors was collected by mail questionnaire. A computerized record linkage with the Dutch national database of pathology reports was used to ascertain cases. After adjustment for most important risk factors for breast cancer, the relative risk of ever use of hormone replacement therapy was 1.0. There were no associations with duration of use, years since first use, years since last use, or age at first use. A sub-analysis of this paper involved evaluating the interaction of oral contraceptive use and hormone replacement therapy use; no interaction or increased risk was identified. This study is of fair quality based on its population base, age of the cohort, and good follow-up, but had only fair evaluation of confounding factors.

Cancer Prevention Study 1996[64]: This study evaluated deaths among a cohort of women enrolled in a cancer-prevention study. It enrolled 422,373 post-menopausal women in 1982 and followed them until December 1991. Breast cancer risk factors, comorbidity, and hormone use were evaluated at entry with a self-administered mailed questionnaire. Hormone use was characterized as ever, current, or former, and by duration of use, age at first use, and years since last use. Vital status was determined by

phone queries utilizing volunteers and the National Death Index. Breast cancer deaths were defined as those with breast cancer as the underlying diagnosis. Within this cohort, the overall risk of breast cancer death among ever versus never users was reduced with a relative risk of 0.84 (95% CI, 0.75-0.94). Past versus never use of HRT was also associated with reduced risk of BCA death (RR 0.78; 95% CI, 0.68-0.89). When duration and risk of death were evaluated, there was not a significant duration effect. This study is of fair quality, based on its lack of information on participation, the use of self-administered questionnaires, and relatively short follow-up.

Finnish Cohort 1998[38]: A prospective study of women born between 1923 and 1930 and living in Finland utilized data from a free mammography screening program between 1987 and 1990. The women were presumed to be menopausal because of their age. These 6,433 women were followed for 8 years (53,305 person years) for breast cancer or breast-cancer-related death using a national registry of hospital discharge data, death certificates, and the Finnish Cancer Registry. Estrogen exposure, comorbidity, and breast cancer risk factors were evaluated by a validated nurse-administered questionnaire, and estrogen use was characterized as ever, never, former, and current, although the formulation was not specified. After 8 years of follow-up, the relative risk of ever breast cancer associated with current hormone replacement therapy was 0.57 (95% CI, 0.27-1.20), and the risk associated with former use 0.94 (95% CI, 0.47-1.9). Duration of use and progesterone use were not evaluated in this study. The quality of the study is rated poor because of poor follow-up and failure to assess confounding factors.

Swedish Cohort 1996[46]: This prospective cohort study of women in Upsala Health Care Region of Sweden followed 22,579 women who received hormone

replacement therapy between 1977 and 1980 for an average of 13.2 years. The mean age of the participants was 54.5 years. Pharmacy records were used to characterize estrogen use by type, and a mailed questionnaire was sent to a random subset of women to ascertain risk factors for breast cancer. Breast cancer cases were identified by record-linkage to Swedish cancer and death registries. Within this cohort, after 13.2 years, 624 incident breast cancers and 102 deaths were identified. The standardized incidence ratio was 1.0, and there was no association with duration of use. The risk of death, which was also evaluated in this cohort and compared to a standard population, was reduced (SMR 0.72; 95% CI, 0.58-0.89). The quality of this study is poor based on poor control of confounding.

Saskatchewan Cohort 1994[41]: This cohort study from Canada, which began in 1976, involved nearly 33,000 women ages 43 through 49 from Saskatchewan, and followed them through 1990. Evaluation of estrogen and progesterone exposure was based on review of a prescription database. This study showed an increased relative risk of breast cancer associated with ERT of 1.33 (95% CI, 1.11-1.59) and, when evaluated by duration, found ERT use for more than 36 months associated with a relative risk of 1.50 (95% CI, 1.06-2.13). No increase in relative risk was shown with ever use of progesterone only or with one year of CHRT. The significance of these findings is limited, however, because there was no adjustment for important breast cancer confounders in the analyses. Also, this is a very young cohort, and their menopausal status is unclear.

Kaiser Cohort 1996[62]: This cohort study, conducted between 1969 and 1971 and involving women in the San Francisco Kaiser health maintenance organization, compared

245 women who had used HRT for 5 or more years with 232 age-matched non HRT users during 1969-1971. Exposure to HRT was based on prescription and medical records. Women were followed until December 1992 or death from BCA. The relative risk of death from BCA was 1.89 (95% CI, 0.43-8.36) among HRT users. However, because of uncertain and potentially biased selection of women for HRT use, lack of adjustment for reproductive risk factors, alcohol use, family history of BCA and benign breast disease, and possible misclassification of hormone use, the quality of the study is poor.

Case-Control Studies

Between 1992 and 2000, 15 case-control studies were published. Fourteen of these evaluated hormone replacement therapy and breast cancer incidence; the other considered breast cancer mortality. Each of the case-control studies was ranked in quality (good, fair, or poor) by size, case ascertainment, population-based versus referral-based, response rates of cases and controls, control of confounding, and adequate and non-biased selection of controls. Each study will be discussed in order from highest to lowest quality.

Newcomb 1995[47]**:** This population-based case-control study was conducted in Wisconsin, New Hampshire, Massachusetts, and Maine between April 1989 and December 1991. The cases were all women with newly diagnosed breast cancer, of which 98% were histologically confirmed. The women were interviewed within 8-21 months of diagnosis, and the response rate was 81%. The 3,130 cases were randomly matched to 3,698 controls by driver's license lists and Medicare files. Assessment of estrogen exposure was evaluated by phone interview, but the type of estrogen and dose

were not evaluated. Recent use was defined as within 2 years of the BCA diagnosis (or index date), and hormone replacement therapy was defined as more than 3 months of consecutive use of estrogen, either with or without progesterone. Ever use of hormone replacement therapy was associated with an odds ratio of 1.05 (95% CI, 0.93-1.18). Former use of hormone replacement therapy had an odds ratio of 1.12 (95% CI, 0.98-1.29). There was no association with duration of HRT and breast cancer. There also was no association with use of CHRT and breast cancer (adjusted OR = 1.01). Finally, there were no interactions with other risk factors identified.

Stanford 1995[48]: This population-based case-control study was conducted in King County, Washington, utilizing the SEER database and enrolling women ages 50 to 64 with newly-diagnosed breast cancer. The study enrolled 450 Caucasian women with invasive breast cancer and 87 women with *in situ* breast cancer. The controls were residents of King County ages 50 through 64 who were identified through random-digit dialing and matched within 5 years of age to the cases. Interviews were used to assess dates of estrogen use, as well as the duration, brand, and dose of estrogen, and progesterone use. Ever use of estrogen alone was associated with an odds ratio of 0.9 (95% CI, 0.6-1.1). Ever use of progestin alone was associated with an odds ratio of 0.5 (95% CI, 0.1-2.0). The only association with longer duration of use was a reduced risk of breast cancer with 8 to 15 years of estrogen use (odds ratio of 0.5). Among women who had started estrogen alone over 15 years earlier, the odds ratios were also reduced, ranging 0.3-0.5, and statistically significant. Among users of estrogen and progesterone who had started over 10 years earlier, the odds ratio was 0.3 (95% CI, 0.1-0.9). These

odds ratios suggest decreased risk of breast cancer among HRT users. This study is rated as good quality.

Grodstein 1997[61]: This is a good quality, nested case-control study based on the Nurses Health Study cohort described above. In this cohort, 3,637 women died and were randomly matched to 10 controls each by age at menopause and at the 2-year period near the case-patient's death. The multivariate adjusted relative risk of death associated with current versus never hormone replacement therapy use was 0.76 (0.56 to 1.02), and past hormone replacement therapy use versus never use relative risk was 0.83(0.63-1.09). Risk of death by duration of use was not evaluated.

Ross 2000[22]: To date only one study has evaluated the risk of BCA associated with cyclic progesterone use. This population-based study involving 2,653 women with breast cancer identified by the Cancer Surveillance Program in California between March 1987 and December 1989 was published in 2000. The cases were individually matched by age, race, and neighborhood to 2,429 controls. Estrogen assessment was determined by interview within one year of diagnosis of the case, with detailed assessment of estrogen use, utilizing pictures. Information on demographics, physical characteristics, and other breast cancer risk factors was also obtained. In this study, each 5 years of all HRT use was associated with an odds ratio of 1.10 (95% CI, 1.02-1.18). Five years' use of combined hormone therapy was associated with an odds ratio of 1.24 (95% CI, 1.07-1.45). Risk estimates were higher for sequential combined hormone replacement therapy, odds ratio 1.38 (95% CI, 1.13-1.68), than for continuous combined hormone replacement therapy, with an odds ratio of 1.09 (95% CI, 0.88-1.35). The odds ratio for estrogen use alone by duration was elevated only after 15 years of use, at 1.24. For combined

hormone replacement therapy, the odds ratio was 1.51 after 5 years' of use. This is the only study to date comparing sequential and cyclical progesterone use. It is of good-fair methodology, its major limitation being that a significant proportion of breast cancer patients were unable to participate because of death or severe illness.

Henrich 1998[52]: This case-control study included 109 post-menopausal women above age 45 with breast cancer initially identified with mammography near New Haven, Connecticut. Five controls per case were matched by age, screening site, prior mammogram, year of mammography, and payment status (n=654). HRT use was associated with an odds ratio of 1.54 (95% CI, 0.94-2.82), any ERT with an odds ratio of 1.66 (95% CI, 0.98-2.82), and CHRT use with an odds ratio of 1.02 (95% CI, 0.32-3.21). When only invasive breast cancer was considered, ever use of HRT was associated with an odds ratio of 1.93 (95% CI, 1.06-3.49). This study is of fair quality limited largely by small size and lack of control of important breast cancer risk factors.

Weinstein 1993[45]: This study compared 837 postmenopausal women from New York state diagnosed with breast cancer between 1984 and 1986 with controls identified by driver's license files who were matched by age, county, and postmenopausal status. Telephone interviews were conducted using a structured questionnaire, although interviewers were not blinded to case or control status. Risk factors were well evaluated and controlled for in the analysis. In this study, ever use of estrogen was associated with an adjusted odds ratio of 1.14 (95% CI, 0.84-1.40). The adjusted odds ratios for increasing duration ranged between 1.22 for less than one year's use to 0.88 for more than 5 years of use, neither of which were statistically significant. The authors reported a statistically significant odds ratio of 1.88 among women who were thinner, but this

finding was not adjusted for other risk factors. A limitation of this study is that small numbers of women reported progesterone use and a large number were uncertain of their hormone formulation. It is of fair quality limited primarily by poor response rates in both cases and controls.

Yang 1992[42]: This study evaluated 699 women younger than age 75 with breast cancer diagnosed between 1988 and 1989. These cases were compared to 685 age-similar controls drawn from voting lists. Risk factors and hormone use were evaluated by questionnaire. After adjusting for age and type of menopause, ever use of ERT was associated with a relative risk of 1.1 (95% CI, 0.8-1.4) and ever use of any progestin with a relative risk of 1.2 (95% CI, 0.6-2.2). There was no increase in risk associated with increasing duration of use until after 10 years (RR 1.6; 95% CI, 1.1-2.5). This study is of fair quality, based on poor response rates.

Brinton 1998[43]: This population-based case-control study involved women in Atlanta under age 55 with newly-diagnosed breast cancer who were frequency matched by region to 919 controls. HRT exposure was evaluated by record review and personal interviews. Attempts were made to define dates, duration, and dose of hormones. Benign breast disease, alcohol use, and family history of breast cancer were not controlled for in the analysis. Ever use of HRT was associated with an odds ratio of 0.9 (95% CI, 0.7-1.2). No duration effect was shown, and, among women taking ERT, ever use was associated with an odds ratio of 0.7 (95% CI, 0.5-0.9); no association was shown with ever use of CHRT (RR 0.99). A limitation of this study is that the cases and controls had relatively low exposure to estrogen because of the young age of the cohort. A subcategory analysis showed significantly increased risk (RR 3.19; 95% CI, 1.4-7.4) of

breast cancer among those using oral contraceptives for over 10 years, and hormone replacement therapy for over 3 years.

Italian case-control studies[44,50,54]**:** A number of reports have been published evaluating a hospital-based set of cases from Milan and 6 other Italian regions. The cases were assembled between January 1983 and February 1984. The largest of these included 5,984 women, ages 22 through 74, with histologically confirmed breast cancer. The 5,504 controls were ages 15 to 74 from the same geographic regions admitted to major teaching hospitals. Estrogen exposure was assessed with an in-hospital interview. The odds ratio for ever versus never use of estrogen was 1.2 (95% CI, 1.0-1.4). There was no effect shown with duration other than among women age 65 and older, where less than 60 months of use was associated with an odds ratio of 1.6 (95% CI, 1.1-2.3), and over 60 months of use was associated with an odds ratio of 2.2 (95% CI, 1.0-4.7). This study is of poor quality; limitations include a low prevalence (10%) of hormone replacement therapy and the fact that the study was not confined to postmenopausal women. In addition, controls were chosen from hospital admissions for orthopedic conditions, which may have led to bias in eliminating hormone replacement therapy use in the controls. This same study evaluated hormone replacement therapy use in nulliparous women and found no significant association between hormone replacement therapy and breast cancer in this subset, with an odds ratio of 1.22 for ever use (95% CI, 0.8-1.84).

Lipworth 1995[49]: A study of 820 women from Athens with newly diagnosed breast cancer from 1989-1991 found an adjusted odds ratio for ever use of ERT of 1.52 (95% CI, 1.24-2.25). Use for less than one year was associated with increased risk (RR 1.75; 95% CI, 1.02-3.01) and risks for more than 2 years of use were not significantly

elevated. The study's quality is poor, however, because risks were not adjusted for family history of breast cancer or benign breast disease. Also, use of orthopedic controls may have biased results in the direction of greater association if some of the controls were hospitalized with osteoporosis or its complications.

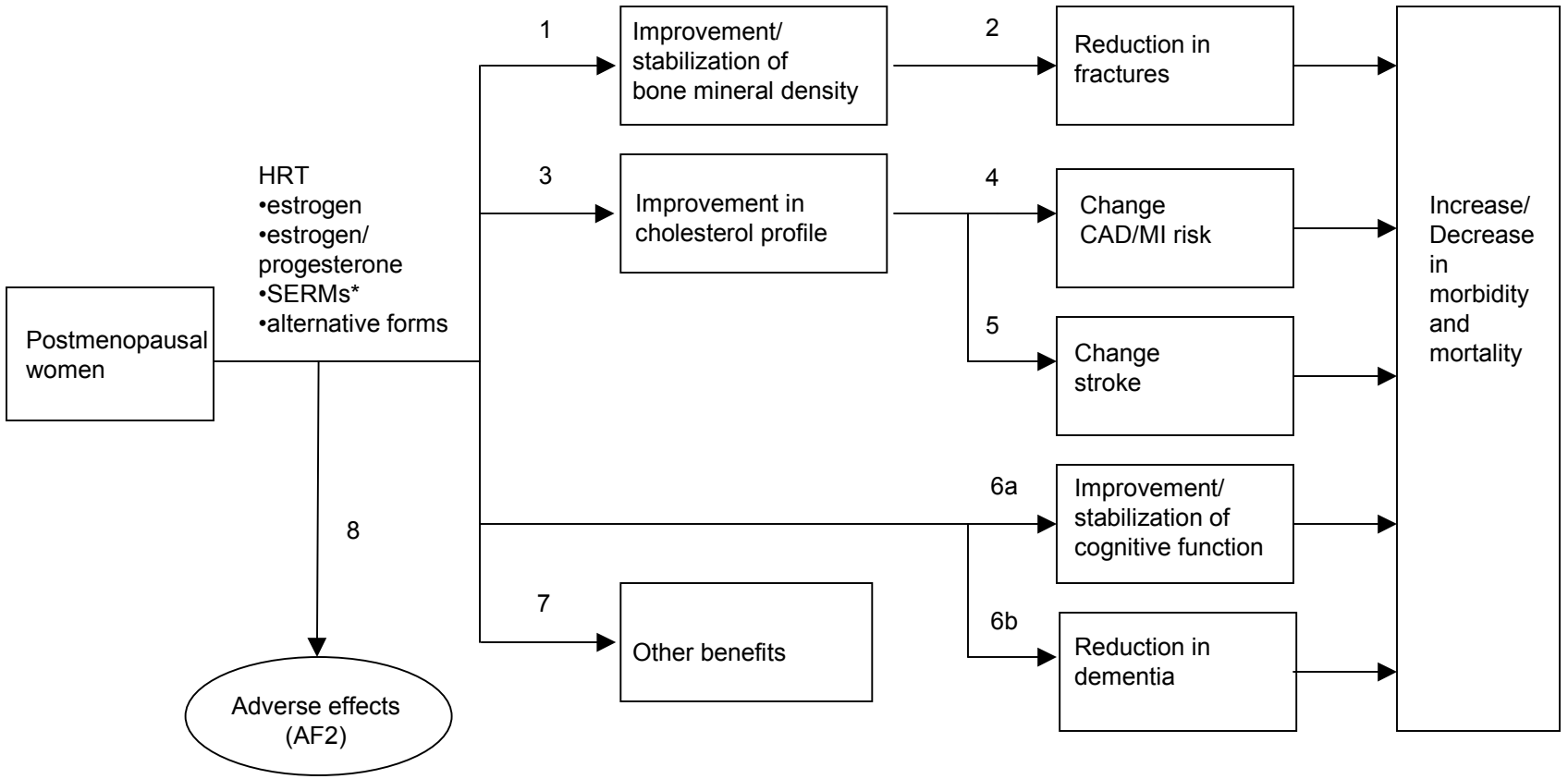
Persson 1997[46]: This population-based study from Upsala, Sweden, conducted between 1990 and 1992, included 435 incident cases of breast cancer, primarily detected by mammogram. The odds ratio for ever use of HRT was 1.1 (95% CI, 0.8-1.4). No increase in risk was shown until after 11 years of HRT use (RR 2.1; 95% CI, 1.1- 4.0). When associations were evaluated by type of HRT, estradiol and conjugated estrogens had an odds ratio of 0.5 (95% CI 0.3-1.0) and CHRT an odds ratio of 1.4 (95% CI, 0.9-2.1), suggesting increased risk with CHRT. This study is of poor quality based on small size and the inclusion of premenopausal women.

Magnusson 1999[53]: This study involved 2,563 cases of incident breast cancer in a cohort of postmenopausal women from Sweden identified between October 1993 and March 1995. Ever use of any HRT was associated with an odds ratio of 1.65 (95% CI, 1.43-1.89). ERT use had an odds ratio of 1.94 (95% CI, 1.47-2.55), and CHRT an odds ratio of 1.63 (95% CI, 1.37-1.94). A dose-related increase in risk of breast cancer was seen in every category of hormone use with longer duration of therapy. The risk associated with HRT was also increased among women with lower body mass index compared to those with higher body mass, suggesting an interaction. The interpretation of this study is limited however, since several important breast cancer risk factors were not controlled for (family history of breast cancer, prior benign breast disease, alcohol use, and socioeconomic status).

Levi 1996[51]: This study evaluated exposure to HRT among 230 women ages 23-70 admitted to a Vaud, Switzerland hospital with breast cancer. The cases were compared to 507 controls admitted for a spectrum of diseases but excluding those potentially associated with HRT. Overall, there was no association identified between BCA and short-term HRT use (OR 1.2), although risk was elevated with use of less than 10 years (OR 1.7; 95% CI, 1.1-2.9). The study is of poor quality because it is not limited to postmenopausal women and there may have been bias in choosing controls by systematically excluding women with HRT exposure.

Figure 1. Potential Benefits of Hormone Replacement Therapy

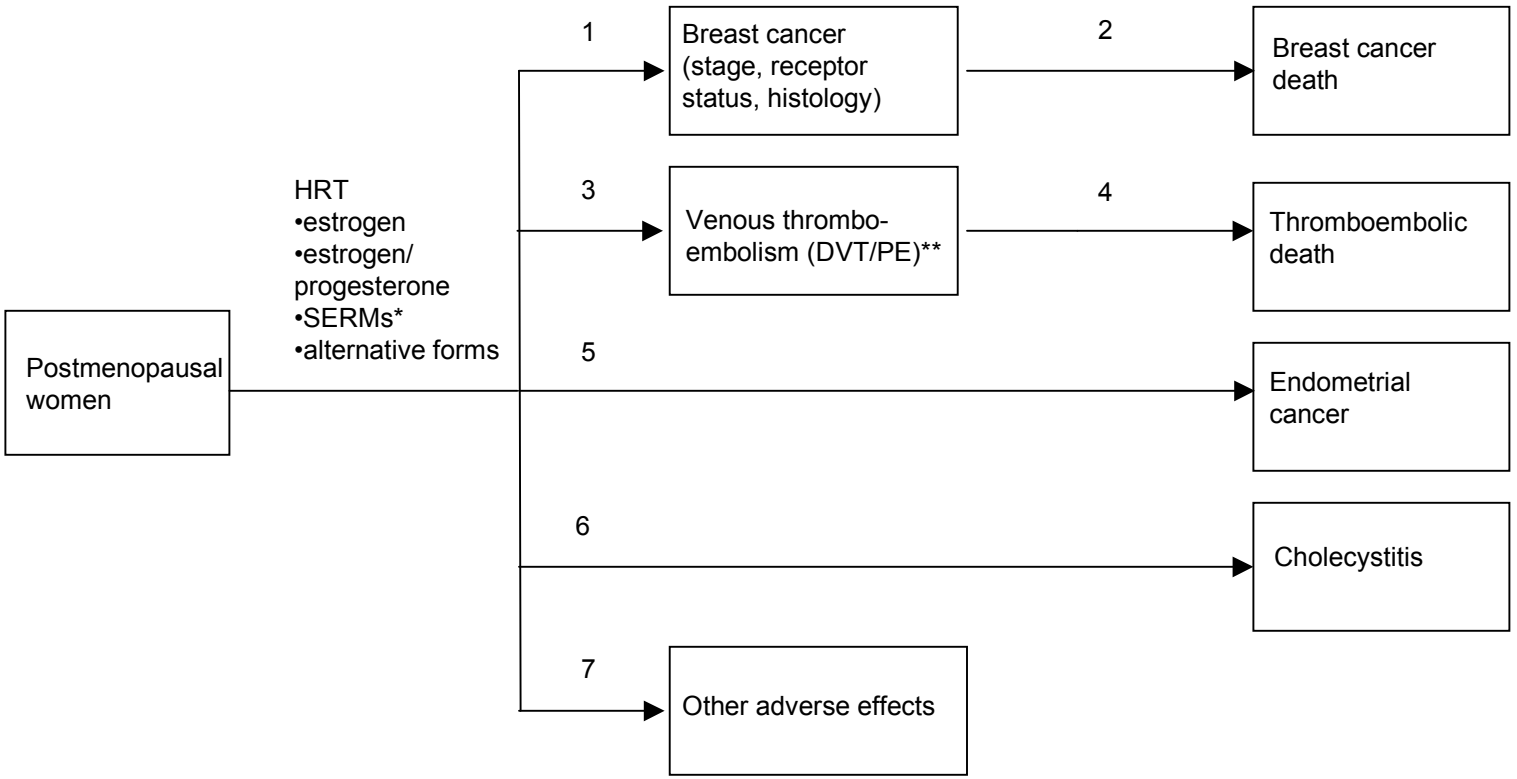
Analytic Framework 1



*Selective estrogen receptor modulators

Figure 2. Adverse Effects of Hormone Replacement Therapy

Analytic Framework 2



*Selective estrogen receptor modulators
**Deep vein thrombosis/pulmonary embolus

Figure 3. Hormone Replacement Therapy and Breast Cancer

Analytic Framework

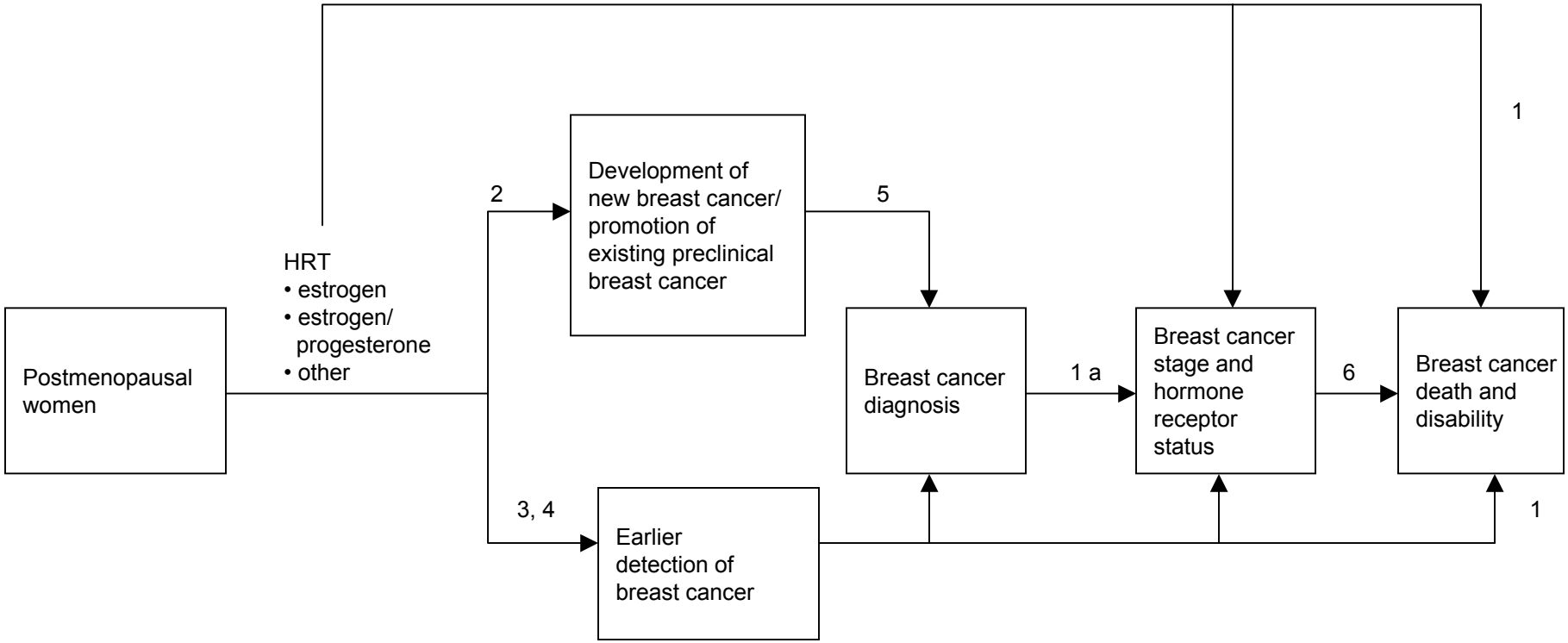


Figure 4. Post-menopausal Hormone Replacement Therapy and Breast Cancer

Key Questions

1. Does exogenous estrogen or estrogen & progesterone increase the risk of fatal breast cancer?

   a. Does HRT influence prognostic characteristics when breast cancer is diagnosed?

2. Does short-term exogenous estrogen increase the risk of breast cancer?
3. Does long-term exogenous estrogen increase the risk of breast cancer?
4. Does estrogen and progesterone increase the risk of breast cancer?
5. Is current use of either estrogen or combined hormone replacement therapy associated with increased risk of breast cancer?
6. Are there sub-populations of women at higher risk of breast cancer in association with hormone replacement therapy?
7. Does hormone replacement therapy change breast density on mammograms?

Table 1. Incidence Meta-Analyses

Author, Journal, Date	Methods	Ever/Never Use RR (95% CI)	Current/Never RR (95% CI)	Long-term Use RR (95% CI)	Comments
Armstrong '88	Data from 16 published case-control studies	1.01 (0.95-1.08)			
Dupont & Page '91	18 case control 10 cohort	1.07 (1.0-1.15)			Dose 1.25 mg RR 1.07 (0.99-1.2) Prior benign breast disease 1.16 (0.89-1.5)
Grady '92	24 case control 10 cohort 1 clinical trial	1.01 (0.97-1.05)		1.25 (1.04-1.51) for use $\geq$ 8 yrs.	
Sillero-Arenas '92	23 case control 13 Cohort 1 clinical trial	1.06 (1.0- 1.12)	1.23 (1.12 – 1.35)	1.23 (1.07-1.42) for use $\geq$ 12yrs., not increased until 12 yrs.	
Colditz '93	31 case control	1.02 (0.93-1.12)	1.40 (1.2-1.63)	$\geq$10 1.23 (1.08-1.40)	No consistent relationship with time since first use
				$\geq$15 1.29 (1.04-1.6)	No relationship with dose
				$\geq$20 1.51 (0.98-2.34)	No relationship with family history or benign breast disease
Steinberg '94	16 case control	1.0		For each year >5 yrs. RR increased by 0.015 (.004 – 0.021) Highest risk 15 yrs. 1.3 (1.2-1.6)	Evaluated relationship with family history and found significant increase (RR 3.4 95% CI 2.0 – 6.0) No association with benign breast disease
Hemminki, '97	22 randomized controlled trials of ERT/CHRT reviewed. Data derived from 9 in which BCA incidence was reported	0.85 (0.38 – 1.89)			

Table 1. Incidence Meta-Analyses

Collaborative Group on Hormonal Factors in Breast Cancer '97	51 case control studies 52,705 with breast cancer 108,411 without breast cancer Main analyses based on 53,865 women with known age at menopause.	1.14 ($p \leq .001$)	1.21 ($p \leq .001$) Current or within 1-4 years previously 1.023 (1.011-1.036) for each year of use	>5yrs. 1.35 (1.21-1.49)	Interaction with BMI No significant increase risk in past users Current = ≤ 12 months *Overall excess due to localized disease Large deficit advanced disease in first 5 years after beginning HRT

Table 2. Incidence Cohort Summary Table Studies 1992-2000

	ERT			CHRT			HRT		
		Duration of Use			Duration of Use			Duration of Use	
Study/Year	**Ever Use**	**Years**	**RR**	**Ever Use**	**Years**	**RR**	**Ever Use**	**Years**	**RR**
Risch '94 n=32,790	1.33*	≥3	1.50*	0.93	1	1.196			
Colditz '95 n=69,586	1.32 ¶¶ *			1.41¶¶ *				10+	1.46*
Schuurman '95 n=62,573							1.0	≥5	0.9
Perrson '96 n=22,579							1.0	>10	1.0
Sourander '98 n=6433							0.57 ¶¶ 0.94 former		
Gapstur '99 n=37,105							≤5y 1.07	≥5	1.11
Lando '99 n=5761	0.8	≥10	0.8						
Schairer 2000 n=40,020	1.1	>8	1.5 (lean)* 1.0 (non-lean)	1.3	≥4	2.0 (lean)* 1.3 (non-lean)			

* = P ≤ 0.05
¶¶ = current use

Table 3. Case-control Summary Table Studies 1992 – 2000 (continued)

Study Number	ERT Ever use OR	ERT Duration Years	ERT Duration OR	CHRT Ever use OR	CHRT Duration Years	CHRT Duration OR	HRT Ever use OR	HRT Duration Years	HRT Duration OR
Yang '92	1.1	≤1	1.2	1.2					
		1-4	0.8						
n=699		5-9	1.0						
		10+	1.6*						
Weinstein '93							1.14	≤1	1.22
								1-5	1.12
n=837								≥5	0.88
Lipworth '95							1.52*	≤1	1.75*
								1-3	1.26
n=820								≥3	1.42
Newcomb '95	0.97			1.01			1.05	≤2	1.02
								2-4	1.09
n=3130								5-9	1.02
								10-14	0.99
								≥15	1.11
Lavechia '95				1.6			1.2	≤1	1.0
								1-4	1.3
n=2569								≥5	1.5
Stanford '95	0.9	1-3 mos.	1.1	0.9 for CHRT	1-3 mos.	1.9			
		4mos – 2.9yrs.	1.0	or HRT	3mos – 2.9yrs.	1.0			
n=537		3 – 4.9	0.9		3 – 4.9	0.6			
		5 – 7.9	1.2		5 – 7.9	1.0			
		8 – 11.9	0.5*		≥8	0.4			
		12 – 14.9	0.5*						
		15 – 19.9	0.5	0.5					
		≥20	1.0	progesterone alone					
Levi '96							1.2	≥10	1.0
n=230									
Persson '97							1.1	1-2	0.9
								3-5	1.0
n=435								6-10	0.9
								11+	2.1*

* = P≤ 0.05
¶ = Invasive breast cancer only

Table 3. Case-control Summary Table Studies 1992 – 2000 (continued)

Study	ERT				CHRT				HRT		
			Duration				Duration			Duration	
Number	Ever use	OR	Years	OR	Ever use	OR	Years	OR	Ever use OR	Years	OR
Tavani '97									1.2	<5	1.2
										≥5	1.3
n=5984											
Henrich '98	1.66				1.02				1.54	≤5	1.55
	¶ 1.93*									≥5	1.61
n=109										≥11	1.45
Brinton '98	0.7				0.99				0.9	≤3	0.86
										3-5	1.0
n=1031										≥6	0.85
Magnuson '99	1.94*		<2	1.72*	1.63*		≤2	1.25	1.65*	≤2	1.29*
			2-5	1.49*			2-5	1.40*		2-5	1.40*
n=2563			>5	2.18*			≥5	2.43*		≥5	2.32*
			>10	2.70*			≥10	2.95*		≥10	2.43*
Fioretti '99									1.22	≥2	1.28
n=655											
Ross 2000			Every 5yrs.				Each 5yrs.			Every 5yrs.	1.10*
			1.06				1.24*			>15	1.36
n=2653			15+				≥5				
			1.24				1.15				

* = P≤ 0.05
¶ = Invasive breast cancer only

Table 4. "Short-term" ERT or CHRT and Breast Cancer Incidence

Study, Year	Duration ERT/HRT (y)	Status ERT/HRT	Subanalysis	RR
Yang '92	≤1			1.20
Weinstein '93	≤1	ever		1.22
Colditz '95	≤2	current	___	1.14
	≤2	past		0.90
Newcomb '95	≤2	ever		1.02
	≤5	recent		0.82
Stanford '95	1-3 months	ever		1.10
	3 month – 2.9 years	ever		1.00
Lipworth '95	≤11 months			1.75*
Persson '96	≤1	ever		0.80
Henrich '98	≤5	ever	Ever BCA	1.55
	≤5		Invasive BCA	1.87
Lando '99	≤3	ever		0.90
Gapstur '99	<5	Ever		1.07
Ross 2000	Per 5 years	ever		1.10

* = P ≤ 0.05

Table 5. Current Use of Estrogen or Estrogen/Progesterone Hormone Replacement Therapy and Breast Cancer Incidence

Study Quality	Hormone Formulation	Duration if described	Type of Breast Cancer if described	RR	95% CI
Colditz '95	HRT	≤ 2 years	___	1.14	0.91 - 1.45
Good	ERT	___	___	1.32	1.14 - 1.54
	CHRT	___	___	1.41	1.15 - 1.74
	Progesterone only	___	___	2.24	1.26 - 3.98
LaVechia '95	___	___	___	0.80	0.50 - 1.40
Poor					
Stanford '95	ERT	___	___	0.90	0.70 - 1.30
Good	CHRT	___	___	0.90	0.60 - 1.20
Sourander '98				0.57	0.27 - 1.70
Poor					
Heinrich '98	___	___	All BCA	1.52	0.77 - 2.99
Fair	___	___	Invasive BCA	1.87	0.85 - 4.12
Gapstur '99	___	≤ 5 years	Ductal carcinoma in situ	0.94	0.41 - 2.16
Good	___	≤ 5 years	Favorable Histology	4.42	2.00 - 9.76
	___	≤ 5 years	Invasive Ductal and/or Lobular	1.38	1.03 - 1.85
Schairer 2000	ERT	___	___	1.10	1.00 - 1.30
Good	CHRT	___	___	1.40	1.10 - 1.90

* = P ≤ 0.05

Table 6. Mortality-Cohort Summary Table: Studies 1992-2000

Study	HRT** Ever Use	Duration of Use Years	RR
Colditz '95	1.14 current	<5	0.99
		≥5	1.45*
Persson '96	0.5*	<5	0.2*
		10+	0.7*
Willis '96	0.84	≥1	0.85*
		2-5	0.78*
		6-10	0.78*
		11+	0.93
Ettinger '96		>5	1.89
Sellers '97	No family history	No family history	
	past ≤5 0.86*	past >5	0.76
	current ≤5 1.00	current >5	0.84
	Family history	Family history	
	past ≤5 0.71*	past >5	0.59
	current ≤5 0.24*	current >5	0.55
Schairer '99	Lymph node negative	Lymph node negative	
	past use ≤4 yrs. 0.8	current use:	
		≤4	0.6
	Lymph node positive	≥12	2.2
	past use ≤4yrs. 0.5*	lymph node positive	
		current use:	
		≤4	0.5*
		≥12	1.9

* = P ≤ 0.05
** = All mortality data based on HRT

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Newcomb '95 American Journal of Epidemiology	Population based Wisconsin N.H. Massachusetts Maine 4/89-12/91	All women with newly diagnosed BCA n=3130 98% histologically confirmed Post-menopausal Overall response 81% Interviewed within 8-21 months of diagnosis	Randomly chosen by drivers license lists and a list of Medicare beneficiaries (HCFA) n=3698 Response rate 84%	Phone interview. Type estrogen, dose not evaluated; recent use=within 2 years; HRT=>3 mos consecutive use estrogen +/- prog	Good adjustment	36% case exp HRT, 38% controls exp HRT, ever use HRT: 1.05(0.93-1.18), former use of HRT: 1.12(0.98 - 1.29)
Stanford '95 JAMA	Population based King County, Washington SEER women ages 50-64 all Caucasian 1/88- 6/30/90	All White women 50 - 64 diagnosed with histologically confirmed incident invasive or in situ breast cancer with phone n = 450 with invasive n = 87 in situ Not all post-menopausal 81.4% response rate	Residents of King County 50 -64 years identified through random digit dialing matched within 5 years of age Response rate 73%	Dates duration brand, dose estrogen or progesterone detailed in-person interview	Excellent evaluation/control of confounders	***ERT***: 0.9(0.6 - 1.1) ***Progestin alone***: 0.5(0.1 - 2.0) ***CHRT***: 0.9(0.7 - 1.3)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Newcomb '95 American Journal of Epidemiology	***Any HRT*:** < 2 yrs: 1.02(0.85-1.21) 2-4 yrs: 1.09(0.89-1.33) 5-9 yrs: 1.02(0.81-1.3) 10-14 yrs: 0.99(0.74-1.32) > 15 yrs: 1.11(0.87-1.43)	Among recent users of HRT (w/in 2 yrs), ≤ 5 yrs duration: 0.82(0.62-1.07) > 5 yrs duration: 0.97(0.79-1.2)		***ERT*:** 0.97 (0.84-1.21) ***ever use CHRT*:** 1.01 (0.7-1.31) ***former use ERT*:** 1.03 (0.87-1.21) ***former use CHRT*:** 1.25 (0.84-1.94)	15% also used progesterone Increasing time since last use not associated with elevated BCA risk Subgroup analyses for use < or > 10 years showed no interaction with age menopause, BBD, FMH, alcohol, BMI, type menopause. No clinically or statistically significant finding. When time since last use, women using HRT had more mammograms, more BBD Quality: good-excellent study
Stanford '95 JAMA	***ERT*:** *1-3 mos*: 1.1(0.5-2.4) *4 mos-2.9 yrs*: 1.0(0.6-1.6) *3-4.9 yrs*: 0.9(0.4-1.8) *5-7.9 yrs*: 1.2(0.7-2.2) *8-11.9 yrs*: 0.5(0.3-0.9) *12-14.9 yrs*: 0.5(0.3-0.9) *15-19.9 yrs*: 0.5(0.3-1.0) *> 20 yrs:* 1.0(0.5-2.0) ***CHRT*:** *1-3 mos:* 1.9(0.7-4.7) *4 mos-2.9 yrs*: 1.0(0.7-1.6) *3-4.9 yrs*: 0.6(0.3-1.3) *5-7.9 yrs*: 1.0(0.4-2.2) *> 8 yrs*: 0.4(0.2-1.0)	***ERT*:** *current:* 0.9(0.7 - 1.3) *< 5 yrs*: 0.6(0.3 - 1.3) *> 5 yrs*: 0.8(0.5 - 1.3) ***CHRT*:** *current:* 0.9(0.6 - 1.2) *< 5 yrs*: 1.4(0.7 - 2.7) *> 5 yrs*: 0.5(0.1 - 1.7)	***ERT*:** *< 5 yrs*: 1.2(0.7 - 2.1) *5-9 yrs*: 1.3(0.8 - 2.2) *10-14 yrs*: 0.9(0.5 - 1.5) *15-19 yrs*: 0.5(0.3 - 0.8) *> 19 yrs*: 0.3(0.1 - 0.9) ***CHRT*:** *<5 yr*: 1.0(0.7 - 1.4) *5 - 9 yr*: 1.2(0.6 - 2.2) *> 10 yr*: 0.3(0.1 - 0.9)	OR 19. (1.8–199.4) for increased risk associated with E + P among women with ovaries removed. No significant changes or risk associated with estrogen alone or E+ P by invasive vs. in situ disease	Only those who had not died participated. A higher proportion of HRT users had mammograms compared to non-users. Control of mammography exposure did not alter findings. 12.1% pre-menopausal Increased RR among thinner women (RR 1.8) though not stat sig and not adjusted for other factors - with both ERT and CHRT No interaction with alcohol Quality: good

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Grodstein '97 NEJM	Population based Nurses Health Study cohort 1976 - 6/1994	All women who died from this cohort and were post-menopausal and provided information about hormone therapy n = 3637 deaths	10 controls per case randomly chosen from women alive at the time of the case subjects' death or diagnosis leading to death post-menopausal and free of cancer and/or cardiovascular disease at baseline or before menopause matched by age (2y), age at menopause and 2 yr period of case pts death	Mailed questionnaire Hormone use ascertained 1976 and biennially through 1992	Alcohol Benign breast disease	
Ross 2000 JNCI	BCA patients population based Los Angles County 3/87 – 12/89	BCA cases identified by Cancer surveillance program and California cancer registry English speaking 3 groups 1) 3/87–12-89: white, ages 55-64 2) 1/92 – 12-92: white or AA ages 55-69 3) 9/95 – 4-96: white or AA ages 55-72 Reviews completed in 2653-3976 (1070 had died or too ill) 894 refused 66% participation	Individually matched by age, race, neighborhood N=2429 Participation 78%	Interviewed within 1 year of diagnosis demographics, physical characteristics, etc. detailed HRT/OCP pictures used. HRT = any hormones ERT = estrogen only CHRT = combination estrogen + progestin	Good control of risk factors	***Any HRT***: *Per 5 yrs*: 1.10 (1.02-1.18) ***ERT***: *Per 5 yrs*: 1.06 (0.97-1.15) ***CHRT***: *Per 5 yrs*: 1.24 (1.07-1.45)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Grodstein '97 NEJM				***Mortality*:** *current vs. never*: 0.76(0.56-1.02) *past vs. never* 0.83(0.63-1.09)	When HRT use evaluated among women with a 1st degree relative and BCA, MAOR all cause death **0.65(0.47 0.90)** in those with affected 1st degree relative and **0.60(0.54 - 0.68)** among those without Quality: good
Ross 2000 JNCI	***Any HRT***: *After 15 yrs*: 1.36 (NR) ***ERT***: *Risk only increased after 15 yrs*: 1.24 (NR) ***CHRT***: *After 5 years*: 1.15 (NR) *> 10 yrs*: 1.23 ***Sequential CHRT***: *>10 yrs*: 1.79 ***Continuous CHRT***: *>10 yrs*: 1.23			***For ERT***: almost all excess risk due to in situ OR **1.41(1.18-1.69)** (other types NS) ***HRT in situ***: OR 1.41(1.18-1.69) localized and advanced ***NS CHRT***: All BCA OR 1.24 (1.04-1.45) *Localized*: 1.26 (1.06-1.49) *Advanced*: 1.22 (0.95-1.51) Overall no increase with CHRT but with ***Sequential HRT***: OR (all BCA) 1.38 (1.13-1.68) OR *Localized*: 1.44 (1.16-1.78) OR	Explored data (but did not report) that increase risk associated with CHRT not only increased in current users but in those who had quit 2 years previously) *good discussion Women with hysterectomy without oopherectory before menopause excluded Majority used medroxy progesterone and most used sequentially Premarin 0.625 mg most common ERT Quality: fair

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Henrich '98 Journal of Clinical Epidemiology	All women who had screening mam through Yale 1 facility hospital based, the other mobile. N=14, 454 Non-population based 7/87- 3/92	Post-menopausal women ≥45 yrs with BCA (invasive or in situ) initially identified with mammography and with biopsy proven BCA n=109 ERT defined as use in women age >45 with 1 or both ovaries Non use = never or <6mos use or stopped age 45	5 controls per case matched by age (1 yr) screening site, prior mammogram and year of mammography, or the mobile unit, payment status n=654	Computerized data file non user = never use stopped before age 45 or use < 6 months	Benign breast disease Reproductive risk factors Alcohol	***All BCA*** : 26.6% cases exposed HRT, 19.6% of controls *HRT use* : 1.54(0.94-2.82) *estrogen alone* : 1.66(0.98-2.82) *estrogen + progesterone* : 1.02(0.32-3.21) ***Invasive BCA only (unadj)*** : 1.93(1.06-3.49) *current use* : 1.87(0.85-4.12) *past use* : 2.09(0.93-4.99) *conjugated* : 1.91(0.89-4.11) *non-conjugated* : 2.49(1.04-5.93) *ERT* : 2.22(1.18-4.17) *estrogen + progesterone* : 0.96(0.20-4.57)
Weinstein '93 Int Jnl of Epid	N.Y. State 1/84-12/86	Residents of 2 Long Island counties aged 20-79 diagnosed with breast cancer n = 1436 though only post-menopausal women used n = 837 response rate 66%	Age and county matched by drivers license files n = 1419 Initially n = 860 postmenopausal response rate 41%	Telephone interview using structured questionnaire. Interviewers not blind	Good	***Ever use unadjusted*** *all ages* : 1.09 (0.86-1.38) *age 50-70* : 1.12 (0.86-1.46) *adjusted ever/never* : 1.14 (0.84-1.40)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Henrich '98 Journal of Clinical Epidemiology	***Any BCA*** : *<5 yr*: 1.55(0.79-3.04) *>5 yr*:1.61(0.83-3.13) *>11 yr*: 1.45(0.51-4.11) ***Invasive BCA*** : <*5 yr*: 1.87(0.87-4.03) *>5yr*: 2.27(0.98-5.29)	***All BCA*** : *Current*:1.52(0.77–2.99) ***Invasive BCA*** : *Current*:1.87(0.85–4.12)	***All BCA*** : *Past*: 1.50(0.78-2.88) ***Invasive BCA*** : *Past*: 2.09(0.93-4.66)	***All BCA:*** *Conjugated ERT*: 1.49(0.8-2.76) *Non-Conjugated*: 1.86(0.89-3.91) *Invasive Conjugated*: 1.91 (0.89-4.11) *Non-Conjugated*: 2.49 (1.04 – 5.93)	Age menopause not known Computer files-no info reproduction Screening mam –population all had localized dis. No interaction with family history Quality: fair
Weinstein '93 Int Jnl of Epid	*≤ 1 yr*: 1.22 (0.87-1.43) *1-5yrs*: 1.12 (0.71 – 1.75) *>5 yrs*: 0.88 (0.53 – 1.44)			Increased OR in thinner (1.88*) but not adjusted for other factors	Small number reported progesterone use, 25-37% uncertain Low proportion contacted controls participated Quality: fair

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Yang '92 Cancer Causes Control	British Columbia population based 6/88 - 6/89	699 women, <75 with BCA post-menopausal identified through cancer registry response 68.3	Drawn from voters list matched in 5 year categories n=685 response 68.2	Postal questionnaire, type, duration	Alcohol Good adjustment	Adjusted only for age and type menopause: *ERT*: 1.1 (0.8-1.4) *Any Prog*: 1.2(0.6-2.2)
Brinton '98 Menopause	Population based Atlanta 5/1/90-2/31/92	All women in Atlanta < 55 with newly diagnosed in situ or invasive BCA n=1031 89.5% participation Not all menopausal	Frequency-matched by region n=919 79% participation	Record review and personal interviews. Ever/never dates, duration dosage	Benign breast disease Alcohol Family history BCA	24% cases used HRT, 27% controls exp. HRT, Ever HRT 0.9(0.7-1.2)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Yang '92 Cancer Causes Control	***ERT***: *<1*: 1.2 (0.7-1.7) *1-4*: 0.8 (0.5-1.1) *5-9*: 1.0 (0.6-1.5) *10+*: 1.6 (1.1-2.5)	***ERT***: *<1*: 1.4 (1.0-2.) *1-4*: 1.3 (0.8-2.2) *5-9*: 0.7 (0.4-1.2) *>10*: 1.0 (0.7-1.4)			Women who first used HRT within 12 months prior to reference date considered non-users, decreased chance of association. Quality: fair (poor participation), misclassification of HRT use
Brinton '98 Menopause	*≤ 3yrs*: 0.86(0.6-1.2) *3-5*: 1.0(0.7-1.6) *6+*: 0.85(0.5-1.4)	*≤ 1 yr*: 0.91(0.7-1.2) *+1 yr*: 0.82(0.5-1.2)	*<3 yrs*: 0.91(0.7-1.3) *3 -5*: 0.9(0.6-1.3) *6+*: 0.86(0.6-1.2)	***CHRT***: 0.99(0.7-1.3) ***ERT***: 0.7(0.5-0.9)	Includes in situ and invasive Authors state that control of related factors did not change OR HRT use significantly more common in women with frequent mammograms, history of breast disease Relatively low exposure given young age Significantly increased risk among users of OCP's >10 years and >3 years HRT use Not just menopausal, if menopausal, young with decreased risk of BCA Quality: fair

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Tavani '97 Cancer Epidemiology, Biomarkers and Prevention	Hospital-based Milan, 6 other Italian regions 1/83-5/91 6/91-2/94	All women with incident BCA admitted to major teaching hospital n=5984 ages 22-74 histologically confirmed median age 54 >90% response	n=5504 ages 15-74 from same geographic regions admitted to major teaching hospital 27% orthopedic and fractures 32% non-traumatic orthopedics excluded: if admitted for gynecologic, hormonal, or neoplastic. Unmatched >90% response	In-hospital interview Ever/never use of hormones	Alcohol	Ever use HRT in cases = 6.1%, ever use HRT controls = 5.5%, or ever/never use = 1.2(1.0-1.4)
La Vechia '95 British Journal of Cancer	Hospital-based 6 Italian regions 1991-1994	All women with incident BCA (within 1 year) admitted to major teaching hospital n=2569 ages 23-74 histologically confirmed	n=2588 ages 20-74 from same geographical region admitted for trauma, orthopedic, acute surgery, eye conditions	In-hospital interview Ever/never use of hormones	Alcohol	7.5% cases exposed, 7.5% control expose, ever/never 1.2(0.9 - 1.5)
Fioretti '99 British Journal of Cancer	Hospital-based Milan, 6 other Italian regions	665 cases post-menopausal incident BCA (within 1 year) from 1041 nulliparous women ages 22-80 all admitted to hospital histologically confirmed	582 controls post-menopausal from same geographic region admitted to hospital nuliparous ages 15-80 admitted for variety of conditions	In-hospital interview Ever/never	Alcohol	9% cases exp. HRT 7.9% controls esp. HRT, ever/never 1.22 (0.8 – 1.84)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Tavani '97 Cancer Epidemiology, Biomarkers and Prevention	***Age < 55 yrs***: *<5 yrs*: 0.9(0.6-1.2) >5 yrs: 1.2 (0.5-3.1) ***Ages 55-64 yrs***: *<5 yrs*: 1.3 (1.0 – 1.7) *> 5 yrs*: 0.9 (0.5 – 1.7) ***Ages >65 yrs***: *<5yrs*: 1.6 (1.1 – 2.3) >5 yrs: 2.2(1.0 – 4.7)	*≤ 15 yrs*: 1.4 *≥ 15 yrs*: 1.0	*<15 yrs*: 1.2 (1.1 - 1.5) *>15 yrs*: 1.2 (0.9 - 1.6) ***women age > 65***: *<15 yrs*: 2.1 (0.9 - 4.7) *≥ 15 yrs*: 2.0(1.2 - 3.2)	***By age***: *<55*: 0.8 (0.6-1.1) *55-64*: 1.2 (0.9-1.5) *≥ 65*: 1.6 (1.2-2.3) ***Among those 65 - 74 ever use***: 1.6(1.1-2.3) *<60 mos*: 1.6(1.1-2.3) *>60 mos*: 2.2(1.0-4.7)	***Low prevalence HRT use (10%)*** ***Among women > 65 years*** 1. *Time since stopping HRT*: *<10 yrs*: 1.4 (0.4 - 4.7) *>10 yrs:* 1.7 (1.2 - 2.4) 2. *Time since starting HRT:* *<15 years*: 2.1 (0.9 - 4.7) *>15 years*: 1.5 (1.1 - 2.2) Quality: poor, bias in control selection, broad age range
La Vechia '95 British Journal of Cancer	*<1 year:* 1.0(0.8 - 1.4) *1-4*: 1.3(0.9 - 1.9) *> 5*: 1.5(0.8 - 2.6)	*Current*: 0.8(0.5-1.4) *10 yrs*: 2.0(1.3-2.9) *≥ 10 yrs*: 1.0	*<10 yrs*: 1.2(0.9 - 1.8) *10-14 yrs*: 1.3(0.8 - 2.2) *≥ 15 yrs*: 1.1(0.8 - 1.5)	***Conjugated estrogen***: 1.3(0.8-1.6) ***CHRT***: 1.6 (0.4 - 6.3) ***other estrogens***: 0.9 (0.7-1.4)	Point estimate for CHRT 1.6 (not stat sig)No increased risk among current users Trend towards increased risk with increased duration among those recently stopping HRT Quality: poor, ?bias in control election, broad age range
Fioretti '99 British Journal of Cancer	>2 yrs use: 1.28(0.66 – 2.45), no duration effect noted.				No separation estrogen and progesterone No differentiation invasive vs insitu Important confounders not adjusted for Only evaluated HRT in nulliparous women Quality: poor ?bias in control selection

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Lipworth '95 Int. J. Cancer	Hospital-based 1/83-5/91 6/91-2/94	All women with newly diagnosed BCA residents of Athens from 4 major hospitals n=820 (173 histololgically confirmed)	2 controls for each case, 1 derived from hospital visitors (n=795) and 1 from orthopedic patients (n=753), matched +/- 5 yrs.	In hospital interview by trained interviewer	Benign breast disease Family history	ever use estrogen 9.7% cases 8.5% controls ever use 1.52(1.24 – 2.25)
Persson '97 Inter. Journal of Cancer	Population-based of Swedish women attending mammography screening Upsala 2/90-7/92	435 with incident BCA (75% detected by mammography) 379 invasive 56 in situ	Derived from same population frequency matched by 5 year age intervals n=1740	Nurse interview. Estrogen use evaluated as ever/never, type, duration, age started, use of progesterone	Benign breast disease Alcohol	21.4% cases ever use HRT, 19.8% controls ever use HRT, ever use HRT 1.1(0.8 - 1.4)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Lipworth '95 Int. J. Cancer	***ERT***: *<11mos*: 1.75(1.02-3.01) *2-35 mos*: 1.26(0.63-2.52) *>36 mos*: 1.42(0.62-3.27)				Progesterone use not evaluated; orthopedic controls may have had less use estrogen resulting in false positive association CHRT rarely used in Greece; unclear how many were post-menopausal Quality: fair-poor
Persson '97 Inter. Journal of Cancer	***All types HRT*:** *1-2 yrs*: 0.9(0.6-1.3) *3-5 yrs*: 1.0(0.6-1.8) *6-10 yrs*: 0.9(0.5-1.6) *11+ yrs*: 2.1(1.1-4.0)			***Ever use by type***: *Estradiol-Conjugated E*: 0.5(0.3-1.0) *CHRT*: 1.4(0.9-2.1) *Weak Estrogens*: 1.0(0.6-1.2)	Suggestion of increased risk with CHRT (above ERT) OR 1-10 years: 1.4 (0.9 - 2.2); OR > 10 years: 2.4 (0.7 - 8.6). When analyses restricted to only those diagnosed by mammography OR HRT 10 years=2.0(1.0 - 4.0) Not confined to post-menopausal Quality: poor

Evidence Table 1. Case-control studies

Study, Year, Journal	Setting/ Population/ Dates	Cases	Controls	Exposure Assessment and Classification	Important Confounders not Adjusted for	Major findings- or multivariable, adjusted or (MAOR)
Magnuson '99 International Journal of Cancer	Population based Sweden 10/93- 3/1/1995	Incident cases BCA n=2563 (of which 45 in situ) post-menopausal 84% participation	Randomly selected frequency matched population registry n=2845 post-menopausal 82% participation	Written questionnaire, dates, brand, dose, type, estrogen and progesterone, evaluated by estrogen potency.	Benign breast disease Family history Alcohol	48.3% cases used HRT ever; 40.3% controls used HRTever; ***HRT*** 1.65(1.43 – 1.89) ***ERT*** 1.94(1.47 – 2.55) ***CHRT*** 1.63(1.37 –1.94)
Levi '96 European Journal of Cancer Prevention	Vaud Switzerland Hospitalbased 1/90-8/95	230 cases incident BCA histologically confirmed admitted to university hospital ages 23-70 Response rate NR	507 women admitted for wide spectrum acute conditions ages 24-75 excluded women who had been admitted for breast, gynecological, hormonal, metabolic neoplasia. Response rate NR	In-hospital interview Ever/never use HRT => 6 months use. Type estrogen not reported.	Alcohol benign breast disease	27.8% cases exposed, 22.3% controls exposed, OR ever/never 1.2 (0.86 - 1.8)

Evidence Table 1. Case-control studies

Study, Year, Journal	Major findings by duration use HRT (MAOR)	Time since last use of HRT (MAOR)	Time since starting HRT	Findings by other sub-group analyses (MAOR)	Comments
Magnuson '99 International Journal of Cancer	***HRT***: *1-24 mos*: 1.29(1.05-1.59) *25-60 mos*: 1.40(1.07-1.82) *61-120 mos*: 2.32(1.74-3.09) *>120 mos*: 2.43(1.79-3.36) ***ERT***: *1-24 mos*: 1.72(1.13-2.62) *25-60 mos*: 1.49(0.85-2.63) *61-120 mos*: 2.18 1.07-4.45) *>120 mos*: 2.70(1.47-4.96) ***CHRT***: *1-24 mos*: 1.25(0.96-1.63) *25-60 mos*: 1.40(1.01-1.94) *61-120 mos*: 2.43(1.72-3.44) *>120 mos*: 2.95(1.84-4.72)	*Within 1 yr*: 1.99(1.67-2.38) *1-10 yrs*: 1.13(0.84-1.52) *>10 yrs*: 1.4(1.05-1.87)			No sig. elevated risk with low potency estrogens (treated as never users) – bias/misclassification Suggestion that testosterone derived progesterone elevated increased risk (vs. non-testosterone PG) Suggestion that continuous testosterone PG worse than cyclic Subgroup analyses (many) Greater risk among < BMI shown in other data U-shaped association with recency; formulations not specified. Findings not adjusted for family history, benign breast disease, alcohol Quality: poor
Levi '96 European Journal of Cancer Prevention	≤ *10 yrs*: 1.3(0.9-2.0) ≥ *10 yrs*: 1.0 (0.4-2.4)	*Current*: 1.5(0.9-2.5) *<10 yrs*: 1.4(0.8-2.7) *>10 yrs*: 0.8(0.4-1.8)	*<10 yrs*: 1.7(1.1-2.9) *>10 yrs*: 0.9(0.5-1.6)		?Bias in eliminating HRT use in controls No evaluation for ERT versus CHRT Risk essentially confined to current users No duration effect OR increased among those >65 years suggesting interaction. Not all post-menopausal Quality: poor, hospital-based, small,? bias in control selection

Evidence Table 2. Cohort studies

Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Sourander 1998	Prospective Study of women born between 1923-1930 living in Turku, Finland, 68-75 yrs at study beginning, and participating in free mammography screening in 1987-1980, n = 6433	Validated, nurse-administered questionnaire, estrogen use characterized as never, former & current use and confirmed by nurses**formulation not specified*	Finnish Cancer Registry, death certificates, national registry of hospital discharge data	8 yrs (53,305 person-years) 1947 lost to f/u	Benign breast disease, alcohol use, prior breast cancer, reproductive risk factors	*Never*: 1.0 *Current*: 0.57 (0.27-1.20) *Former*: 0.94 (0.47-1.9)
Colditz 1995	U.S. Nurses Health Study, 121,700 women ages 30-55, n = 69,586 postmenopausal	mailed questionnaire with biennial follow-up	National Death Index, pathology reports in 93%	6/1/92 725,550 person-yrs		*By formulation*: *Conjugated Estrogen*: **1.36(1.14-1.54**) *Other Estrogen*: 1.28(0.97-1.71) *Estrogen + Progesterone*: **1.41(1.15-1.74**) *Progesterone alone*: **2.24(1.26-3.98)** *Estrogen + Testosterone*: 1.64(0.53-5.09)

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Sourander 1998					Progesterone use not evaluated, duration of use not evaluated Quality: fair-poor
Colditz 1995		*<2 yrs*: 1.14 (0.91-1.45) *2-4 yrs*: 1.20 (0.99-1.44) *5-9 yrs*: 0.8 (0.6-1.0) *10 or more yrs*: **1.46 (1.20-1.76)** ***Ages at use < 5 yrs:*** *50-54*: 1.46 (0.98-2.17) *55-59*: **1.37 (1.07-1.76)** *60-64*: 1.13 (0.79-1.63) ***Age at use 5+ yrs:*** *50-54*: 1.46 (0.91-2.33) *55-59*: **1.54 (1.19-2.0)** *60-64*: **1.7 (1.34-2.18)**	*<2 yrs*: 0.90 (0.77-1.05) *2-4 yrs*: 0.86 (0.71-1.05) *5-9 yrs*: 1.00 (0.80-1.26) *10 or more yrs*: 1.03 (0.76-1.41)	***Current Users:*** RR death adjusted for FMH & BBD 1.14(0.85-1.51) ***Ever Users:*** *< 5 yrs*: 0.99(0.66-1.48) *5+ yrs*: **1.45(1.01-2.09)** ***Past Users:*** RR = 0.80(0.6-1.07)	18% women taking progestin-almost all cyclic, dose evaluated 1990 Quality: good

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Persson 1996	Prospective cohort study in Uppsala health care region, Sweden, study population consisting of all women who had ever received HRT between 1977-1980, mean age 54.5 at entry, n = 22,579	Pharmacy records Estrogen categorized by type: 1. estradiol only or conjugated estrogens 2. fixed estrogen/ progestin dose 3. other estrogens Mailed questionnaire sent to random subset (n = 795)	record linkage to Swedish Cancer and Death Registries	mean =13.2 yrs (297,977 person-years)	Benign breast disease, prior history breast cancer, family history breast cancer, reproductive risk factors	624 incident breast cancers, 102 deaths *SIR*: 1.0 (0.9-1.1)
Sellers 1997	Prospective cohort -- Iowa Women's Health Study, random sample of all post-menopausal women between age 55-69 yrs who had valid drivers license in 1986, n = 35,919	Mailed questionnaire	State Health registry (SEER)	8 yrs (275,000+ person-years)	benign breast disease	

Evidence Table 2. Cohort studies

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Persson 1996	***SIR*** *≤ 1 yr* : 0.8 (0.5-1.0) *1-4 yrs* : 1.1 (0.9-1.3) *5-9 yrs* : 0.9 (0.8-1.0) *10+ yrs* : 1.0 (0.9-1.2)			*SMR* : **0.5(0.4-0.6)** ***By duration use*** *<5 yrs* : **0.2(0.1-0.3)** *5-9 yrs* : **0.7(0.5-0.9)** *10+ yrs* : **0.7(0.5-0.9**)	use of estrogen/ levonorgestrel compound associated with overall risk **1.3 (1.1-1.4)**, *SMR* : **0.6(0.4-0.9)** Quality: poor
Sellers 1997	***Overall*** **:** *5 yrs or less* : 1.04 *≥ 5 yrs* : 0.89	***Overall*** **:** *5 yrs or less* : 1.34(0.98-1.8) *≥ 5 yrs* : 1.17(0.9-1.51) ***No family hx BCA*** **:** *5 yrs or less* : 1.31(0.94-1.83) *≥ 5 yrs* : 1.13(0.86-1.50) ***Family hx BCA*** *:* *5 yrs or less* : 1.37 (0.59-3.18) *≥ 5 yrs* : 1.35 (0.72-2.53)	***No family hx BCA*** : *5 yrs or less* : 1.01 (0.85-1.20) *≥ 5 yrs* : 0.80 (0.53-1.19) ***Family hx BCA*** *:* *5 yrs or less* : 1.19 (0.81-1.73) *≥ 5 yrs* : 1.17(0.55-2.47)	***No family hx BCA*** : *Past vs never (duration 5 yrs or less)* : **0.86 (0.76-0.97)** *Past vs never (duration ≥ 5 yrs)* : 0.76 (0.57-1.00) *Current vs never(duration 5 yrs or less)* : 1.00 (0.75-1.35) *Current vs never (duration ≥ 5 yrs)* : 0.84 (0.67-1.06) ***Family hx BCA*** : *Past vs never (duration 5 yrs or less)* : **0.71(0.51-0.98)** *Past vs never (duration ≥ 5 yrs)* : 0.59(0.90-1.16) *Current vs never (duration 5 yrs or less)* : **0.24(0.06-0.97)** *Current vs never (duration ≥ 5 yrs)* : 0.55(0.28-1.07)	Evaluated association with HRT in those with family history breast cancer. No significant increased risk, e.g., no interaction with family history Quality: good

Evidence Table 2. Cohort studies

Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Gapstur 1995	Post menopausal women 55-69 yrs at baseline (in 1986), n = 37,105 Prospective cohort -- Iowa Women's Health Study, to study relationship between HRT use and BRC	Never/ ever **formulation not specified*	Incident BRC: State Health registry ER/ PR Status: from medical records, when available	7 yrs, 2.5% lost due to immigration	Age at menopause, exercise, SES, smoking, hx benign breast disease, parity/ nulliparity, education, other medical conditions	***Among EtOH non-users*** ***ER+/ PR+*** *Never use* : 126 *Ever use* : 81 ***ER+/ PR-*** *Never use* : 33 *Ever use* : 14 ***ER-/ PR-*** *Never use* : 27 *Ever use* : 10 ***ER/ PR status unknown*** *Never use* : 117 *Ever use* : 56

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Gapstur 1995				Not reported	Increased risk of ER+/ PR+ (p= 0.03) and ER-/ PR- (p= 0.04) tumors with increased alcohol intake, trend not as clear for ER+/ PR- (p= 0.19) ***Quality:??***

Evidence Table 2. Cohort studies

Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Gapstur 1999 JAMA	Prospective cohort -- Iowa Women's Health Study, population based, post-menopausal women 55-69 yrs at baseline (in 1986) randomly selected from 1985 Iowa Department of Motor Vehicles registry n = 37,105	Self-reported mailed questionnaire	Follow-up questionnaires, SEER network '87, '89, '92 and '97, National Death Index	11 yrs (371,477 py) 1520 incident breast cancers	benign breast disease	***Ever use (all types BCA)*** **:** *<5 yrs* : 1.07(0.94-1.22) *≥ 5 yrs* : 1.11(0.92-1.35)
Risch 1994 American Journal of Epide-miology	Saskatchewan women ages 43-49 in 1976, n = 32,790	Prescription database -- all prescriptions for estrogen and progestins between 1976 and 6/97	Hospital reports and death certificates, Saskatchewan cancer registry	Vital status followed until 12/31/90		***Estrogen alone*** : **1.33(1.11-1.59)** ***Progestin only*** : 0.93(0.51-1.68)

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Gapstur 1999 JAMA	***DCIS*** *(age-adjusted)*: *≤ 5 yrs or less vs never*:1.08(0.77-1.52) *≥ 5 yrs vs never*: 1.10 (0.68-1.77) ***Favorable histology*** *(age-adjusted)*: *≤ 5 yrs vs never*: **1.67(1.02-2.71)** *> 5 yrs*: **2.22(1.22-4.02)** ***Invasive ductal and/ or lobular (age adjusted)***: *≤ 5 yrs*: 1.05 (0.92-1.20) *≥ 5 yrs*: 1.07 (0.88-1.28) ***Multivariate adjusted RR invasive breast cancer with favorable histology*:** *≤ 5 yrs*:**1.81 (1.07-3.07)** *≥ 5 yrs*: **2.65 (1.34-5.23)**	***DCIS***: ≤5 yrs: 0.94(0.41-2.16) ≥ 5 yrs: 1.35(0.77-2.36) ***Favorable histology***: *≤ 5 yrs*: **4.42(2.0-9.76)** *≥ 5 yrs*: **2.63(1.18-5.89**) ***Invasive ductal and/ or lobular***: *≤ 5 yrs*: **1.38(1.03-1.85)** *≥ 5 yrs*: 1.16(0.9-1.45)	***DCIS*** *≤ 5 yrs vs never*: 0.91(0.61-1.34) *≥ 5 yrs vs never*: 0.29(0.07-1.18) ***Favorable histology*** *≤ 5 yrs*: 1.44(0.8-2.58) *≥ 5 yrs*: **2.68(1.08-6.69)** ***Invasive ductaland/ or lobular*** *≤ 5 yrs*: 1.01(0.87-1.18) *≥ 5 yrs*: 0.92(0.66-1.28)	Not reported	Formulation not specified, progesterone use not evaluated, women using HRT had signivicantly greater use of mammography but adjustment did not change risk estimates. Quality = good
Risch 1994 American Journal of Epide-miology	***Estrogen only***: *6 mos or less*: 1.039(0.78-1.38) *6-18 mos*: 1.161(0.83-1.63) *18-36 mos*: 1.041(0.66-1.63) *36 mos or more*: **1.498(1.06-2.13)** ***Estrogen + Progestins*** *12 mos*: 1.196(0.71-2.01)				? latency times Quality: poor

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Schairer 1994 Cancer Causes and Control	Prospective cohort -- postmenopausal women who were participants in the US breast cancer screening program (BCDDP), 1973-1980, mean age 57.4 yrs at start of f/u, n = 42,020	Baseline telephone interview and up to 6, usually 4, annual telephone interivews, mailed questionnaire 1987-1989 Non-users users (estrogens alone -- also includes ES w/ PG uncertain or unascertained) estrogen plus progestins current Duration Never/ ever for progestin use	self-report, death certificates, path reports (avail on 92% of identified BRC)	mean f/u = 6.4 yrs, 86% of non-cases and 85% of cases completed f/u, 313,902 person yrs	Age at menarche, BMI, age at 1st birth, exercise, SES, smoking, hx benign breast disease, family hx BRC, parity/ nulliparity, other medical conditions	***All Cases*** *Ever use estrogen only*: 1.0(0.9-1.2) *Ever use estrogen + progestins*: 1.2(1.0-1.6) ***Invasive*** *Ever use estrogen only*: 1.0(0.9-1.1) *Ever use estrogen + progestins*: 1.1(0.9-1.4) ***In Situ*** *Ever use estrogen only*: 1.0(0.9-1.1) *Ever use estrogen + progestins*: 1.0(0.9-1.4)

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Schairer 1994 Cancer Causes and Control	***Estrogen Only*** **All Cases** *≤ 5 yrs*: 1.0(0.9-1.2) *5-9 yrs*: 1.0 (0.8-1.2) *10-14 yrs*: 1.0(0.8-1.3) *15-19 yrs*: 1.2(0.9-1.6) *20 + yrs*: 1.2(0.8-1.6) **In situ cases** *≤ 5 yrs*: 1.1(0.7-1.7) *5-9 yrs*:1.5(0.8-2.6) *10-14 yrs*: **2.1(1.2-3.7)** *15-19 yrs*: 1.8(0.9-3.9) *20 + yrs*: 2.0(0.9-4.5) **Invasive cases** *≤ 5 yrs*: 1.0(0.9-1.2) *5-9 yrs*: 1.0(0.8-1.2) *10-14 yrs*: 0.9(0.6-1.1) *15-19 yrs*: 1.1(0.8-1.5) *20 + yrs*: 1.1(0.8-1.5) ***Estrogen + Progestin*** **All Cases** *<2 yrs*: 1.5(1.1-2.1) *2-3 yrs*: 1.0(0.6-1.8) *4+ yrs*: 1.4(0.9-2.2) **In situ cases** *<2 yrs*: 3.3(1.7-6.3) *2-3 yrs*: 3.9(1.5-9.7) *4+ yrs*: 0.7(0.1-4.7) **Invasive cases** *<2 yrs*: 1.3(0.9-1.9)	***Estrogen Only*** **All cases**: **1.3(1.1-1.5)** *≤ 5 yrs*: **1.4(1.1-1.8)** *5-9 yrs*: 1.2(0.9-1.7) *10-14 yrs*: 1.2(0.8-1.6) *15+ yrs*: **1.4(1.1-1.8)** **In Situ**: **1.8(1.1-2.7)** *≤ 5 yrs*: 1.4(0.6-3.1) *5-9 yrs*: 1.3(0.5-3.2) *10-14 yrs*: **2.3(1.1-4.8)** *15+ yrs*: **2.4(1.2-4.9)** **Invasive**: 1.2(1.0-1.5) *≤ 5 yrs*: **1.4(1.1-1.9)** *5-9 yrs*: 1.2(0.9-1.7) *10-14 yrs*: 1.0(0.7-1.5) *15+ yrs*: 1.3(1.0-1.7) ***Estrogen + Progestin*** **All cases:** 1.2(0.9-1.6) **In Situ: 2.4(1.2-4.7)** **Invasive:** 1.0(0.7-1.4)	***Estrogen Only*** ***All cases***: 0.9(0.8-1.1) *≤ 5 yrs*: 1.0(0.8-1.2) *5-9 yrs*: 0.9(0.7-1.2) *10-14 yrs*: 0.9(0.6-1.2) *15+ yrs*: 0.9(0.6-1.4) ***In Situ***: 1.3(0.9-1.9) *≤ 5 yrs*: 1.0(0.6-1.6) *5-9 yrs*: 1.5(0.8-3.0) *10-14 yrs*: **2.3(1.1-4.7)** *15+ yrs*: 1.8(0.7-4.4) ***Invasive***: 0.9(0.8-1.1) *≤ 5 yrs*: 1.0(0.8-1.2) *5-9 yrs*: 0.8(0.6-1.1) *10-14 yrs*: 0.7(0.5-1.1) *15+ yrs*: 0.8(0.5-1.3) ***Estrogen + Progestin*** **All cases**: 1.4(1.0-2.0) **In Situ**: 2.3(1.0-5.4) **Invasive**: 1.3(0.9-1.9)		Small sample size for ES/ PG analysis, small # in situ cases, dose not evaluated, formulation not specified Quality: fair

Evidence Table 2. Cohort studies

Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Willis 1996 Cancer Causes and Control	Cancer Prevention Study, U.S., n = 676,526, enrolled 1982	self-administered questionnaire	personal inquiries 1984, '86, '88, National Death Index/ Death Certificate	Dec. 31, 1991		not assessed
Schuurman 1995 Cancer Causes and Control	Prospective study of 62,573 women ages 55-69 in the Netherlands beginning Sept. 1986	mailed self-administered questionnaire	computerized record linkage with Dutch national database pathology reports	3.3 yrs	family history of breast cancer, benign breast disease	**Ever use**: 0.99 (0.68-1.43)

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Willis 1996 Cancer Causes and Control				Ever vs never: **0.84 (0.75-0.94)** Current vs never: 0.90 (0.75-1.09) Past vs never: **0.78 (0.68-0.89)** **Duration** (vs never): 1 yr or less: 0.85 (0.71-1.02) 2-5 yrs: **0.78 (0.65-0.93)** 6-10 yrs: **0.78 (0.62-0.98)** 11+ yrs: 0.93 (0.75-1.15) **Age at first use** ≤40: **0.66 (0.51-0.85)** 40-49: **0.84 (0.73-0.97)** 50+: 0.89 (0.76-1.05)	Women who take HRT more likely to have BBD, early menopause, surgical menopause, women who died of BRC tended to report later ages at 1st use than other estrogen users (p= 0.07), no discernible trend w/ duration of use, ever use w/ menarche at 14 yrs or later had decreased fatal BRC risk. Quality: good-fair
Schuurman 1995 Cancer Causes and Control	never: 1.0 1 yr or less: 0.8 (0.5-1.5) 2-4 yrs: 1.4 (0.7-2.7) 5+ yrs: 0.9 (0.4-2.1)			not reported	No association shown with time since last use, time since first use or age at first use, in situ cases excluded. Quality: good-fair Induced menopause: RR 1.72 (0.95-3.12) Non-induced 0.81 (0.54-1.21) Wt<70 kg RR ever 1.46 (0.99-2.16) Wt>70 RR 0.66

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Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Schairer 2/1999 Journal of the National Cancer Institute	Participants in BCDDP diagnosed with BCA 1973-1980 and postmenopausal n= 2675	Mailed questionnaire determining vital status through 6/95, n = 2675, original exposures evaluated by annual questionnaire, in home interview and phone interview	Standard pathology reports, death certificates obtained for 92%	average 14.1 yrs		
Folsom 1995 American Journal of Public Health	Iowa 41,837 ages 55-69	Questionnaire, risk factors anthropometric measures, HRT -- ever use and duration, not formulation	Cancer registry	Not given	Not adjusted for benign breast disease or family history	***HRT*** (formulation not known) *Former use* : 0.96(0.81-1.14) *Current use* : 1.24(0.99-1.56)

Evidence Table 2. Cohort studies

Author Date	Breast Cancer Relative Risk by Duration (yrs) Multivariate Adjusted Relative Risk	Relative Risk Breast Cancer associated with current use and duration (yrs)	Relative Risk Breast Cancer associated with past use and duration (yrs)	Breast Cancer Mortality Multivariate Adjusted Relative Risk	Comments/ Quality of Study
Schairer 2/1999 Journal of the National Cancer Institute				***Lymph node negative*** **Current users** *48 mos or less*: 0.6(0.3-1.2) *49-96 mos*: 0.4(0.2-0.8) *97-144 mos*: 0.6 (0.2-1.5) *>145 mos*: 2.2 (0.9-5.2) **Past non users** *48 mos or less*: 0.8 (0.4-1.4) *49-96 mos*: 0.7 (0.4-1.2) *97-144 mos*: 1.2 (0.6-2.5) *>145 mos*: 1.8 (0.8-4.3) ***Lymph node positive*** **Current users** *48 mos or less*: **0.5 (0.3-0.8)** *49-96 mos*: 1.2 (0.6-2.2) *97-144 mos*: 0.8 (0.3-1.7) ≥ *145 mos*: 1.9 (0.6-5.7) **Past non-users** *48 mos or less*: 0.5 (0.3-0.9) *49-96 mos*: 1.6 (0.9-2.8) *97-144 mos*: 1.2 (0.6-2.4) *>145 mos*: 4.4 (1.7-11.8)	See paper for comulative probabilities of death Quality: fair Quality: good
Folsom 1995 American Journal of Public Health		≤5 yrs: **1.45 (1.03-2.06)** > 5 yrs: 1.21 (0.92-1.60)			

Evidence Table 2. Cohort studies

Author Date	Setting/ Study Population	Measurement of Hormone Exposure, Comorbidity, Other Risk Factors	Method of documenting Breast Cancer	F/u length and loss to f/u	Important Exposures/ Risk Factors Not Adusted for:	Breast Cancer Incidence Multivariate Adjusted Relative Risk
Schairer 2000 JAMA	BCDDP participants		2082 BCA 82% had path reports review, of the 82% , 255 in situ, 1456 invasive	10.2 yrs 473,687 person-yrs		**Ever use:** Estrogen Only: 1.1 (1.0-1.3) Estrogen + Progestin: 1.3 (1.0-1.6) Estrogen alone + Prog/Est: 1.2 (1.0-1.5) Progestin only 0.9 (0.5-1.6) Estrogen (progestin unknown) 1.3 (1.0-1.5)
Schairer 1994	Prospective study of health care region study population consisting of all women who had received HRT 1977-80 age n=23.246	Pharmacy records Estrogen categorized: 1. Estrdial or conjuaged estrogen. 2. Combined E/P 3. Other estrogen	Linkage to national causes of death registry	3/77 - 12/86 n=1472 deaths 199,811 person-year	BBD, FMLT, alcohol repreductive risk factors	

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Schairer 2000 JAMA	***Time since last use*:** **Estrogen Only** *current*: 1.1(1.0-1.3) *1-2 yrs*: **1.4(1.1-1.8)** ≥ *2-4 yrs*: 1.2(0.9-1.6) ≥ *4-6 yrs*: 0.9(0.6-1.3) ≥ *6 yrs*: 1.1(0.9-1.2) **Estrogen + Progestin** *current*: **1.4(1.1-1.9)** *1-2 yrs*: 1.2(0.6-2.4) ≥ *2-4 yrs*: 1.2 (0.5-2.5) ≥ *4-6 yrs*: 0.6(0.2-2.6) ≥ *6 yrs*: 0.6(0.3-1.6)				**Subcategory analysis** women with BMI 24.4 or higher had increased risk with Estrogen only (RR **1.6 (1.2-2.2))** at 4 or more years duration, and Estrogen + Progestin at 4 or more yrs RR **2.0 (1.3-3.0)** Quality: fair
Schairer 1994				RR death (SMR) 0.72 (0.58-0.89)	56% estradiol compounds 22% conjugated 22% other comparison group external Quality: fair

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Ettinger 1996 Obstetrics & Gyne-cology	Kaiser SF 1969-73 women who had used HRT ≥5 years and women with <1yr. Date menopause known with HRT begun within 3 years of menopause n=245 estrogen users n=232 age matched non-users age 55-69	Prescription records medical records	Death BCA	12/1992 or Death	Family BBD, Reproductive risk factors Alcohol	
Lando 1999 American Journal of Preventive Medicine	NHANES I Epidemiologic follow-up Study Post-menopausal women interveiwed 1971 - 1974 n = 5761	Baseline exam and 4 follow-up interviews by phone . HRT use ever/never and length. Confounders well characterized	Record, Review and NCI review	Average 12.71 yrs. Follow-up. 73,253 person/yrs,	Alcohol benign breast disease	219 incident cases ever/never 0.8 (0.6 - 1.1)

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Ettinger 1996 Obstetrics & Gyne-cology				RR 1.89 (0.43 - 8.36)	Poor study design comparing longterm users mean daily does 0.9 mg. Quality: poor
Lando 1999 American Journal of Preventive Medicine	≤ *3 yrs* : 0.9(0.6-1.4) *3-9yrs* : 0.5(0.3-0.9) ≥ *10yrs* : 0.8(0.5-1.3)				Good methodology. No interaction with family history. No interaction with type menopause. Quality: good-fair