Appendix F: Evidence on Breast Cancer and Hormonal Replacement Therapy

F

Breast cancer, after lung cancer, is the second leading cause of death from cancer. The American Cancer Society estimates that one in nine American women will develop breast cancer during her lifetime (65). The impact of hormone replacement therapy (HRT) on the risk of breast cancer, even if small, would be substantial given the high baseline risk, as well as the societal cost, of this illness. For this reason, this question has been one of the most widely studied with modern epidemiologic techniques. Unfortunately, given the complexity of the issues involved, no clear-cut answer is available at this time.

This appendix reviews the evidence linking HRT to an increase in the risk of breast cancer. First, the biological plausibility of a link between HRT and breast cancer risk will be reviewed. Second, the epidemiological evidence of HRT and breast cancer risk will be reviewed. Virtually all of the epidemiological evidence is observational, consisting of case-control studies and cohort studies. The findings, and discussion of the strengths and weaknesses of the studies on which they are based, follow.

BIOLOGICAL PLAUSIBILITY

The relationship of HRT and breast cancer is consistent with a number of observations. Bittner first suggested that estrogen could increase the incidence of breast cancer, by examining the role of estrogens in the development of mammary tumors in mice (3). Subsequently, Moolgivkar and Knudson proposed that estrogen could increase the risk of breast cancer by increasing the rates of division and numbers of breast cells, which increases the likelihood that an initiating factor (such as ionizing radiation, chemicals, or viruses) will damage cellular DNA (51). Such DNA damage, in turn, leads to a series of errors in cell division, producing so-called "intermediate" cells, which finally results in transformed, or malignant cells.

The hypothesis that HRT increases breast cancer risk is further supported by observations that factors that increase a woman's exposure to estrogen and progestin increase her risk of breast cancer. Thus, early menarche (age of onset of menstruation) and late menopause are associated with an increased breast cancer risk (75). Also, women who have had surgical removal of the ovaries have a lower breast cancer risk (77). There is also strong evidence that obese postmenopausal women are at an increased risk of breast cancer (19). This may be because the chief source of estrogen after menopause is the conversion in fat tissue of the hormone androstenedione, made in the adrenal gland, to the estrogen estrone (46).

It is uncertain whether the addition of progestins would increase the risk of breast cancer above estrogen alone. Key and Pike have reviewed the experimental evidence bearing on the hormonal control of breast cell division (42). They noted that breast cell division peaks during the later phase of the menstrual cycle, corresponding to a progesterone peak. They concluded that, although knowledge of the hormonal control of division rates was incomplete, the available data could support two possible interpretations.

The first model suggests that women receiving a combination of estrogen and progestin will have an increased risk of developing breast cancer over those receiving estrogen alone. This "estrogen plus progesterone" model posits that estradiol, the major ovarian estrogen, itself may induce breast cell division in the early phase of the menstrual cycle. However, the addition of progesterone, produced in the later phase of the menstrual cycle, induces much more cell division, perhaps because estrogen produced in the early phase of the menstrual cycle has stimulated the formation of progesterone receptors on breast cells (42). This increased cellular proliferation then places the breast tissue at risk for malignant change.

The alternative model suggests that the addition of a progestin will have little effect on the risk of breast cancer associated with estrogen. This "estrogen alone" hypothesis is supported by experimental data demonstrating that progesterone shows little significant cell division-stimulating effect. These results suggest that cell division is induced by estradiol alone, with little contribution by progesterone (42). Such an explanation, the authors note, requires a dose-response relationship between the plasma concentration of estradiol, which peaks at the end of the early phase of the menstrual cycle, and the amount of breast cell division. Furthermore, such a model must account for the 4-to 5-day lag between these changes in estradiol concentration and the subsequent changes in rates of cell division observed in breast tissue.

CASE-CONTROL STUDIES

Tables F-1 and F-2 at the end of this appendix present the results of 30 case-control studies of the risk of breast cancer in users of hormonal replacement therapy. The fourth column of the table compares the risk of breast cancer among never users of hormonal replacement therapy with those who have ever used hormonal replacement therapy. Of these 30 case-control studies, five showed an increased risk of breast cancer among ever users (30,33,37,44,83). Nineteen studies demonstrated no increased risk of breast cancer in ever users of hormonal replacement therapy. However, most of these latter studies found increased risks among certain subgroups of users. The other 6 studies either did not compare ever users to never users (2,23,35) or did not provide statistical analysis of results (19,48,60).

Duration

The fifth column of tables F-1 and F-2 describe the relationship of breast cancer risk to duration of estrogen use. Most of the studies finding no increase in the risk of breast cancer among ever users also found no correlation of breast cancer risk with duration of use. However, several studies, including most studies which have found the risk of breast cancer to increase among ever users have found that the risk of breast cancer increases with longer durations of use (2,6,18,23,27,28,44,63, 84). In addition, two studies found increased risks among users with the greatest cumulative dose, which is based on average daily dose multiplied by the duration of use (63,82). However, Jick found an increased risk among ever users, but did not find a correlation with duration of use (80). Three studies found increased risk only among women with shorter durations of use (33,35,53). In these studies, increased risk of breast cancer among the groups of users of the longest duration may have been difficult to detect because of the relatively smaller number of women in these groups.

Dose

The sixth column of tables F-1 and F-2 describe the relationship of breast cancer to the dose of estrogen. Bergkvist found a significantly increased risk of breast cancer among users of the potent estrogen diethylstilbesterol and among users of "other" estrogens, which included users of relatively high dose injectable forms of estrogen (2). However, the study found no correlation of risk with the doses of oral conjugated estrogens (CE) that are commonly used in hormonal replacement therapy (2). Hoover found a trend toward increased risk among users of high doses of estrogens (greater than 1.25 mg CE per day or the equivalent) (28). Hulka found an increased risk of breast cancer among users of injectable estrogens, but no significant increased risk among users of the highest doses of oral estrogens (greater than 1.25 mg CE per day or the equivalent) (33). Four studies found no correlation between risk of breast cancer and dose of estrogen (37,39,40,49).

Recency

The sixth column of tables F-1 and F-2 describe the relationship of the recency of estrogen use, or the time since last use of estrogen, to the risk of breast cancer. Thirteen case-control studies have examined this issue. Of those, seven found no relationship between recency of estrogen use and breast cancer risk. Hulka found an increased risk of breast cancer among users whose last dose was two to five years past, but no increase in risk among users whose last dose was within the past year or among those whose last dose was six or more years ago (33). Kaufman found a reduced risk of breast cancer among women with a surgical menopause whose last dose was 10 or more years ago (39). The author explains that this low relative risk may be due either to chance or the fact that women who have had their ovaries removed and are more likely to be prescribed estrogen generally for a short period of time also have a lower risk of breast cancer (39). La Vecchia found a significantly increased risk of breast cancer among users of estrogens whose last dose was 10 or more years ago, but this risk was only marginally significant when adjusted for a number of confounding factors (44). Nomura found a significantly increased risk of breast cancer among women of Japanese ancestry whose last dose was eight or more years ago when compared with community controls but not when compared with hospital controls (53). No correlation of risk with recency of use was found among white women (53).

Time Since First Use

The sixth column of tables F-1 and F-2 present data on the relationship of breast cancer to the time since first use of HRT, or latency. Eleven of the case control studies address this issue. Eight of the case control studies show no correlation of risk with time of first HRT use. Ewertz found an increased risk among women with natural menopause more than five years prior to breast cancer diagnosis, and whose first dose of hormonal replacement therapy was more that 12 years ago. No similar increase in risk was found in women with natural menopause within five years of breast cancer diagnosis or women with surgical menopause (18). Hulka found an increased risk among women whose first dose of hormonal replacement therapy was five to nine years ago, but no significant increase in risk was detected in users whose first dose was 10 or more years ago (33). Weinstein found on increased risk of breast cancer only in women 10 to 19 years since first use (80).

COHORT STUDIES

Cohort studies of the relationship of breast cancer to use of hormonal replacement therapy are presented in tables F-3 and F-4 at the end of this appendix. Of the 18 studies identified by OTA, seven demonstrated a statistically significant increased risk of breast cancer among users of hormonal replacement therapy. Six studies did not show an increased risk of breast cancer that was statistically significant. One study found a decreased risk of breast cancer among users of hormonal replacement therapy (78). Three studies provided no statistical analysis of results. One study demonstrated a decreased risk of breast cancer among users of estrogen with progesterone,

but this study did not control for confounding variables (20). A decreased risk of breast cancer among users of estrogen and progesterone was also found in the only clinical trial to examine this issue (52) (described below); however, a lower risk of breast cancer in users of estrogen and progesterone has not been confirmed by other studies (2,67).

Duration

Tables F-3 and F-4 also show the effect of the duration of use of hormonal replacement therapy on breast cancer risk. Some studies were able to demonstrate an increase in risk of breast cancer with increasing duration of use (2,29,61). However, five studies were not able to detect an increase in risk with increased duration of use. Colditz found an increased risk among current users of five to 10 years, but not among users of shorter or longer durations (13). Schairer found an increased risk only of preinvasive *(in situ)* cancers with duration of ERT use (67).

Dose

The few cohort studies that have looked at the relationship of dose to risk of breast cancer have not consistently demonstrated an increased risk with increasing dose of estrogen (13,29,61).

Recency and Time Since First Use

Some studies have demonstrated an increased risk with current users of estrogen, but not with past users (13, 14,89). Other studies have found that the risk of breast cancer increases with time since first use (34,35).

CLINICAL TRIALS

Only one clinical trial has examined the relationship of hormonal replacement therapy to breast cancer risk (52). Subjects were continuously hospitalized postmenopausal women. Treated women and control group members were matched for age, smoking history, and medical diagnosis. The treatment group received estrogen-progestin hormone replacement therapy. The control group received placebo. Double-blinded randomization was discontinued after 10 years. In the subsequent 12 years, women were offered the choice of starting, stopping, or continuing hormone replacement therapy. During the 10-year clinical trial, there were no significant differences in breast cancer incidence between the treated and the placebo group. After 22 years of follow-up, there was a statistically significant increase in breast cancer risk in never users of hormonal replacement therapy versus ever users. However, the size of this study was quite small, involving 89 pairs of women, and the results are unstable.

COMBINED ESTROGEN-PROGESTIN THERAPY AND BREAST CANCER RISK

It is uncertain whether the addition of progestins to estrogen replacement therapy would alter HRT users risk of breast cancer, as few studies have examined this issue. Bergkvist and colleagues examined this issue in a study of breast cancer in a cohort of 23,000 women from the Uppsala Health Care Region of Sweden. They found a significant increase of breast cancer in users of estrogen alone; they also found a similar increase in risk of breast cancer among users of combined estrogen and progestin. The increase in risk among combined estrogen-progestin users, however, did not reach statistical significance, in part due to the relatively small number of users of combined estrogen-progestin in the cohort. The investigators concluded that progestins offered no protection against the development of breast cancer (2).

A recent cohort study by Schairer and colleagues found- that users of estrogen-progestin combinations may have a higher risk of breast cancer than users of estrogen alone (67). The study examined the incidence of breast cancer among 49,017 postmenopausal women who had participated in the Breast Cancer Detection Demonstration Project (BCDDP). For ever users of estrogen alone, there was no increased risk of breast cancer. For users of estrogen and progestin combinations, however, there was an increased risk of breast cancer that was of marginal statistical significance

(relative risk 1.2 (95 percent confidence interval 1.0 to 1.6)).

All of the studies of hormone replacement and breast cancer risk, except one, are observational, so the possible impact of selection bias cannot be entirely ruled out. Barrett-Connor explained that it is uncertain how selection bias may affect the results of studies of HRT use and breast cancer (1 a). Some biases may result in an exaggerated estimate of breast cancer risk in HRT users. For example, women who take hormonal replacement therapy tend to be more educated and of higher socioeconomic status than other women (la). Studies have shown that women of higher socioeconomic class are at higher risk of breast cancer. Therefore, epidemiological studies that fail to account for differences in socioeconomic status between HRT users and nonusers may overestimate the risk of breast cancer in HRT users.

Women on HRT have been found to be more likely to have mammograms (2a). Breast tumors in HRT users are therefore more likely to be detected. This bias may explain for the lower stage and grade of tumors detected in HRT users, and the improved prognosis of breast cancers in HRT users (la,9). (See discussion below.)

Other biases may result in an underestimate of breast cancer risk in HRT users (la). Women who have an early menopause or surgical removal of the ovaries (oophorectomy) are more likely to be treated by their physicians with HRT. Breast cancer risk in these women may be underestimated because both early menopause and oophorectomy are associated with decreased risks of breast cancer. Women are more likely to be prescribed estrogen if they have menopausal symptoms, and thin women tend to have more severe menopausal symptoms. Thin women are also at decreased risk of breast cancer, so this is another source of bias.

Physicians may be reluctant to prescribe HRT to women with benign breast disease or a family history of breast cancer, another source of decreased estimate of risk (la). And some physicians will not prescribe HRT until their patient has had a mammogram, and if the mammogram is abnormal, will not prescribe HRT.

Women who take hormonal replacement therapy are more likely to engage in other healthy behaviors. And women who are willing to take hormonal replacement therapy long-term are, by definition, more compliant. As has been discussed in detail in Appendix I, compliant women are less likely to get heart disease, cancers, and other diseases. Although epidemiological studies have attempted to statistically control for many of these sources of bias, it has not been possible to completely control for so-called compliance bias because of its ill-defined nature.

The uncertainty about the relation between breast cancer risk and hormone replacement therapy will not be resolved until we have the results of a randomized clinical trial of HRT in postmenopausal women (32). Because the increase in risk of breast cancer in HRT users appears to be small, a large study would be required to have sufficient statistical power to detect this small increase in risk. Given that the risk of breast cancer increases with duration of use, the controlled clinical trial would take 10 or more years to complete.

The Women's Health Initiative, sponsored by the National Institutes of Health, is a large long-term randomized clinical trial examining the effect of hormone replacement therapy on heart disease and osteoporosis in postmenopausal women. (See description in Appendix I.) This trial will also help to resolve many of the questions about the relationship between hormone replacement therapy and breast cancer risk and other diseases affected by hormone replacement therapy.

Problems with conducting such a study arc the expense of the trial and the practical problems in conducting a clinical trial long-term. Also, because sequential and continuous hormonal replacement therapy causes bleeding and other symptoms, both the investigator and the subject will become aware of their assignment, introducing a source of bias. Finally, by the time the trial is completed, new HRT regimens may be available, raising the question of whether the results of the Women's Health Initiative apply to these new regimens.

STAGE OF BREAST CANCER AT DIAGNOSIS IN HRT USERS VERSUS NONUSERS

There is some evidence that estrogen users develop breast cancer of lower stage and grade than breast cancers in nonusers. This maybe an artifact of surveillance bias or may be because estrogen induces a less malignant form of breast cancer. In a population-based case control study of breast cancer in postmenopausal women, Brinton and colleagues found that there was a significant trend of greater risk of breast cancer with increased duration of HRT use, and that this increase in risk was greatest for the lowest stage tumors (6). After 10 or more years of estrogen use, the increase in risk of large (greater than 1 cm) invasive breast cancers was 1.29 (p less than 0.05), but the increase in risk of small (1 cm or less) tumors and carcinoma in situ was 1.51 (p less than 0.05) and 1.90 (p less than 0.05), respectively.

Hunt and colleagues, in a study of a cohort of 4544 British women receiving HRT at menopause clinics, found that, of the 40 breast cancers that developed among the cohort that were identified by stage, 27 (68 percent) were classified as Stage I (nonmetastatic tumors 2 cm or less) at diagnosis, which is a higher proportion of early stage tumors at diagnosis than expected based on comparison with stage at breast cancer diagnosis in the general population (34). The lower than expected stage of breast cancer at diagnosis in cohort members, however, could be explained by the fact that 1) the average member of the cohort had been followed for less than 5 years, and 2) cohort members, all of whom were on HRT at recruitment, presumably did not have any previous diagnosis of breast cancer at that time (57).[10]

Squiteri and colleagues found that hormone users present with slower growing breast tumors of earlier stage than nonusers, possibly resulting in improved prognosis (70). Breast cancers from 35 women who had taken HRT (mostly estrogen and progestin combinations) were compared to breast cancers from postmenopausal women who had never taken hormones, matched for age and type of breast cancer to HRT users. They found that HRT users had smaller tumors, significantly less spread to lymph nodes, and had significantly lower S-phase fractions (a measure of the rate of cancer cell division). The investigators concluded that the small tumor size, low S-phases, and limited nodal involvement of HRT users suggests that, despite a possibly increased risk of breast cancer, the mortality rate for breast cancer in HRT users will not be increased in comparison with nonusers. The investigators could not rule out the possibility, however, that the results may have been due to better surveillance and earlier diagnosis of breast cancer in HRT users.

Bonnier and colleagues concluded that the lower stage of breast cancers in HRT users was not due to surveillance bias (4). The investigators compared 68 postmenopausal women who were receiving HRT at the time of diagnosis of breast cancer with 282 breast cancer patients who had not received prior HRT, and whose date and age of onset of breast cancer were similar to that of the breast cancer patients that had received HRT. Patients who developed breast cancer during HRT had fewer locally advanced cancers (tumors that had extended into lymph nodes) and more well-differentiated cancers. In addition, the probability of metastasis-free survival tended to be better in HRT users. The investigators found that the favorable prognosis in HRT users was not likely to be due to better cancer surveillance among HRT users, because x-ray detection was not more frequent among patients undergoing HRT. In addition, the delay between first symptoms and

[1] Hunt and colleagues also found that short term users of HRT had a significantly lower death rate from breast cancer than would be expected by comparison with population age-specific breast cancer death rates (observed to expected ratio = 0.55 (0.28-0.96)) (34). As Pike and colleagues explained, however, for a member of the cohort to die during the five year follow up, she had to first be diagnosed with breast cancer and then die of that disease (57). The expected number of such deaths cannot be derived straightforwardly from population age-specific death rates.

diagnosis was slightly but not significantly shorter in HRT users.

Additional information is needed on whether the addition of progestin has an impact on the stage and grade of breast cancer related to estrogen. Schairer and colleagues, reporting on the results from the BCDDP cohort (described above) found that estrogen-progestin combinations were related to a larger risk of preinvasive (in situ) cancers (relative risk 2.3 (95 percent confidence interval 1.3 to 3.9)) than estrogen alone (relative risk 2.3 (95 percent confidence interval 1.3 to 3.9)), but neither estrogen or estrogen-progestin combinations were related to an increased risk of invasive cancers (67).

Jones and colleagues found evidence that tumors induced by estrogen-progestin combinations may have a better prognosis than tumors induced by estrogen alone (38). The investigators identified 460 perimenopausal and postmenopausal breast cancer patients hospitalized in Perth, Western Australia, between January 1990 and December 1991. They questioned each of the patients about HRT use, and reviewed medical records and pathology reports for data related to breast cancer prognosis. They found that the mean level of estrogen and progestin receptors was lowest in users of estrogen alone highest in users of estrogen-progestin combinations, consistent with a better prognosis for estrogen-progestin users. Levels of Cathepsin D, which is inversely related to breast cancer risk, were highest in users of estrogen alone, and lowest in nonusers. The tumors were smallest in estrogen-progestin users, and largest in users of estrogen alone, although the difference was not statistically significant. There was no significant difference in lymph node involvement of cancer between estrogen-progestin users and users of estrogen alone. The percentage of all HRT users with involved lymph nodes (23 percent), however, was significantly lower than the percentage of nonusers (44 percent). The authors stated that they could not rule out that this last finding could have been due to differences in surveillance.

BREAST CANCER MORTALITY IN HRT USERS VERSUS NONUSERS

There is conflicting evidence about whether an increased incidence of breast cancer among HRT users results in an increased rate of breast cancer deaths. A number of studies have found that estrogen users do not have an increase in deaths from breast cancer. Petitti and colleagues analyzed the 26 breast cancer deaths that occurred during 13 years followup of the 6,093 women in the Walnut Creek cohort (56). The relative risk of death from breast cancer for women who used HRT but not oral contraceptives was 0.8 (0.4 to 1.8) compared to women who used neither HRT nor oral contraceptives.

Vakil and colleagues also found reduced breast cancer mortality among postmenopausal estrogen users in a cohort of 1,483 postmenopausal women from Ontario and Saskatchewan (78). The ratio of observed to expected mortality from breast cancer among HRT users was 0.48 (p less than 0.01) for the Ontario women and 0.45 (p less than 0.01) for the Saskatchewan women.

In a cohort study of 8,881 postmenopausal residents of Leisure World Retirement Community in Los Angeles, Henderson and colleagues found a reduction in breast cancer mortality among estrogen users of 0.81 (no confidence interval provided) (26). Although the investigators did not have information about breast cancer stage at diagnosis, they suggested that estrogen users may have less extensive cancers at diagnosis than nonusers because of increased breast cancer surveillance among estrogen users and better health awareness of women who use estrogens.

Bergkvist and colleagues, in an analysis of survival rates in women with breast cancer in the Uppsala Health Care Region of Sweden, found that ever users of HRT had significantly greater survival rates than never users (2). The investigators compared survival rates in 261 breast cancer patients who used HRT prior to diagnosis with 6,617 breast cancer patients from the same geo-

graphic region who did not have any recorded use of HRT.

Information on estrogen use was obtained from a regional prescription database and from a mailed questionnaire, and information on breast cancer survival was obtained from the Swedish National Cancer Registry (2). (The registry did not, however, have information about tumor stage and grade.)

The investigators found that the relative 8 year survival rate of women diagnosed with breast cancer who used hormonal replacement therapy was 10 percent higher than those who had not taken hormonal replacement therapy, which corresponded to a 40 percent reduction in excess mortality (2). Separate analysis of relative survival by age at diagnosis showed a significant survival advantage for estrogen-treated women at each age over 50, and was greatest for estrogen-treated women 60 years old and older at diagnosis, with an approximately 40 percent lower mortality rate than never users with breast cancer.

The relative survival rates were highest for women who were current users of HRT at diagnosis, and the survival advantage of estrogen users was decreased with longer time between cessation of estrogen and diagnosis, so that the survival rates of estrogen users who had stopped taking estrogens more than 12 months before diagnosis was close to that of never users of estrogens (l). Also, the relative survival rates were best among women treated with progestins combined withestrogen during part or all of the course of HRT.

There were several possible alternative explanations of these results. First, a favorable impact of estrogens on forces of mortality other than breast cancer, most notably heart disease, may have accounted for the favorable survival rates of HRT users. Second, women who are prescribed HRT represent a healthy selection of the general population. Third, the favorable survival rates of HRT users maybe due to surveillance bias (2).

A subsequent study of breast cancer mortality by the same group attempted to correct for the "healthy user" effect (85). Despite these corrections, the investigators found no increase in breast cancer mortality, either overall or in subgroups, despite increased incidence.

Results of a study by Strickland and colleagues suggest that the favorable survival of breast cancer patients who used HRT is due to surveillance bias (73). The investigators compared the survival time between diagnosis and death of 256 postmenopausal women with breast cancer, 174 of whom were never users of estrogens, 21 of whom were past users of estrogens, and 61 of whom were currently using estrogens at the time of diagnosis. Information on survival time, as well as stage of breast cancer at diagnosis, was obtained from the Southwestern Oncology Group Tumor registry. They found that the median time between breast cancer diagnosis and death was less than 84 months for never users and past users of estrogens, and was 143 months for current users of estrogens. After controlling for stage of breast cancer at diagnosis, however, the survival time for never users and past users of HRT was not significantly different from current users.

CONCLUSIONS

Although the evidence on the link between estrogen therapy and the risk of breast cancer is based almost entirely on case-control and cohort studies, which cannot entirely control for biases and confounding factors (64), the inconsistency in results among both kinds of studies suggests that the effect of estrogens on breast cancer is likely to be small. Indeed, when they were found, such associations were generally weak. Discrepancies in the results among studies are not readily explained by study design or implementation and may likely be due to chance.

For purposes of this model, we assumed in the base case that the relative risk of breast cancer with HRT would be a modest 1.35 times the baseline rate in the population of women of a certain age, but the higher risk would not occur until the duration of use had exceeded 9 years. This increase in risk is consistent with the range of estimates of breast cancer risk with long-term use

from several recent metaanalyses and epidemiological reviews (Grady (relative risk 1.25 (95 percent confidence interval 1.04 to 1.51) for eight or more years of ERT use) (21); Steinberg (relative risk 1.3 (1.2 to 1.6 after 15 years of use) (72); Colditz (relative risk 1.23 (95 percent confidence interval 1.08 to 1.40) for 10 or more years of estrogen use) (12); Sillero-Arenas (relative risk 1.23 (1.07 to 1.42) after more than 12 years use) (69); Hulka (relative risk approximately 1.3 to 1.5 with long-term use) (31); Steinberg (relative risk 1.15 to 1.29 after 10 years of CEE use) (71); Mack (relative risk 1.2 at 5 years of use, increasing to 1.4 at 10 years of use) (47); Prentice (relative risk 1.3 for ever use, and possibly larger risks with long-term use) (59).

Once duration exceeds nine years, the relative risk of breast cancer is assumed to remain elevated for the rest of the woman's lifetime. This assumption is consistent with the observation that breast cancer risk remains elevated in women with late menopause and the hypothesis by Pike that HRT induces a hormonal milieu similar to late menopause (57,58).

Because of the great uncertainty about the magnitude and exposure pattern of risk elevation, the best case assumption was that there would be no increased risk of breast cancer among users of HRT. This estimate is consistent with the metaanalysis by Dupont and Page (16), who limited their analyses to studies of conjugated estrogens, and excluded European studies where use of stronger synthetic estrogens is common. This estimate is also consistent with the metaanalyses of Khoo and Chick (43) (no increase in breast cancer risk), Henrich, (24) (no increased risk of breast cancer among ever-users of estrogens) and Armstrong (summary relative risk 0.96 (0.89 to 1.05) after adjustment for menopausal status; no effect of duration of use) (l).

Under the worst case, we assumed a relative risk of 2.0 after 9 years of therapy. This worst-case estimate is consistent with the largest relative risks of breast cancer found in cohort studies of HRT users (2,35,50,76); these large increases in risk were generally associated with long-term use. This estimate is also within the range of estimates from epidemiological reviews by Persson and colleagues (relative risk 1.5 to 3.0 with 10 to 15 years of use) (55), Pike (relative risk 1.75 after 20 years of ERT use) (57) and Henderson and colleagues (relative risk 1.5 to 2.0 if moderate doses of CEE are used for 10 to 20 years) (26). We have also assumed that there was no difference in stage distribution or mortality from breast cancer in estrogen users. Observational studies that have found better stage and grade breast cancers in HRT users have inherent risks of surveillance bias.

Finally, we have assumed that, once diagnosed with breast cancer, women would be taken off HRT. There is, however, a debate in the literature over whether women previously treated for breast cancer may start or resume HRT (11, 15,36,45,74). Proponents argue that there is little direct evidence that HRT has an adverse effect on women previously treated for breast cancer who subsequently received HRT (81). The National Cancer Institute recently announced the initiation of a randomized clinical trial to determine the influence, if any, of HRT on the clinical course of breast cancer (79).

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TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 1 of 10)

Author	Description of cases and controls	Number of oases and controls	Relationship of breast canoer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Boston Collaborative Drug Surveillance Program (1974)	Cases and controls were consecutive postmenopausal patients, ages 45 to 64 years, admitted to the general medicine and surgical wards of 24 hospitals in the Greater Boston area in 1972. Cases had surgically confirmed breast cancer. Controls were postmenopausal women who were admitted to these hospitals with acute illnesses, elective surgery, or orthopedic treatment. Patients were interviewed during admission.	51 breast cancer cases; 774 controls	9% of cases were estrogen users; 8% of controls were estrogen users; the difference was not statistically significant	"Duration of use in the cases of breast cancer . . was similar to that of control users."	
Sartwell (1977)	Cases were women 20 to 74 years of age with carcinoma of the breast admitted to Johns Hopkins Hospital between 1969 and 1972. Controls were chosen from among other patients except those from the obstetric or gynecology services. All subjects were given a questionnaire by an interviewer.	284 cases (65,8% post menopausal) (1 9.7% noncontraceptive estrogen users); 367 controls (76.8% postmenopausal) (26.7% noncontraceptive estrogen users)	Adjusted RR: 0.82 (0.6-1 .2)* ● adjusted for age, race, marital status, menopausal history, and pregnancy history.	<6 mo.: 0.87 6-11 mo.: 0.61 1-1.9 yrs.: 1.40 2-4.9 yrs.: 0.70 >5 yrs.: 0.62 None of the adjusted relative risks were significantly different from unity.	
Wynder (1 978)	Cases were pre- and postmenopausal white women selected from seven hospitals in New York City, with diagnosis of breast cancer between 1969 and 1975. Controls were white women admitted to the surgical services of these same hospitals during the same period. All subjects were interviewed.	785 cases (267 postmenopausal); 2,231 controls (630 postmenopausal)	34.1 % of postmenopausal cases and 36.8% of postmenopausal controls used estrogen (nonsignificant difference).		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 2 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ravnihar (1979)	Cases and controls were women ages 15 to 64 years selected from patients admitted to a Slovenian hospital. Cases were women admitted for aspiration or biopsy of malignant or benign breast diseases. Two controls from other hospital services were selected for each case and matched for age and date of admission. Interviews were conducted between 1972 and 1974.	374 breast cancer cases (184 were ages 50 to 64), 748 breast cancer controls (368 were ages 50 to 64)	Ages 50-64. cases 11.4% controls 11.7% No tests of statistical significance were performed.	Ages 50 to 64: <24 mo.: 11/1 84 breast cancer cases 30/368 controls >24 mo.: 3/1 84 breast cancer cases 8/368 controls unknown duration 7 cases, 5 controls	Current users (ages 50 to 64). 1/1 84 breast cancer cases 5/368 controls Past use: 20/1 84 breast cancer cases 38/368 controls
Jick (1980)	Cases were postmenopausal women, ages 45 to 64, identified from a prepaid health care organization's (Group Health Cooperative of Puget Sound) records as having the diagnosis of breast cancer between 1975 and 1978. Controls were postmenopausal women ages 45 to 64 years matched for age with cases and hospitalized about the same time. Information on cases and controls was obtained from interviews and medical and pharmacy records.	97cases (39% current estrogen users); 139 controls (37% current users)	Natural menopause: 3.4 (90% 2.1 -5.6) for current users (last use within 12 months of date of diagnosis) versus nonusers, Hysterectomized women. 1,1 (90% 0.7-1 .9)	Duration had no effect on risk of breast cancer.	Dose had no effect on risk of breast cancer.

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 3 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Kelsey (1 981)	Cases were women ages 45 to 74 years admitted to Connecticut hospitals between 1977 and 1979 with newly diagnosed breast cancer. Controls were women of the same age span admitted to other surgical services (excluding gynecology) between 1977 and 1979. All cases and controls were interviewed.	330 cases (9% users); 1,348 controls (10% users)	One or both ovaries intact (pre- and postmenopausal). O.R. 0.9 (0.6-1 .2) Both ovaries removed: O.R. 0.9 (0.5-1 .5)	At least one ovary intact (pre- and postmenopausal). 1-49 mg - months. O.R. 0.9 (no c.i.) >50 mg - months: O.R. 0.6 (test for trend: p= 0.08) Both ovaries removed: 1-49 mg - months: O.R. 0.7 (no c.i.) >50 mg - months: O.R. 1.0 (test for trend: P= O.88) "For estrogen-replacement therapy, there is a nonsignificant decrease of less than 5 percent in risk for breast cancer with each year of use. "	

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 4 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Hulka (1 982)	Cases were postmenopausal women admitted to two North Carolina hospitals between 1977 and 1978 with a diagnosis of breast cancer. Hospital controls were postmenopausal women admitted to these same hospitals with problems that were not gynecologic or referable to the breasts. Controls were matched to cases by age, race, date of admission, and hospital. Postmenopausal community controls were obtained from hospital referral regions. All study subjects were interviewed.	163 cases (52 users), 372 hospital controls (90 users), 737 community controls (171 users)	Estrogen use was defined as use greater than 6 months. Ever use: natural menopause 1.8 ($p < 0.05$) (comm. controls); 1.7 ($p < 0.05$) (hosp. controls) Ever use (oral estrogens only, excluding users of injectable estrogens): 1.3 (NS) (comm. controls); 1.2 (NS) (hosp. controls) Surgical menopause. 1.3 (NS) (comm. controls); 1.2 (NS) (hosp. controls)	Natural menopause. 0,5-3 yrs.: 2.1 ($p < 0.05$) (comm. controls); 2.6 ($p < 0.05$) (hosp. controls) 4-9 yrs. :1.5 (NS) (comm. controls); 1.6 (NS) (hosp. controls) 10+ yrs.: 1.7 (NS) (comm. controls); 0.7 (NS) (hosp. controls)	Natural menopause. <0,625 mg conjugated estrogen (or equivalent). 1.9 (NS) (comm. controls), 1.8 (NS) (hosp. controls) >0,625 mg: 1,0 (NS) (comm. controls), 0.8 (NS) (hosp. controls) Injectable, 4,4 ($p < 0.05$) (comm. controls) 4.0 ($p < 0.05$) (hosp. controls) Recency (time since last use): Natural menopause. O-1 yr.: 1.6 (NS) (comm.); 1,3 (NS) (hosp.) 2-5 yrs., 2,2 (NS) (comm.), 3.2 ($p < 0.05$) (hosp.) 6+ yrs.: 1.8 (NS) (comm.); 1.8 (NS) (hosp.) Latency (time since first use): Natural menopause: 0.5-4 yrs.: 1.2 (NS) (comm.); 1,7 (NS) (hosp.) 5-9 yrs.: 2.4 ($p < 0.05$) (comm.), 3.1 ($p< 0.05$) (hosp.) 10-14 yrs.: 2.1 (NS) (comm.): 1.3 (NS) (hosp.) 15+ yrs.: 1,5 (NS) (comm.); 1.4 (NS) (hosp.)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 5 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Sherman (1983)	Cases were white patients seen for breast cancer surgery at the University of lowa Hospitals between 1974 and 1978. Controls were patients without history of cancer from the general medicine and surgery wards, matched for age and hospital payment category. A trained interviewer administered a questionnaire to all subjects.	113 cases (32% users), 113 controls (45% users)	Estrogen use was defined as use for more than one month, Unadjusted RR 0.71 (0.34-0.1 1) Adjusted RR* 0.55 (p= 0.029) *adjusted for weight and height		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 6 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Horowitz (1984)	Cases and controls were postmenopausal women, age 45 or older, evaluated at Yale New Haven Hospital, Connecticut, between 1976 and 1979. Patients with clinical conditions making them unlikely to have received postmenopausal estrogens were excluded from control groups chosen to reduce the likelihood of ascertainment bias and detection bias. Four case control groups were compared. Group 1.150 breast cancer patients initially diagnosed by mammography were compared to 150 women with mammographically normal breasts. Group 2: same 150 breast cancer patients were matched with 150 women with benign breast disease by mammography. Group 3:107 breast cancer patients with initial diagnosis by breast biopsy were matched with 107 control patients with histologically benign disease. Group 4:257 breast cancer patients were matched to 257 control patients chosen from the medical or surgical wards of the hospital (conventional control group). Data were obtained from hospital and physician office records.	257 breast cancer cases, including 150 breast cancer cases diagnosed by mammography, and 107 breast cancer cases diagnosed by biopsy. Control group 1: 150 (normal by mammography) Control group 2: 150 (benign breast disease by mammography) Control group 3: 107 (histologically normal biopsy) Control group 4: 257 (hospitalized patients with other diagnoses) (conventional control group)	Estrogen use was defined as at least 0.3 mg/day of estrogen for at least three months. Group 1: O.R. 0.4 (0.3-0.7) Group 2: O.R. 0.5 (0.3-0.8) Group 3: O.R. 0.8 (0.5-1.4) Group 4: O.R. = 0.9 (0.5-1 .7) when only those medical records which had specific notations about use or nonuse of estrogens were used; O.R. = 3.3 (2.2-5.0) when those medical records with no specific notations about estrogen use were classified as nonusers.		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 7 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Kaufman (1984)	Cases and controls were from several hospitals in the United States and Canada. Cases were pre- and post-menopausal women younger than 70 years of age (median age 51) admitted to these hospitals between 1976 and 1981 with the diagnosis of breast cancer made no more than six months prior to admission. Controls were women less than 70 years of age (median age 51) who were admitted to these hospitals for malignant conditions judged to be unrelated to noncontraceptive estrogen, and with age within one decade of control subjects.	1,610 cases (925 postmenopausal), 1,606 controls (1 ,127 postmenopausal)	Estrogen use was defined as use at least 18 months prior to admission, Pre- and postmenopausal ever use of noncontraceptive estrogens: conjugated estrogens: 0.9 (0.7-1.1) nonconjugated estrogens: 0.8 (0.6-1 .1) all estrogens: 0.8 (0.5-1 .2) Premenopausal use of conjugated estrogen: 1.3 (0.6-2.9) Postmenopausal use of conjugated estrogen: 0.8 (0.7-1 .1)	Duration of conjugated estrogen use: Natural menopause: <1 year: 0.9 (0.5-1 .5) 1-4 years: 0.9 (0.5-1 .5) 5-9 years: 0.7 (0.4-1 .5) >10 years: 1.3 (0.6-2.8) Hysterectomy only: <1 year: 1.3 (0.5-3.3) 1-4 years: 1.2 (0.5-2.8) 5-9 years: 0.7 (0.2-1 .7) >10 years: 0.3 (0.1-1 .0) Hysterectomy and oophorectomy: <1 year: *0.4 (0,1 -1 .0)* 1-4 years: 0.8 (0.4-1 .6) 5-9 years: 1.1 (0.5-2.3) >10 years: 0.5 (0.2-1 .0)	Natural menopause: <1.25 mg: 1.2 *(0.5-2.5)* *>1.25* mg: *0.7 (0.3-1.5)* Hysterectomy: <1.25 mg: *0.7 (0.2-3.3)* *>1.25* mg: 0.4 (0.2-1 .0) Hysterectomy and oophorectomy: <1.25 mg: 2.0 (0.6-6.4) >1.25 mg: 0.5 (0.3-1 .0) Natural menopause: —all use within 10 yrs. before admission: 1.0 (0.6-1 .5) —all use ending >=10 yrs. before admission: 0.5 (0.3-1.1) —use spanning 10 yrs. before admission: 1.4 (0.8-2.4) —last use within 10 yrs. plus current use (use within past year): 0.6 (0.3-1 .2) Hysterectomy and oophorectomy: —use within 10 yrs. before admission: 1.0 (0.5-1 .8) —use ending >= 10 yrs. before admission: 0.3 (0.1 -0.8)[c] —use spanning 10 yrs. bef ore admission: 0.5 (0.3-1 .0) —use within 10 yrs. plus current use (use within past year): 1.2 (0.5-2.6)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 8 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Nomura (1986)	Cases were white women or women of Japanese ancestry, ages 45 to 74 (average age 57 for Japanese, 61 for white), diagnosed with breast cancer between 1975 and 1980 in one of seven hospitals in Oahu, Hawaii. One hospital control was selected for each case, matched for sex, race, age, Oahu residency, time of hospitalization, and hospital. Controls with a diagnosis of cancer were excluded. One neighborhood control was selected for each case, matched for sex, race, age and Oahu residency. Patients were interviewed.	161 white cases; 161 hospital controls, 159 neighborhood controls 181 Japanese cases; 183 hospital controls, 181 neighborhood controls	Japanese: 1.1 (0.7-1.6) compared with neighborhood controls, 1.0 (0.6-1 .4) compared with hospital controls Whites: 0.9 (0.5-1.3) compared with neighborhood controls; 0.7 (0.4-1 .1) compared with hospital controls	Whites: 1-12 me.: 0.9 (0.4-2.0) community controls; 0.5 (0.2-1.0) hospital controls 13-72 me.: 0.7 (0.4-1.5) community controls; 1.4 (0.6-2.9) hospital controls 73+ mo.: 1.3 (0.7-2.6) community controls; 0.8 (0.4-1 .6) hospital controls Japanese. 1-12 me.: 2.4 (1 .3-4.7) community controls; 1.0 (0.6-1.8) hospital controls 13-72 mo.: 0.7 (0.3-1.5) community controls; 0.6 (0.3-1 .2) hospital controls 73+ mo.: 1.9 (0.8-4.4) community controls; 1.2 (0.6-2.4) hospital controls	Recency (time since last use), Whites: <8 yrs.: 1.3 (0,6-2.8) community; 1.2 (0.6-2.6) hospital 8-16 yrs.: 0.7 (0.3-1.4) community, 0.5 (0.2-1 .0) hospital 16 + yrs.: 1.1 (0.6-2.2) community; 0.8 (0.4-1.5) hospital Japanese: <8 yrs.: 1,0 (0.5-1 .9) community; 0.8 (0.4-1.7) hospital 8-16 yrs.: 2.3 (1 .1-4.7) community; 1.1 (0.6-1 .9) hospital 16 + yrs.: 2.6 (1 .1-6.1) community, 1.0 (0.5-2.0) hospital
Kaufman (1991)	Followup on cohort described in Kaufman (1987). Cases were postmenopausal women ages 40 to 69 years (median age 59 years) diagnosed with breast cancer between 1980 and 1986 and hospitalized in one of several hospitals in seven U.S. and Canadian cities. Controls were postmenopausal women ages 40 to 69 years (median age 59 years) hospitalized with malignant and nonmalignant nongynecological conditions judged to be unrelated to estrogen use. Data were obtained form interviews and hospital records.	1,686 cases (18Y0 users); 2,077 controls *(17%* users)	RR 1.2 (1 .0-1.4) Type of estrogen: unopposed: 1.2 (1 .0-1.4) conjugated: 1.3 (1 .0-1.6) other estrogen. 1.3 (0.6-2.8) opposed by progestin: 1.7 *(0.9-3.3)*	< 1 year: 1,3 (1 ,0-1.8) 1-4 years: 1.2 (0.9-1.6) 5-9 years: 1.4 (0.9-2.2) 10-14 years: 1.0 (0.6-1.6) >15 years. 0.9 (0.4-1 .9)	<1.25 mg: 0.8 (0.4-1 .5) > 1.25 mg: 1,2 (0.7-2.0) mixed mg: 1.6 (0.6-4.0) Recency (time since last use): <12 mo.: 1.1 (0,7-1.6) 12-35 mo.: 1.3 (0.8-2.4) 36-59 mo.: 0.8 (0.4-1 .4) 60-119 mo.: 1.5 (1 ,0-2.2) >120 mo.: 1.2 (0,9-1 .6) Number of years since 5 years of use. <5 yrs.: 2.0 (0.9-4.2) 5-9 yrs.: 1.3 (0.9-2.1) 10-14 yrs.: 0.5 (0.2-1 .0) >15 yrs.: 1.3 (0.7-2.4)

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 9 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use[a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use[a,b]
Harris (1992)	Subjects were part of an ongoing study by the American Health Foundation and were selected for interview from hospitals in the New York City area from January 1987 to December 1989. Cases were women with newly diagnosed breast cancer. Control subjects did not have breast cancer and were matched with controls by age, hospital, and time of diagnosis.		< 5 years use: adjusted O.R. 2.0 (no c.i.) > 5 years use: adjusted O.R. 2.2 (no c.i.) (test for trend: $p < 0.02$)		

TABLE F-1: HRT and Breast Cancer Risk (Hospital-Based Case-Control Studies) (Page 10 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
La Vecchia (1992)	European multicenter study (1986 study updated to Dec. 1990); cases were ages 26 to 74 years (median age 56 years) with histologically confirmed breast cancer admitted to one of several hospitals in Northern Italy. Controls were 25 to 74 years (median age 56 years) admitted to hospitals in Northern Italy for acute conditions that were not hormonal, gynecological, or malignant. Cases and controls were questioned by trained interviewers. Results include both pre- and postmenopausal women, Subjects were followed from 1983 to 1990	3,037 cases (4.9% users); 2,569 controls (3.5% users)	RR 1.4 (1.1-1.8) adjusted for age Adjusted RR * 1.3 (1 .0-1 .8) (This represents a lower risk estimate than the 1986 study, with regression towards the mean overall results from other studies.) Updated results may be overestimated by using orthopedic controls, which may be inversely related to estrogen use (but separate analyses by diagnostic subcategories did not lead to any appreciable difference in risk). Risk estimates may be affected by higher socioeconomic status of users but risk estimates were not modified by alliance of indicators of socioeconomic status. *Adjusted for age, geographic area, marital status, education, benign breast disease, family history of breast cancer, nulliparity, age at first birth, age at menarche, type of menopause, age at menopause, body mass index, and oral contraceptive use	<3 years, RR 1,2 (0.9-1 ,7) adjusted for age Adjusted RR 1.2 (0.9-1 .7) >3 years, RR 1,5 (0,9-2.5) adjusted for age Adjusted RR 1.5 (0,9-2.6) (test for trend, p < 0.05)	Recency (time since last use). <10 yrs.: RR 1,3 (0.9-1 .5) adjusted for age Adjusted RR: 1.2 (0.8-1 .8) >10 yrs.: RR 1.5 (1.1 -2,3) adjusted for age Adjusted RR: 1.5 (1 .0-2.3) Latency (time since first use). <10 yrs.: RR 1,5 (1 ,0-2.3) adjusted for age Adjusted RR 1.3 (O 8-2.0) >10 yrs.: RR 1.4 (1 ,0-2.0) adjusted for age Adjusted RR 1.4 (1 .0-2.0)

[a]Unless otherwise specified, measured relationships are relative risk of breast cancer in HRT
b 95% confidence interval is given in parentheses
C This low relative risk may be due to chance or due to the fact that women who have ovaries removed at a young age' 1) have lower risk of breast cancer, (2) are more likely to be prescribed estrogen, generally for a short period of time
KEY: C.I. = confidence interval; NS = not statistically significant; O R = odds ratio; RR = relative risk

SOURCE: Office of Technology Assessment, 1995

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 1 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Mack (1 975)	Cases and controls were white female residents of a retirement community in Southern Los Angeles, median age 71. Cases were diagnosed with breast cancer between 1971 and 1975. Controls were selected from a roster of all women in the community, matched with cases for age and date of entry into the community. Information was gathered from questionnaires and medical records.	99 cases breast cancer, 396 controls (26% ever users of estrogen among controls)	Ever use 1.6 (no c.i.) Use at least 5 years before diagnosis. 1.7 (no c.i.)		
Casangrande (1976)	Two groups of subjects were selected. Group I was composed of case-control pairs who were white residents of Los Angeles County Cases were between 50 and 64 years of age at diagnosis of breast cancer, diagnosed between 1969 and 1972. A control, matched for age and socioeconomic status, was selected from the outpatient rosters of each index cases' referring physician. Group II cases were white patients whose breast cancers were diagnosed between 1972 and 73, and who were between the ages of 50 and 59 at disease diagnosis, lived in SIX middle class white health districts of eastern Los Angeles Cases were matched with healthy control neighbors ages 50 to 59 years	Group 1: 60 cases; 53 controls Group II 33 cases, 27 controls	For women with natural menopause. Group 1: unadjusted RR 0.47 (no c.i.); adjusted RR* 0.75 Group 11: unadjusted RR 2,15 (no c.i.); adjusted RR* 3.1 Pooled estimate, 1.2 (p - 0.40) *adjusted for age at menopause		

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 2 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ross (1980)	Cases were white women diagnosed with breast cancer between 1971 and 1977, between 50 and 74 years of age, from two Los Angeles retirement communities. Two postmenopausal controls were selected for each case from the same community, matched for age, race, move-in date, and marital status. Estrogen use was ascertained from interviews, medical records, and pharmacy records.	138 cases of breast cancer, 281 controls	Estrogen use was defined as use beginning more than 4 months preceding diagnosis. All: 1.1 (0.8-1.9) Ovaries intact: 1.4 (0.7-2.4) Ovaries removed. 0.8 (0.5-3.5)	> 7 yrs.: 1.8 (test for trend. p = 0.02)	Total mg dose (TMD) (= daily dose x duration) No exposure (O TMD). ovaries intact. 1.0 ovaries removed: 1.0 all. 1.0 Low exposure (< 1.500 TMD): ovaries intact: 0.9 (0.4-1.7) ovaries removed: 0.9 (0.2-3.2) all: 0.8 (0.5-1 .5) High exposure (>= 1,500 TMD) (3 yrs. x 1.25 mg/d): ovaries intact: 2.5 (1 .2-5.6) ovaries removed: 0.7 (0.2-2.4) all: 1.9 (1 .0-3.3)
Hoover (1981)	Cases were all women with breast cancer identified from the tumor registry of Kaiser Foundation Health Plan of Portland, Oregon occurring from January 1969 to December 1975. Controls were drawn from 5% of a random sample of all members of the Kaiser Foundation Health Plan. Information was gathered from medical records. Average age of cases and controls was 57.	345 cases; 611 controls (69% estrogen users)	Ever use: 1.4 (1 .0-2.0) Natural menopause: 1.3 (0.8-2.1) Oophorectomized women. 1.5 (0.3-6.6)	Number of prescriptions noted, 0.1.00 1 : 1.1 2-4: 1.3 5-9. 1.8 > 10: 1.8 (test for trend: p = 0.013) Years between first and last prescription. none 1.00 <4, 1,4 >5, 1.7 (test for trend. D = 0.022)	Usual daily dose: nonuser: 1.00 < 1 .25mg, 1.4 > 1.25mg, 1.8 (test for trend. p = 0.005)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 3 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Hiatt (1 984)	Study subjects were identified from list of operations performed in all Northern California Kaiser Foundation Health Plan hospitals between 1953 and 1979. Cases were identified by hospital discharge records. Controls were chosen from women with same age, year of oophorectomy, and date of entry into health plan membership. Information was gathered from medical records.	119 cases, 119 controls (90% estrogen users)	RR 0.7 (0.3-1 .6)	Chart of notations of estrogen use >=5 yrs.: 2.1 (1 .2-3,6) Duration >= 3 yrs.: 1.8 (0.9-3.6)	Three or more years since first use, 0.8 (0.4-1.9)
Brinton (1986)	Subjects for the study were from a multicenter breast cancer screening program. Cases were white women who underwent natural or surgical menopause at least three months prior to the diagnosis of breast cancer; cases were diagnosed between 1973 and 1980. Controls were chosen from women who did not have biopsy during course of screening and were matched to the cases for race, age, time of entry, medical center and length of continuation in the program. Information was gathered through home interviews.	1,960 cases; 2,258 controls	1.03 (0.9-1.2)	<5 yrs.: 0.89 (0,8-1.0) 5-9 yrs.: 1.09 (0.9-1.3) 10-14 yrs.: 1.28 (0.9-1 .6) 15-19 yrs.: 1.24 (0.9-1 .8) 20+ yrs.: 1.47 (0.9-2.3) (test for trend: p < 0.01)	Premarin 0.3 mg: <10 yrs. use: 1.04(NS) 10+ yrs. use: 0.76(NS) total: 0.99 (0.7-1 .4) Premarin 0.625 mg: <10 yrs. use: 0.90(NS) 10+ yrs. use: 1.94 (p < 0.05) total: 1.05 (0.8-1 .3) Premarin 1.25 mg: <10 yrs. use: 0.94(NS) 10+ yrs. use: 1.13(NS) total. 1.02 (0.9-1.2) Premarin 2.5 mg: <10 yrs. use: 0.77(NS) 10+ yrs. use: 1.00(NS) total: 0.84 (0.5-1.4) Years since initial use: <1 o: 1.03 (0.9-1 .2) 10-14: 1,15 (0.9-1.4) 15-19: 0.95 (0.7-1.2) 20+: 0,97 (0.7-1 .2) (test for trend. p = 0.45)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 4 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
McDonald (1986)	Cases were white female residents of King County, Washington, ages 50 to 74, in whom breast cancer was diagnosed from July 1977 through August 1978, cases were identified from a cancer reporting system. Controls were white female residents of King County, 50 to 74 years old, without breast cancer. All cases and controls were interviewed.	183 cases, 531 controls	Estrogen use was defined as at least 1 yr. of estrogen use Overall. 0.74 (0.51 -1 .08) Natural menopause O 76 (0.46-1 .26) Hysterectomy with oophorectomy: 1.28 (0.43-3.80) "[S]ome variation In proportions was present between different hysterectomy-oophorectomy subgroups. However, each of these differences could easily have been due to chance "	1-5 yrs.: O 83 >6 yrs.: 0,68 (test for trend p = 0.06)	Never: 1.00 0.2-1.0 mg: 0.55 > 1.0 mg: 0,81 (test for trend. p = 0.22) Recency (time since last use): Never 1,00 current user or <= 5 yrs.: 0.75 >6 yrs.: 0.76 (test for trend. p = 0.14) Latency (time since first use). Never. 1.00 <10 yrs.: 0,73 > 10 yrs.: 0.74 (test for trend: p=O.11)
Hunt (1987)	Subjects were women, ages 45 to 54 receiving hormonal replacement therapy, recruited from 21 menopause clinics around Britain. Recruitment was both retrospective and prospective. Subjects were followed from 1978 to 1982. Two controls were selected for each case from cohort.	53 breast cancer cases, 106 controls		Adjusted' RR 12-30 months 1.0 (no c.i.) 31-48 months 48 (1 .5-156) 49-72 months 5.3 (1 .4-202) >73 months, 36 (0,9-1 5,0) *adjusted for uterine and ovarian status	

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 5 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Wingo (1 987)	CASH study, all subjects were postmenopausal women enrolled from eight different geographic areas in the United States. Cases were women 25 to 54 years old with cancer diagnosed between 1981 and 1982 and Identified through the SEER cancer registry. Controls were selected from the same geographical area by random digit dialing of residential telephone numbers. Information was gathered through interviews.	1,369 cases, 1,645 controls	Adjusted RR for users of more than 3 months versus nonusers. 1,0 (0,9-1.2) All women. 1.0 (0.9-1.2) ever users versus nonusers Hysterectomy and bilateral oophorectomy: ever users versus nonusers: 1.3 (0.9-1.9) Hysterectomy only ever users versus nonusers: 1.1 (0.8-1 .5) Natural menopause: ever users versus nonusers: 0.8 (0.6-1 .1)	All women < 1 year 1,0 (0,7-1 .3) 1-4 yrs.: 1.1 (0.8-1.3) 5-9 yrs.: 1.1 (0.8- 1.5) 10-14 yrs.: 0.8 (0.5-1.3) 15-19 yrs.: 1.3 (0.6-2.6) >20 yrs.: 1.8 (0.6-5.8) (test for trend. p = 0.7) Hysterectomy with bilateral oophorectomy. <1 year: 1,6 (0.9-2,8) 1-4 yrs.: 1.3 (0.9-2.0) 5-9 yrs.: 1.1 (0.7-1 .8) 10-14 yrs.: 1.5 (0.8-2.9) >15 yrs.: 1.7 (0,7-4,4) (test for trend: p = 0.9) Hysterectomy only. <1 year: 0.9 (0.6-1 .5) 1-4 yrs.: 1.1 (0.8-1 .6) 5-9 yrs.: 1.6 (1 .0-2.8) 10-14 yrs.: 0.6 (0.3-1 .2) >15 yrs.: 2.0 (O. 7-5.5) (test for trend: p = 0.7) Natural menopause. < 1 year: 0.8 (0.4-1 .4) 1-4 yrs.: 0.9 (0.6-1 .3) >5 yrs.: 0.7 (0.3-1.4) (test for trend. p = 0.6)	Dose (ever users compared with never users) (milligram-months): <25 1 1 (0,8-1 .5) 25-499. 1.3 (0.9-1.9) 50-749. 1.1 (0.7-1.8) 75-99 .9.1.9 (1.1 -3.3) > 100: 0.8 (0.6-1 .2) (test for trend p = 0.03) Recency (time since last use): <1 yr.: 1.0 (0.8-1.2) 1-4 yrs.: 1.2 (0.9-1 .6) 5-9 yrs.: 1.1 (0.8-1 .6) >10 yrs.: 1.0 (0.5-1 .8) (test for trend: p = 0.06) Latency (time since first use): All women: < 1 year: *0.9 (0.5-1.5)* 1-4 yrs.: 1.1 (0.8-1.4) 5-9 yrs.: 1.1 (0.8-1.4) 10-14 yrs.: 0.9 (0.7-1 .3) 15-19 yrs.: 1.1 (0.6-2.1) >20 yrs.: 1.7 (0,8-3,7) (test for trend: p = 0.8)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 6 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Ewertz (1 988)	Cases were pre- and postmenopausal women below 70 years of age diagnosed with breast cancer between 1983 and 1984, Identified from the files of a Danish clinical trial of breast cancer therapy and from a Danish cancer registry. Controls were a random sample of women from the general population, stratified for age, identified from a Danish population registry. Data were collected by mailed questionnaire.	1,484 cases (56.2% postmenopausal), 1,334 controls (58.9% postmenopausal)	Menopausal.' 1,16 (0.64-2.1 1) Post-menopausal" 1,28 (0.96-1 .71) Artificial menopause. 1.04 (0.69-1 .57) ● "menopausal" defined as natural menopause within 5 years of diagnosis **"postmenopausal" defined as natural menopause more than 5 years before diagnosis "Exposure to estrogen or progestagen, alone or in combination-type therapy, did not affect the breast cancer risk. Sequential therapy with oestrogen and progestagen ., was associated with an increased risk of borderline statistical significance (RR=1.36 (0.98-1 .87))."	Menopausal: <3 years, 1.08 (0,51 -2.27) 3-5 yrs.: 1.10 (0.38-3.21) 6+ yrs.: 1.57 (0.55-4.44) (test for trend: p = 0.44) Postmenopausal. <3 yrs.: 0,89 (0,56-1 .41) 3-5 yrs.: 0.93 (0.52-1 .68) 6-8 yrs.: 1.82 (0.98-3.37) 9-11 yrs.: 1.34 (0.70-2.54) 124 yrs.: 2.32 (1 .31 -4.12) (test for trend: p = 0.002) Artificial menopause: <3 yrs.: 1,01 (0.55-1 .85) 3-5 yrs.: 0.81 (0.39-1 .70) 6-8 yrs.: 1.52 (0.65-3.53) 9-11 yrs.: 1.44 (0.70-2.96) 12+ yrs.: 0.88 (0.48-1 ,64) (test for trend p > 0.5)	Recency (time since last use). Menopausal: <3 yrs.: 1,59 (0,80-3,16) 3+ yrs.: 0.53 (0.19-1 .45) Postmenopausal: <3 yrs.: 1.48 (1 .01 -2.15) 3-5 yrs.: 1.13 (0.56-2.30) 6-8 yrs.: 0.99 (0.52-1 .88) 9+ yrs.: 1.18 (0.68-2.02) Artificial menopause: <3 yrs.: 1.09 (0.70-1 .71) 3-5 yrs.: 0.57 (0.21-1 .51) 6-8 yrs.: 2.76 (0.73-10.5) 9+ yrs.: 0.91 (0.39-2.11) Latency (time since first uses): Menopausal: <6 yrs.: 1,84 (0,84-4,04) 6+ yrs.: 0.57 (0.25-1 .30) Postmenopausal: <6 yrs.: 0,95 (0.45-2,02) 6-8 yrs.: 1.10 (0.60-2.04) 9-11 yrs.: 103 (0.62-1 .73) 12+ yrs.: 1.74 (1.19-2 55) Artificial menopause. <6 yrs.: 1,07 (0,53-2.16) 6-8 yrs.: 1,48 (0.71-3.09) 9-11 yrs.: 127 (0.64-2 49) 12+ yrs.: 0.89 (0.52-1 .50)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 7 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Rohan (1988)	Cases were women from Adelaide, South Australia, with breast cancer reported to a cancer registry between 1982 and 1984, and who were 20 to 74 years old at the time of diagnosis. Controls were women from Adelaide with no history of breast cancer, identified from electoral rolls. Information was obtained through questionnaires. Reported here is information only on those women who were postmenopausal (no menses within 12 months or surgical menopause).	281 cases; 288 controls	Unadjusted RR 0.88 (0.57-1 .37) Adjusted RR .1.03 (0.62-1 .69) Women with bilateral oophorectomy: 0.30 (0.09-0.94) adjusted for age Natural menopause: 1.01 (0.69-1 ,47) adjusted for age * adjusted for years of educalion, practice of breast self-examination, history of breast cancer in first degree relative, age at last menstrual period, and history of bilateral oophorectomy	<24 me,, unadjusted, 1.02 (0,61-1 .72) adjusted: 0.99 (0.56-1 .76) >24 me,, unadjusted: 0.61 (0.29-1 .31) adjusted: 0.94 (0.40-2.21) A relatively small number of women used exogenous estrogens and only a minority reported relatively long durations of use	Recency (time since last use): <= 2 yrs.: unadjusted. 0.85 (0.32-2.25) adjusted. 1.25 (0.44-3.58) >2 yrs.: unadjusted, 0.90 (0.54-1 .48) adjusted: 0.88 (0.51 -1 .54) Latency (time since first use):<= 15 years since first use: unadjusted: 0.80 (0.44-1 .45) adjusted: 0.79 (0.41-1 ,55) >15 years, unadjusted: 1.10 (0.58-2.08) adjusted: 1.27 (0.63-2.54) > 15 years since first and estrogen therapy >=24 me.: 1.54 (0.43-5.45) Age at first use: <45 y.o.: unadjusted: 0.64 (0.31-1 .33) adjusted. 0.79 (0.35-1 .80) >45 y.o.: unadjusted: 1.12 (0.66-1 .92) adjusted. 1 12 (0.61-2.04)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 8 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use[a,b]	Relationship of breast cancer to duration of estrogen use[a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use[a,b]
Bergkvist (1989)	Women who had been prescribed estrogens for conditions related to the menopause were identified through records of the pharmacies in the health care region around Uppsala, Sweden. Recruitment began in April 1977 and ended in March 1980 and subjects were followed for an average of 6 years. Cases were women in the cohort who developed breast cancer. Controls were women with six months or less of estrogen use, were selected from the subcohort, and were matched for year of birth and year of inclusion into the cohort.	207 breast cancer cases (one to five controls matched to each case)		Adjusted O.R.: < 6 mo.: 1.0 7-36 mo.: 1.0 (0.6-1.6) 37-72 mo.: 1.2 (0.7-2.0) 73-108 mo.: 1.5 (0.8-2.9) > 109 mo.: 2.3 (1.1-4.8) (test for trend: p = 0.02) *Odds ratio was adjusted for education, previous breast biopsy for benign breast disease, and type of menopause.	
Folsom (1990)	86-1987). Cases were women with incident breast cancer. Controls were randomly selected participants in the survey.	229 cases; 1,839 controls	Estrogen replacement therapy use: <5 years: 86% of cases, 90% of controls >5 years: 14% of cases, 10% of controls No statistical analysis of the data was presented.		

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 9 of 10)

Author	Description of cases and controls	Number of oases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Palmer (1991)	Cases were women under age 70 who had breast cancer diagnosed more than six months before interview, identified at a major cancer treatment hospital in metropolitan Toronto between 1982 and 1986. Controls were identified from tax assessment rolls of all residents of Ontario. Two controls were matched to each case for age and neighborhood; 41 percent of cases and 42 percent of controls were pre- or postmenopausal. Cases and controls were interviewed in their homes.	607 breast cancer cases; 1,214 controls	Estrogens alone: 1.0 (0.7-1.3) Estrogen plus progesterone: 0.6 (0.2-2.0)	Conjugated estrogens. <1 yr.: 0.9 (0,5-1 .7) 1-4 yrs.: 0.7 (0.4-1 .3) 5-9 yrs.: 0.8 (0.4-1 .6) 10-14 yrs.: 0.6 (0.2-1 .8) >15 yrs.: 1.4 (0,6-3,3)	Recency (time since last use). Never: 1.0 <1 yr.: *0.4 (0.2-0,9)* *1-2* yrs.: 5.2 (2.0-13) 3-4 yrs.: 1.0 (0.3-3.1) 5-9 yrs.: 0.4 (0.2-1 .1) >10 yrs.: 0.8 (0.4-1.4) Latency (time since first use): Never: 1.0 Less than 5 yrs. total use and < 10 yrs. since first use. 0.8 (0.4-1 .5) 10-19 yrs.: 0.9 (0.5-1 .8) >20 yrs.: 0.5 (0.2-1 .6) Five or more years total use and < 10 yrs. since first use: 0.9 (0.3-2.5) 10-19 yrs.: 0.5 (0.2-1 .0) >20 yrs.: 2.1 (0,9-5.0)
Yang (1992)	Cases were all British Columbia women under 75 years of age who were diagnosed with breast cancer during 1988 and 1989. Controls were drawn from voter registration lists from the same province, and were matched with cases on the basis of age. Analysis included only postmenopausal women. Information was gathered by mailed questionnaire.	669 cases; 685 controls	O.R. 1.0 (0.8-1 .3) for ever use of unopposed estrogen O.R. 1.2 (0.6-2.2) for ever use of estrogen and progesterone	Long-term use (>= 10 years): O.R. 1.6 (1 .1-2.5)	Current use: O.R. 1.4 (1 .0-2.0)

TABLE F-2: HRT and Breast Cancer Risk (Population-Based Case-Control Studies) (Page 10 of 10)

Author	Description of cases and controls	Number of cases and controls	Relationship of breast cancer to estrogen use [a,b]	Relationship of breast cancer to duration of estrogen use [a,b]	Relationship of breast cancer to dose, recency, and latency of estrogen use [a,b]
Weinstein (1993)	Cases were female residents of Long Island, NY, aged 20 to 79, who were diagnosed with breast cancer from January 1984 to December 1986. Age- and county-matched controls were selected from driver's license files.	1,436 cases; 1,419 controls	There was no significant association between ever-use of HRT and breast cancer risk.	There was no significant association of risk with duration of use.	There was no significant association of HRT with recency of estrogen use. There was a significant increased risk of breast cancer in women with 10 to 19 years since first exposure.

[a] Unless otherwise specified, measured relationship is relative risk of breast cancer in HRT.
[b] 95% confidence interval is given in parentheses.

KEY: CI, = confidence interval; NS = not statistically significant; O R = odds ratio; RR = relative risk.

SOURCE: Office of Technology Assessment, 1995.

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 1 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Thomas (1982)	White women who were initially treated for biopsy-proven benign breast diseases from 1942 to 1975 in a single private surgery practice were followed through 1976 for development of breast cancer. Patients were followed up through letters, phone calls, clinic records, and death certificates. Average follow-up was 12,9 years.	1,439 women (66 cases breast cancer) (504 estrogen users)	Unadjusted RR 1.80 (1 ,04-3.10) adjusted RR 1.84 (1 ,05-3,23) There was no variance for age or year of first use.	No evidence was seen of an increased relative risk of breast cancer with increased duration of estrogen use.	
Bush (1983)	Participants were white women, aged 40 to 69 years at baseline, and followed for an average of 5.5 years. All women in the cohort were participants in the Lipid Research Clinics Program Follow-up Study, conducted in 10 North American Clinics between 1972 and 1976. All subjects were examined at initiation, and were followed with clinic visits and by review of death certificates. Information on decedents was gathered from medical records and family members.	2,270 white women (593 users, 1,677 nonusers)	Breast cancer deaths: users: O nonusers. 12 No statistical analysis of breast cancer deaths was provided.		
Petitti (1987)	Walnut Creek Contraceptive Drug Study; subjects were women aged 18 to 54 recruited from December 1968 to February 1972. All subjects received a history and physical exam at initiation and were followed by subsequent exam or questionnaire through 1977 Until the end of 1983, deaths were Identified through the California Death Index Users of oral contraceptives were excluded from this analysis.	3,437 women who never used oral contraceptives or estrogen; 2,656 women who had used estrogens, but not oral contraceptives	Risk of breast cancer death in users 0.8 (O 4-1.8) adjusted for age		

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 2 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Bergkvist (1989)	Women who had been prescribed estrogens for conditions related to the menopause were identified through records of the pharmacies in the health care region around Uppsala, Sweden. Recruitment began in April 1977 and ended in March 1980 and subjects were followed for an average of 6 years. Expected numbers of breast cancer cases were estimated according to incidence rates of breast cancer in the region. Median age of women in the cohort was 53.7 at time of inclusion into study. Information was gathered by mailed questionnaire from a subcohort of 1 in 30 women randomly chosen from the cohort.	23,224 women age 35 and older who had filled at least one prescription for estrogen; 253 breast cancer cases	RR 11 (1 .0-1 .3) Study suggested there was no protection from the addition of progesterone.	All HRT users. <6 mos.: *0,7 (0,4-1 .0)* 7-36 mos.: 1.1 (0.9-1 .4) 37-72 mos.: 1.0 (0,8-1 .4) 73-108 mos: 1.3 (0.9-1 .9) > 109 mos,: 1.7 (1,1 -2,7) estrogen only. <6 mos,: 0.8 (0,5-1 ,4) 7-36 mos.: 1.1 (0.8-1 .5) 37-72 mos.: 0.9 (0.6-1 .3) 73-108 mos.: 0.9 (0.5-1 .6) >109 mos,. 1,8 (1 ,0-3.1) estrogen plus progesterone.' <6 mos.. 0.5 (0,2-1 .8) 7-36 mos.: 0.7 (0.3-1 .3) 37-72 mos.: 0.9 (0.3-2.6) 73-108 mos,: 4.4 (0,9-22.4) >109 mos,: (no estimate)	

*Only a small number of women received combination therapy, so confidence Intervals are wide

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 3 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Mills (1989)	Subjects were white Seventh-Day Adventist women, residing in California, who completed a questionnaire and who were followed for 6 years, from 1976 and 1982. Mean age of cohort in 1976 was 55,4 years. Information was gathered from annual questionnaires, tumor registries and for cases, from medical records.	20,341 women in cohort (80% postmenopausal at study initiation) (66% ever users of HRT); 215 cases of breast cancer	Unadjusted RR 1.67 (1.1 7-2.39) adjusted RR' 1.39 (1 ,00-1 .94) *adjusted for age, ages at menarche, first birth, and menopause, Quetelet's Index, maternal breast cancer, and a history of previous benign breast disease natural menopause: 1.74 (1 .10-2,74) hysterectomy, 1.30 (0.78-2.18)	*<1 yr.: 2,28* (1 .38-3.79) 1-5 yrs.: 1.56 (0.95-2.56) 6-10 yrs.: 2.75 (1.64-4.64) 10+ yrs.: 1.53 (0.92-2.54) There was no strong increase in risk with duration of HRT.	*<1 yr,: 2.28* (1 .38-3.79) 1-5 yrs.. 1.56 (0.95-2.56) 6-10 yrs.. 2.75 (1 .64-4.64) 10+ yrs.. 1.53 (0.92-2.54) There was no strong increase in risk with duration of HRT.

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 4 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Colditz (1 990)	Female registered nurses 30 to 55 years of age completed a mailed questionnaire. Follow-up questionnaires were mailed every 2 years. Data were gathered between 1976 and 1986. Only those RNs that were postmenopausal are included in these results.	23,607 postmenopausal female registered nurses; 722 cases of breast cancer	Current use: 1.40 (1 ,16-1 .67)	Current users: 1-11 mos.: 1,28 (0.8-2.1) 12-23 mos.: 1,32 (0.8-2.2) 24-35 mos.: 1.44 (0.9-2.2) 36-59 mos.. 1.26 (0.9-1 .9) 60-119 mos.. 1.62 (1 .2-2,1) 120-179 mos.: 1.28 (0.8-2.0) >180 mos,: 1,19 (0,6-2.2) past users: 1-11 mos.: 1.00 (0.7-1 .4) 12-23 mos.: 1.05 (0.7-1 .5) 24-35 mos.: 0.65 (0.4-1 .1) 36-59 mos.. 1.02 (0.7-1 .5) 60-119 mos.: 1.05 (0.7-1 .5) 120-179 mos.: 0.92 (0.5-1.7) >180 mos.: 0,79 (0,3-2.5)	Current users 0.3 mg/d:1 .55 (1 .0-2.5) 0.625 mg/d: 1.42 (1 .0-1 .9) 1,25 mg/d:1.48 (1 .0-2.2) <1,25 mg/d: *2.27* (1 .0-5,3) Trend with increasing dosage was not significant (test for trend: p = 0.56). current use. 1.40 (1 .16-1 .67) past use. 0.99 (0.82-1.19) time since last use: current 1.36 (1.1 1-1 ,67) 1-11 mos.. 1.62 (0.98-2.67) 12-35 mos.. 1.09 (0.79-1 .50) 36-59 mos.: 0.89 (0.60-1 .31) 60-119 mos.. 0.93 (079-1 .47) > 120 mos. 0,70 (0.45-1 .10)

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 5 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Henderson (1991)	Prospective study of postmenopausal female residents of Leisure World Retirement Community in Southern California. Residents are predominantly white, moderately affluent, and well-educated. Median age of cohort was 73 at study initiation. Study was initiated in 1981, average follow-up is 7.5 years. Information was gathered through mailed questionnaires and death registries.	8,881 postmenopausal women (the number of deaths from breast cancer was not specified in report) (57% ever estrogen users)	RR 0,81 (c. I. not reported) for breast cancer deaths in ever users versus never users of estrogen	After adjusting for age, there was no evidence of increased risk with increasing duration of use among current users (test for trend: p =0.41) or past users (test for trend p = 0.46).	Breast cancer incidence current use. RR 1.33 (1,1 2-1 ,57) adjusted for age past use: RR 0.90 (0.77-1 .04) adjusted for age
Colditz (1 992)	Subjects were female registered O nurses 30 to 55 years of age 1976. Reported here are results of 12 years of follow-up. Data was obtained by questionnaires mailed every two years, cases of breast cancer were confirmed by review of pathology reports and hospital records.	480,665 person-years of follow-up, 1,050 incident cases of breast cancer	Ever use 1.08 (0.96-1 .22) adjusted for age current use of hormones: 1.33 (1 .12-1 .57) adjusted for age current use of unopposed estrogen: 1,42 (1.1 9-1 .70) current use of estrogen and progesterone: 1.54 (0.99-2.39) current use of progesterone alone: 2.52 (0.66-9.63) current use of conjugated estrogens 1,42 (1 .19-1 .20) current use of estrogen/ progestin 1.54 (0.99-2.39) current use of estrogen/ testosterone 2.45 (0.95-6.35)		

TABLE F-3: HRT and Breast Cancer (Cohort Studies) with Internal Controls (Page 6 of 6)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Schairer (1994)	Subjects were participants in the Breast Cancer Detection Demonstration Project, a breast cancer screening program conducted between 1973 and 1980. (The analysis reported here included all women who did not have a menses for at least 3 months prior to an interview. Reported here is followup through 1989). Information was collected by telephone interviews mailed questionnaires, and pathology reports. Average age at start of followup was 57.4 years. Mean duration of followup was 6,2 years.	**49,017** (1,185 breast cancer cases) (46.2 of person-years in study involved ERT, 6% with combined PERT)		Current ERT users: 1.3 (1 .1-1 .5) past users: 0.9 (0,8-1 .1) Current PERT users: 1.2 (0.9-1 .6) past users: 1.4 (1 .0-2.0) estrogen alone: 1.0 (0.9-1 .2) estrogen and progestin. 1.2 (1 ,0-1 .6) in situ tumors only: estrogen alone: 1.4 (1 ,0-2.0) estrogen and progestin. 2.3 (1.3-3.9) no significant association of ERT or PERT with invasive tumors duration of use: There was no significant association of use of ERT with duration of use. However, risk of in situ breast cancer rose with increasing duration of use, with users of 10 years or more having about twice the risk as non users (test for trend, p= 0.02). There was no clear pattern of risk associated with duration of use for PERT users, either for all cancers, in situ cancers or invasive tumors.	

[a]Unless otherwise specified, measured relationships relative risk of breast cancer in HRT
b 95 % confidence interval is given in parentheses.

KEY: c.i. = confidence interval; O.E. ratio = observed to expected ratio: OR = odds ratio; NS = not statistically significant; RR = relative risk

SOURCE: Office of Technology Assessment, 1995

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 1 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Burch (1 974)	Subjects were hysterectomized women on estrogen replacement therapy, followed for an average of 14.32 years. Expected number of deaths from U.S. Public Health Service cancer morbidity statistics.	1,000 hysterectomized women	Observed breast cancer cases. 33, expected. 23.7 observed breast cancer deaths: 6: expected: 7,85 No statistical analysis of the data was presented.		
Hoover (1976)	The medical records of all white women seen in one private practice in Louisville, KY, from 1939 to 1972, were reviewed. Expected rates for the general population were obtained from Second and Third National Cancer Surveys. Average age of women in the cohort was 49 years. Mean follow-up was 12 years.	1,891 women in cohort; 49 cases of breast cancer developed	RR 1.3 (1 .0-1 .7)	<5 yrs.: 0.9 (0,5-1 .5) 5-9 yrs.: 1.2 (0.6-2.0) 10-14 yrs.: 1.3 (0.6-2.4) 15+ yrs,: 2.0 (1,1 -3.4) Trend of greater risk with increased duration is statistically significant (p= 0.02). A finer breakdown of the follow-up duration after 10 years indicated that the excess becomes manifest after about 12 years of estrogen use. 10-12 yrs.: 1.2 (no c.i.) 13-16 yrs.: 1.9 17-24 yrs.: 2.0	"The increased risk associated with stronger medication and non-daily regimens are based on small numbers but are statistically significant. " 10+ years follow-up. 0.3 mg: 1.6 (0.9-2.7) 0.625 mg. 1.1 (0.5-2.0) >0,625 mg: 2.7(1 ,2-5.3) There was no statistically significant increase in breast cancer risk with less than 10 years followup.

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 2 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk [a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Hammond (1979)	Subject had been followed at least 5 years at Duke University Medical Center, Durham, NC, with diagnoses associated with a hypo-estrogenic state (e.g., premature ovarian failure or pituitary tumor). Information was gathered retrospectively from medical records, and in some cases from referring physicians, patients, or death certificates. Subjects were divided into two groups. those who never received estrogen and those who received estrogen for longer than 5 years. (Those estrogen users for 5 years or less were excluded.) The observed incidence of breast cancer was compared to age and race-specific incidence rates from the Third National Cancer Survey (southeast United States).	301 patients treated with estrogen and 309 untreated patients	Estrogen users. O.E. ratio 1.06 (O 3-2.7) for whites No breast cancers occurred in nonwhite estrogen users. nonusers of estrogen O.E. ratio 0.5 (O.1-1.5) for whites O.E. ratio 0.5 (0.0-2.9) for nonwhites		
Gambrell (1983)	Subjects were women from Wilford Hall USAF Medical Center in San Antonio, Texas who received various forms of hormonal therapy. Patients with a diagnosis of breast cancer between 1975 through 1981 were identified from a tumor registry. Expected values were obtained from the Third National Cancer Survey (1975) and the National Cancer Institute Surveillance, Epidemiology, End Result (SEER) data (1980). Information was gathered from mailed questionnaires, clinic and hospital records, and registries.	5,563 women; 53 cases of breast cancer	Estrogen plus progesterone O 3 (0.1-0.8) estrogen only. 0.7 (0.5-1.1) estrogen vaginal cream: 0.4 (0.2-1 .6) progesterone or androgen users. 0.7 (0.3-1.5) untreated women 1,4 (1 .1-1 9) This study was criticized for falling to control for confounding functions, including age,		

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (P

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Vakil (1983)	Incidence of breast cancer in a cohort of women, 32 to 62 years of age, receiving estrogen treatment for menopausal symptoms among the patients of 20 gynecologists in the metropolitan Toronto area was compared to two control groups: the age-specific breast cancer incidence rates of the female populations of Ontario and of Saskatchewan. Estrogen therapy was begun between 1960 and 1970 and subjects were followed up to 17 years. Information was gathered from gynecologists and cancer and death registries.	1,483 menopausal women	Standard mortality ratio for breast cancer. 0.48 (p < 0,01) compared with Ontario controls, 0.45 (p< 0.01) compared with Saskatchewan controls standard incidence ratio of breast cancer. 0.62 (p < 0,01) compared with Ontario controls; 0.70 (p < 0.01) compared with Saskatchewan controls		
Hunt (1987)	Subjects were women receiving hormonal replacement therapy, recruited from 21 menopause clinics around Britain. Subjects were followed from 1978 to 1982. Most women were 45 to 54 years of age at time of recruitment. Subjects were recruited both retrospectively and prospectively. Expected numbers were obtained from cancer registry roles. All patients were interviewed at study initiation. Deaths were reported from central registries.	*4,544* women; 503 cases of breast cancer	O.E. ratio breast cancer incidence 1.59 (1 18-2,10) hysterectomy only O.E. ratio 3.08 hysterectomy and oophorectomy O.E. ratio 166 natural menopause. O.E ratio 1.19	There was no significant increase in incidence with increasing duration of estrogen use	Interval since first use of HRT: O-4 years. O.E. ratio 1.40 (0.85-2.46) 5-9 years. O.E. ratio 1.45 (0.88-2.24) 10+ years O.E. ratio 3.07 (1 .47-5.64) There was evidence of a trend in ratio with interval since first use (test for trend. p = 0.08).

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 4 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Dupont 1989)	Study subjects were women who underwent biopsy for benign breast disease at three Nashville hospitals between 1950 and 1968. Median duration of follow-up is 17 years. Reference population consisted of white women from Atlanta who participated in the Third National Cancer Survey. Ninety percent of study subjects were either postmenopausal or were at least 50 years old by the end of their follow-up. Information was gathered from clinic and hospital records, questionnaires, and death certificates.	10,366 biopsies evaluated; follow-up information obtained on 3,303 women; 35 cases of breast cancer	RR 0.98 (no c.i. reported)	Breast cancer risk was not elevated in women who took estrogens for more than five years."	
Hunt (1990)	Breast cancer death rates in women recruited from 21 menopause clinics in Britain and who had taken at least one year's continuous HRT at the time of recruitment to the study were compared with age-specific death rates in the female population in England and Wales. Subjects were recruited both retrospectively and prospectively. Subjects were followed from 1978 to December 1988. Most women were age 45 to 54 years of age at time of recruitment. All subjects were interviewed at study initiation. Deaths were reported from central registries.	4,544 women in cohort; 31 breast cancer deaths	Breast cancer death: all women: O.E. ratio 1.00 (0.55-1.45) hysterectomy only: O.E. ratio 0.74 hysterectomy and oophorectomy: O.E. ratio 0.82 natural menopause: O.E. ratio 0.74		Deaths from breast cancer by years since first exposure (O.E. ratio): 0-4 years: 0.38 (0.00-1.07) 5-9 years: 0.74 (0.27-1.21) 10+ years: 0.97 (0.47-1.47) (test for trend: NS)

TABLE F-4: HRT and Breast Cancer (Cohort Studies) with External Controls (Page 5 of 5)

Author	Description of study	Number of study subjects	Relationship of estrogen use to breast cancer risk	Relationship of duration of estrogen use to breast cancer risk[a,b]	Relationship of dose, recency, and latency of estrogen to breast cancer risk[a,b]
Risch (1 994)	Subjects were women ages 43 to 49 years of age in 1976, resident in Saskatchewan, Canada, who were identified for the master file of the government health Insurance plan that covers virtually all residents of the province. These women's health plan registration number was used to obtain their prescription records form the plan's pharmacy database for the period from January 1976 to June 1987, The women's health plan registration number allowed the investigators to Iink the women's pharmacy records to the Saskatchewan Provincial Cancer Registry. Thirty-one percent of the cohort used in opposed estrogens (mostly conjugated estrogens), 2,07 percent used opposed estrogens, Estrogen use was defined as use of 3.5 years or more.	32,790 women(742 breast cancer cases)	Unopposed estrogen 1,33 (1.1 1-1 ,59) both opposed and unopposed estrogen 1.10 (O *35-O 42)* No breast cancer cases occurred among the 171 subjects who used opposed estrogens progestins (both alone or combined with estrogen) 0,93 (0.51 -1 68)	For unopposed estrogen, risk increased by 7 percent for each 252 tablets prescribed (approximately I year of use) (RR 1072 (1 02-1.13) For opposed estrogens, there was no significant increase in risk for each 252 tablets prescribed (RR 1,211 (0.72-2.05). For unopposed progestins, there was no significant increase in risk for each 84 tablets prescribed (equal to seven tablets per month for 12 months) (RR 1,0003 (O 80-1 25)).	Unopposed estrogens, 1 to 126 tablets/yr. 1,039 (O 78-1 38) 127-378 tablets/yr 1,161 (0,83-1 63) 379-756 tablets/yr 1,041 (0,66-1 63) >757 tablets/yr 1.498 (1 ,05-2,13)

[a]Unless otherwise specified, measured relationships relative risk of breast cancer in HRT
b 95% confidence Interval is given in parentheses

KEY: c.i. = confidence internal; NS = not statistically **significant; O.E.** ratio = **observed to** expected ratio; O.R. = odd ratio; RR = relative risk

SOURCE: Office of Technology Assessment, 1995