Appendix G: Evidence on HRT and Endometrial Cancer

G

Endometrial cancer, the most common gynecologic cancer, occurs in about one woman out of 1,000 in the population each year (15). An average 50-year-old white woman has a 2.6 percent lifetime risk of endometrial cancer (l). And about eight out of every 100 women diagnosed with endometrial cancer die of this disease (l). Evidence that estrogen replacement therapy increases the risk of endometrial cancer is well established and is consistent with a variety of observations.

The relationship of endometrial cancer with use of estrogen replacement therapy is consistent with trends in the incidence of endometrial cancer. In the United States, there was a dramatic increase in prescriptions for estrogen replacement therapy between the mid- 1960s and the early 1970s (47). Estrogen was usually prescribed alone, without a progestin, and was given for three weeks out of a four-week cycle. A rise in incidence of endometrial cancer coincided with this increase in prescriptions for estrogen. By 1976, the first case-control studies were published that revealed significant increases in risk of endometrial cancer in estrogen users compared with nonusers (57,73, 92). After these reports, sales of estrogen replacement therapy began to drop, as did endometrial cancer rates (47). Since 1980, prescriptions for estrogen replacement therapy have been on the rebound as physicians have been prescribing progestins in sequence with estrogens to prevent estrogen from inducing endometrial hyperplasia (19,47).

Obesity and other conditions associated with a high level of endogenous estrogens are associated with an increased risk of endometrial cancer, so it is not surprising that estrogen replacement therapy also increases the risk of endometrial cancer (7).

The increase in endometrial cancer with estrogen replacement therapy is also physiologically plausible, and is consistent with observations about the relationship of estrogen to the endometrium. Estrogen is a growth hormone for the endometrial tissue lining the inside of the uterus. In premenopausal women, estrogen levels begin to rise at the beginning of the monthly menstrual cycle, and progesterone levels increase near the end of the cycle, causing the endometrial tissue to mature. In the absence of implantation of a fertilized egg into the endometrium, estrogen and progesterone levels fall and the endometrial tissue is sloughed off, resulting in menstruation.

If estrogen stimulation continues unopposed by progesterone, the endometrium continues to grow, producing hyperplasia, or overgrowth of the

endometrium (19). Hyperplasia has been shown to advance to carcinoma in situ, and eventually to endometrial cancer (31,52,63). This progression has been observed in patients with diseases characterized by excessive unopposed estrogen secretion, such as Stein-Leventhal Syndrome (74), estrogen-producing tumors (32), and certain types of infertility (69). Progestins have been shown to produce maturation of estrogen-primed endometrium and regression of hyperplastic tissue to normal endometrium (79). It has even led to regression of some well-differentiated carcinomas in some patients (24,67).

Numerous case-control and cohort studies have documented an increase in endometrial cancer with use of estrogens. These are presented in tables G-1 to G-4 at the end of this appendix.

Up to 20-fold increases in risk of endometrial cancer have been detected in case-control studies of estrogen replacement therapy. (See tables G-1 and G-2.) Among case-control studies, relative risks are generally lower in hospital-based case-control studies that use as controls women with gynecologic problems, probably because uterine bleeding is one of the most common gynecologic problems and estrogen commonly causes this symptom (28). Relative risks are generally higher in population-based case-control studies and hospital-based case-control studies that use as controls women without gynecologic problems, in part because surveillance for endometrial cancer is increased among women taking estrogen (28).

DURATION AND DOSE OF ESTROGEN

Studies of the relationship of endometrial cancer to duration of estrogen replacement therapy indicate that significant increases in risk of endometrial cancer can be detected in as little as six months to one year after initiation of estrogen replacement therapy (4,58,72,75,92). Epidemiologic studies have shown that the risk of endometrial cancer increases with increased duration of use. (See tables G-1 to G-4.) For 10 or fewer years of use, the risk ranges from no significant increase to a 36-fold increase in risk. For more than 10 years of use, the increase in risk has been estimated to be as little as 2.6 to as great as 63.

The risk of endometrial cancer has been shown to be related to dose of estrogen. (See tables G-1 to G-4.) Hence, the minimum effective dose to maintain bone mineral density and to relieve postmenopausal symptoms is commonly prescribed. (See appendix E.)

RECENCY OF USE OF ESTROGEN

The risk of endometrial cancer decreases after cessation of therapy. Some studies have reported that risks of endometrial cancer returned to levels of nonusers after only six months to two years (40, 57), while others have found the increase in risk to persist for up to 15 years after estrogen replacement therapy is stopped (8,62,70,72). The data comparing the trends of estrogen prescription volume with endometrial cancer incidence are more consistent with a short time interval between cessation of estrogen replacement therapy and decline in endometrial cancer risk (5).

STAGE AND GRADE OF ENDOMETRIAL CANCER

Endometrial cancer arising in estrogen users is of lower stage and grade and much less likely to result in death than endometrial cancer arising in nonusers of estrogen. A number of case-control studies have consistently found a lower stage and grade of endometrial cancer in estrogen users. (See table G-3.) Virtually all endometrial cancers in estrogen users are diagnosed before they have spread beyond the uterus. In cases where endometrial cancer has not spread beyond the uterus, hysterectomy is usually curative. The survival among estrogen users diagnosed with endometrial cancer is favorable (12). Barrett-Connor reported that women not on estrogen survive less well than women with endometrial cancer taking estrogen (6). Furthermore, there was little evidence that mortality from endometrial cancer increased during the period of rising incidence of the disease from estrogen use in the population (47).

However, some users of estrogen replacement therapy do develop cancers that have spread beyond the uterus (Stage III and Stage IV) (23, 70, 72), and some estrogen users die of this complication (18,57,62).

There are several factors that may account for this relatively favorable prognosis. First, the lower stage and grade of endometrial cancer in estrogen users may be due to detection bias. Estrogen users are closely monitored with endometrial biopsies annually and at times of irregular bleeding. Vaginal bleeding is an early symptom of endometrial cancer, and women taking estrogen replacement therapy may bleed earlier and be biopsied earlier than women receiving less regular medical care (7,56). The favorable stage and grade may also be due in part to case ascertainment — the detection of occult cancers in the endometrium of users who bleed because they are taking estrogen (38). The apparently favorable survival experience of user cases is also likely due in part to patients with estrogen-induced benign hyperplasia mislabeled as cases (56). Bias may also be introduced by a greater likelihood of estrogen treatment in women who have menopausal problems associated with unsuspected cancer or a greater likelihood of cancer (56).

The lower stage and grade of estrogen-induced tumors may be because these tumors are more benign than tumors that arise in the absence of estrogen. Estrogen-induced endometrial cancers may be better differentiated and slower growing than endometrial cancers that arise in the absence of inducement by exogenous estrogen.

Estrogen-induced irregular bleeding, hyperplasia, and localized cancers of the endometrium result in an increased prevalence of hysterectomy among estrogen users (20). Thus, even though the endometrial bleeding, hyperplasia, and cancers associated with estrogen use do not substantially increase mortality, they do contribute to medical costs associated with estrogen replacement therapy **(15).**

Weiss and colleagues were among the first to suggest that endometrial cancers that arise in women taking estrogen replacement are on average less aggressive than those that arise in women who have not taken estrogen replacement (82). The author reviewed five case-control studies examining the association between prior postmenopausal estrogen use and endometrial cancer prognosis. They found that, although estrogen use is associated with an increased risk of endometrial cancer, that association tended to weaken when only invasive and high-grade tumors are considered. The authors explained that one possible reason for this finding was that tumors that arise in the presence of exogenous estrogens are on average less aggressive than those that arise in their absence. Another possible explanation, they noted, was detection bias, that endometrial cancer in estrogen users may be detected earlier than in nonusers of estrogen. This may be because estrogen users may tend to seek care more promptly than nonusers, their access to medical care may be greater, or the physicians of estrogens may detect endometrial cancers early because they are particularly wary of the development of these cancers in their patients on estrogen.

A third possible explanation, according to the authors, is overdiagnosis of endometrial cancer in estrogen users. Because the histological criteria for separating the more advanced cases of endometrial hyperplasia are ambiguous, some cases of estrogen-related advanced hyperplasia are being incorrectly labeled as early endometrial cancer, giving rise to a false association of estrogen use with low-grade, low-stage cancers.

Deligdisch and Holinka have provided additional evidence that patients known to be at increased risk of endometrial cancer due to exposure to estrogen are likely to develop better differentiated and less aggressive forms of cancer (16). The researchers examined the cellular characteristics of the tumors of 95 patients with Stage I endometrial cancer. Noting that endometrial hyperplasia is excessive growth of endometrial tissue caused by estrogen stimulation, they found that endometrial cancers with hyperplasia were better differentiated and less invasive than endometrial cancers without hyperplasia.

ESTROGEN USE AND SURVIVAL FROM ENDOMETRIAL CANCER

Epidemiologic studies have consistently found that, among postmenopausal women diagnosed with endometrial cancer, estrogen users have markedly better survival than never users of estrogen.

Robboy et al. concluded that survival differences between estrogen users and nonusers was due to differences in grade of tumor at diagnosis (68). The authors identified 274 women treated for endometrial cancer at the Massachusetts General Hospital between 1940 and 1971. Pathological specimens for each woman were examined to confirm the diagnosis of endometrial cancer. Hospital and clinic records were available for 190 of these women, and were reviewed for a history of postmenopausal estrogen use. They found that 85 percent of the 274 patients with endometrial cancer were stage I at diagnosis, and 7 percent were stage II, with no significant difference in stage at diagnosis between estrogen users and nonusers. However, the tumors that developed in estrogen users were significantly more differentiated than those that developed in nonusers (p less than 0.05). Five- and 10-year survival was also significantly better in users than in nonusers, but survival in users and nonusers was not significantly different once adjusted for differences in grade of tumor.

The authors did not rule out that their findings could be explained by earlier detection in estrogen users because of better endometrial cancer surveillance. This explanation was supported by the fact that the average age of estrogen users at diagnosis was four years less than nonusers (56 versus 60 years of age, p less than 0.02).

Elwood et al. concluded that survival differences between estrogen users and nonusers is almost entirely due to differences in the stage and grade of endometrial cancers at diagnosis (1 8). Elwood et al. studied 494 women seen at a Vancouver clinic between 1968 and 1972 for treatment of newly diagnosed endometrial cancer. All patients were followed until death or to 1975. Information on estrogen use was based on both the patient's history and the response of the family physician to a letter requesting more detailed information. The investigators compared the stage and grade of endometrial cancer in ever users of CEE to never users of postmenopausal estrogens. Only 8 percent of CEE users had Stage H or III cancers at diagnosis, compared with 16 percent of nonusers. And 43 percent of tumors in CEE users were well differentiated, compared with 29 percent of nonusers.

The 5-year survival rate, after adjustment for age, was 94.2 percent in ever users of CEE and was 81.3 percent in nonusers, a difference that was highly significant ($p = 0.001$). When differences in stage were taken into account, survival was not significantly different between the two groups.

Collins et al. studied endometrial cancer stage, grade, and survival in 860 women referred to a London, Ontario cancer clinic between 1967 and 1976 (13). Information on prior estrogen use was obtained through a questionnaire. About one third of the patients had a history of estrogen use, defined as use of estrogen for 6 months or more before diagnosis.

At all stages of endometrial cancer, estrogen users had a significantly greater 5-year survival than nonusers. The researchers found that, after adjusting for a number of risk factors for mortality, endometrial cancer patients with no history of prior estrogen use had a 5.4 times greater risk of death from cancer than endometrial cancer patients with a history of prior estrogen use.

The authors posited that endometrial cancer patients with a history of estrogen use had higher survival rates because cancers associated with prior estrogen use are less aggressive tumors. The authors, however, did not rule out the possibility that selection or surveillance bias may have confounded their findings.

In a study of 379 white women ages 50 to 74 from King County, Washington, with newly diagnosed endometrial cancer, Chu and colleagues concluded that although the use of postmenopausal estrogen leads to an increased risk of endometrial cancer, there is no increased risk of endometrial cancer death in postmenopausal estrogen users (12). The authors obtained information on

cases of endometrial cancer diagnosed between January 1975 and April 1976 from the Cancer Surveillance Center, a population-based registry serving western Washington State. Additional information was obtained from interviews of the patient's physician. Information on estrogen use, medical and reproductive history, and risk factors for endometrial cancer was obtained by interviewing the patient; for the 12 percent of study participants who could not be interviewed, this information was obtained by reviewing the medical records of primary care physicians. Fully 98 percent of estrogen users (defined as use of estrogen for one or more years after menopause) had tumors stage O or I at diagnosis, compared with 88 percent of nonusers. Only 2 percent of estrogen users had stage II or III cancers at diagnosis, compared to 12 percent in nonusers, a difference that was statistically significant.

Estrogen users with endometrial cancer had a small but significantly better four-year survival rate than women of the same age in the general population, as calculated from Washington state life tables for white women (relative survival ratio 1.05 (1.04-1.06)). Estrogen users with endometrial cancer also had a significantly better four-year survival than nonusers with endometrial cancer, the latter group having a relative survival ratio of 0.89 (0.80-0.99) compared with women of the same age.

The authors stated that the possibility that these results were due to self selection or detection bias could not be ruled out. They also mentioned that other factors that may confound the interpretation of their results include differences in follow-up between estrogen users and nonusers, differences in cancer therapy between estrogen users and nonusers. They also noted that the interpretation of results may be limited by the relatively short (four-year) follow-up period.

ESTROGEN/PROGESTIN REPLACEMENT THERAPY

Because even a relatively benign cancer is an unacceptable complication, most physicians add a progestin to suppress endometrial hyperplasia (16). There is substantial evidence that women who take progestins with estrogen are at no increased risk of developing endometrial cancer compared with postmenopausal women who do not take estrogen.

Until recently, only large-scale cross-sectional studies were available on the effect of combined estrogen and progestin therapy on endometrial cancer risk, and these studies showed that the combination reduced the incidence of endometrial cancer to below that of an untreated population (25). A number of prospective studies have shown that the incidence of endometrial cancer is increased with unopposed estrogen replacement therapy, but not with combined estrogen and progestin therapy (25, 64).

Persson et al. examined the incidence of endometrial cancer in hormone replacement therapy (HRT) in the Uppsala health care region, which serves one-sixth of the population of Sweden (64). Using the region's prescription database, he was able to identify 23,244 women over age 35 who filled one or more prescriptions for HRT between April 1977 and March 1980. Women from the cohort who developed endometrial cancer were identified from the region's cancer registry. Information on lifetime exposures to estrogen and progestin, compliance, and sociodemographic data were obtained on 735 randomly selected members of the cohort. Comparison was made to women in the general background population.

A relatively high proportion of the HRT users in this cohort were receiving progestin and estrogen replacement therapy (PERT), allowing comparison to be made with estrogen replacement therapy (ERT) (64). The investigators found that, while users of ERT has a significantly increased risk of endometrial cancer (relative risk 1.8 (95 percent confidence interval 1.1 to 3.2) after exposure to any estrogen for 6 years), users of PERT were at no increased risk (relative risk 0.9 (95 percent confidence interval 0.4 to 2.0)).

However, for some of the less androgenic progestins (such as medroxyprogesterone acetate (Provera), the most commonly used progestin in the United States), and in the regimens and lower

doses commonly used today, there are insufficient studies with endometrial cancer as an endpoint; most studies of efficacy look at an intermediate endpoint, such as reversal of endometrial hyperplasia. Medroxyprogesterone acetate, in a dose of 10 mg for 12 days, is the least androgenic regimen that has been best documented to prevent hyperplasia (63,85).

Although courses of medroxyprogesterone acetate of fewer than 12 days have been shown to reduce the incidence of estrogen-induced endometrial hyperplasia (86), the minimum duration to reduce the incidence to zero is 12 days per month (64,78,87).

Some clinicians prefer a lower dose, 2.5 or 5 mg, of medroxyprogesterone acetate. These smaller doses are often given concurrently with estrogen throughout the month (7,84). A continuous low-dose regimen avoids the withdrawal bleeding of cyclic progestin, which may lead to poor compliance. In addition, these lower doses are less likely to induce premenstrual-type symptoms associated with progestins Long-term data on the ability of continuous low-dose progestin to protect the endometrium overtime is limited (85). Additional data is also needed on the effects of these treatments on lipids, lipoproteins, and other metabolic parameters (11).

One recent case-control study provides evidence that menopausal women taking estrogen replacement therapy can significantly reduce their risk of endometrial cancer if they also take medroxyprogesterone (45). The study examined women between the ages of 50 and 64 who were treated from 1979 to 1989 at Group Health, a Seattle, Washington health maintenance organization. Researchers identified 172 cases of endometrial cancer and compared use of hormones in these women with that of 1,720 women who did not have cancer. Users of combined therapy used medroxyprogesterone acetate, 10 mg per day, most for 10 days each month.

Current users of estrogen alone had a relative risk of endometrial cancer of 6.5 (95 percent confidence interval 3.1 to 13.3), whereas current users of estrogen and progesterone had a relative risk of 1.9 (95 percent confidence interval 0.4 to 8.7). Past users of estrogen alone or estrogen and progestin had no increased risk of endometrial cancer. The study found that users of estrogens for three to four years had a relative risk of 1.9 (95 percent confidence interval 0.4 to 8.7), and that users of five years or more had a relative risk of 22 (95 percent confidence interval 1.5 to 24.1). Users of estrogen and progestin for more than three years had a relative risk of 1.3 (95 percent confidence interval 0.5 to 3.4). The researchers concluded that there does not appear to be any substantial increase in risk associated with combined use with increasing duration of therapy. The researchers cautioned, however, that there were relatively few women who used combined therapy for more than five years.

A number of clinical trials have demonstrated that the sequential or continuous addition of a progestin reduces the incidence of or eliminates endometrial hyperplasia, thought to be a precursor to endometrial cancer. Woodruff and Pikar examined the incidence of hyperplasia in a one-year, randomized clinical trial of conjugated estrogens (Premarin) and medroxyprogesterone acetate (Provera) in 1,724 postmenopausal women (91). The subjects were divided into five groups: two groups received continuous estrogen/progestin regimens, two groups received sequential estrogen/progestin regimens, and one group received unopposed estrogen regimen.[1] They found that, while endometrial hyperplasia developed in 20 percent of women on Premarin alone, hyperplasia

1 The regimens examined were as follows: (1)0.625 mg Premarin plus 2.5 mg Provera daily; (2) 0.625 mg Premarin plus 5 mg Provera daily; (3) 0.625 mg Premarin daily plus 5 mg Provera for 14 days per month; (4) 0.625 mg Premarin plus 10 mg Provera for 14 days per month; and (5) 0.625 mg Premarin daily unopposed by progestin (Woodruff, 1994).

developed in one percent or less of women in the four Premarin/Provera groups (91).[2]

Other trials of sequential or continuous regimens using other estrogens and progestins have demonstrated less hyperplasia in PERT users than in users of estrogen alone (21,90).

Although the incidence of endometrial cancer is reduced in estrogen-progestin users, the risk of endometrial cancer is not eliminated completely. One group of investigators reported on 25 postmenopausal women who developed endometrial cancers while taking PERT for one or more years (59). Twenty-three (98 percent) of the women had cancers limited to the uterus, but two had disease extending beyond the uterus. All of the women were alive and disease free after a median follow-up of 26 months. The endometrial cancers that did occur among PERT users were usually associated with regimens that had inadequate doses of progestins.

IMPLICATIONS FOR OTA'S COST EFFECTIVENESS MODEL

The evidence is strong that endometrial cancer risks begin to rise soon after the initiation of ERT. Following the weight of the evidence presented in tables G-1 and G-2, OTA assumed that the relative risk of endometrial cancer during the first nine years of ERT would be 2.5 and in subsequent years would rise to 7.0. The sensitivity of results to changes in these assumptions was also tested. For the case most favorable to ERT, OTA assumed that relative risk of endometrial cancer is 1 for the first nine years of therapy and rises to 2.0 during the 10th and subsequent years of ERT. This best case is based on the assumption that the apparent increased risk of endometrial cancer in ERT users is largely due to surveillance bias. In the worst case, the relative risk would be 7.5 in the first nine years of ERT and 15.0 thereafter. This estimate is based on epidemiological studies that detected the highest risks of endometrial cancer in HRT users.

In a recent metaanalysis, Grady et al. estimated a risk of endometrial cancer in ERT users that was intermediate between OTA's base case and worst case estimates (28). They concluded that the risk of endometrial cancer increased with prolonged duration of ERT use, from a relative risk of 1.4(95 percent confidence interval 1.0 to 1.8) for less than one year of use, 2.8 (95 percent confidence interval 2.3 to 3.5) for two to five years of use, 5.9 (95 percent confidence interval 4.7 to 7.5) for six to 10 years of use, and 9.5 (95 percent confidence interval 7.4 to 12.3) for more than 10 years of use (28).[3]

For PERT users, OTA assumed that there would be no increase in endometrial cancer risk over that of the baseline population. This is consistent with the estimates of endometrial cancer risk from the metaanalysis by Grady and colleagues, who found that case-control studies estimated a slightly increased risk of endometrial cancer in PERT users (relative risk 1.8), whereas the few cohort studies of PERT users have estimated a slightly decreased risk of endometrial cancer (relative risk 0.4) (28).

In modeling the impact of HRT on endometrial cancer, OTA made a number of simplifying assumptions. In the case of ERT, OTA assumed that the relative risk of endometrial cancer would subside to that of the baseline population in the year following cessation of HRT. This assumption is consistent with observations that the risk of endometrial cancer drops rapidly after discontinuing estrogen use. There are, however, a number of studies that have been able to detect relatively small elevations in risk of endometrial cancer that persist several years after cessation of therapy. Grady et al. estimated a relative risk of endometrial cancer of 2.3 (95 percent confidence intervals 1.8 to 3.1) five or more years after discontinuation of long-term ERT use (28).

OTA assumed that endometrial cancers in HRT users would be early stage and grade, and would

2 Although the incidence in endometrial hyperplasia did not differ significantly among the Premarin/Provera groups, none of the women who received the sequential or continuous regimens with the highest dosages of progestins developed endometrial hyperplasia (91).

3 An earlier metaanalysis by Grady and colleagues estimated a relative risk of 8 in long-term estrogen users (28).

be cured by hysterectomy. OTA also assumed, for simplicity, that there would be no endometrial cancer deaths in HRT users. The metaanalysis by Grady et al. estimated that ERT is related to a large increase in risk of early stage cancers (relative risk 4.2 (95 percent confidence interval 3.1 to 5.7) for Stage O and 1 cancers) (28). They found a trend toward later stage endometrial cancers in ERT users that did not reach statistical significance (relative risk 1.4 (95 percent confidence interval 0.8 to 2.4) for Stage 2 to 4 cancers).

Observational studies have been unable to detect a significantly increased risk of endometrial cancer death in ERT users (20,49,62,65). This may be due in part to the small number of endometrial cancer deaths in these studies. In a metaanaly - sis, Grady and colleagues were able to use pooled data from these studies to detect a trend toward increased endometrial cancer deaths in ERT users that failed to reach statistical significance (relative risk 2.7 (95 percent confidence interval 0.9 to 8.0)) (28). Because endometrial cancer is less common than breast cancer, hip fracture, or heart disease, and because there are relatively small numbers of invasive endometrial cancers and deaths due to HRT-induced endometrial cancer, OTA's simplifying assumptions about endometrial cancer stage and endometrial cancer deaths in ERT users should not have a substantial impact on the results of OTA's analysis.

OTA also assumed that women diagnosed with endometrial cancer would remain off hormonal replacement therapy. It was previously thought that HRT could induce the growth of any residual endometrial cancer cells, and thereby increase the risk of recurrence. There is a growing consensus, however, that a history of endometrial cancer is not a contraindication to continuing HRT, at least with respect to women who have had hysterectomies for tumors that have not spread beyond the uterus (3,14,60). It is doubtful, however, that most women would be willing to resume HRT after having had endometrial cancer.

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TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 1 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Smith 1975)	Cases were patients from Mason Clinic, Virginia Mason Hospital, Seattle, WA, and University of Washington Medical School Hospital who were 48 years of age or older with diagnosis of endometrial carcinoma made between 1960-1972 after curettage or hysterectomy. Matched controls were selected from patients with other gynecologic neoplasms at the same institutions. Controls were matched with cases for age at diagnosis and year of diagnosis. Cases and controls were selected from regional tumor registry. Information was gathered from medical records	317 cases (48% estrogen users); 317 controls (17% estrogen users)	Unadjusted relative risk 4.5 (no confidence intervals provided) Relative risk 7.5, adjusted for year and age at diagnosis			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 2 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Gray (1977)	Cases were endometrial cancer patients seen in one private practice between 1947 and 1976. One control was chosen for each case from among those patients who had a hysterectomy for a benign condition performed in the same year in which the patient with endometrial cancer was diagnosed. Once the year was determined, the specific control was chosen from all those available matched as closely as possible to the case on the basis of age and parity. Average age of cases was 56.5 years, controls 56.0 years. Information was obtained from medical records.	205 cases (27% estrogen users); 205 controls (15% estrogen users)	All estrogens: 2.1 (1.2-3.5) Conjugated estrogens: 3.1 (1.5-6.8) Systemic estrogens: 2.6 (1.5-4.6) No evidence of increased risk associated with vaginal estrogenic preparations: 0.7 (0.1-3.6)	0-4 yrs.: 1.2 (0.4-3.5) 5-9 yrs.: 4.1 (0.8-28.4) 10+ yrs.: 11.6 (1.5-242.7)	♀.3 mg: 4.1 (0.8-40.♀ ♀.625 mg: 1.8 (0.7-4.9) 1.25 mg: 12.7 (1.8-552.3)	
Hoogerland (1978)	Cases were all patients treated for invasive cancer of the endometrium in the Wisconsin Clinical Cancer Center from 1960 to 1974. Controls were hospital patients with a different gynecological malignancy, matched for age and date of diagnosis. Information was gathered from medical records.	587 cases (18.4% estrogen users); 587 controls (9.2% users)	2.2 (1.6-3.2)	1-6 mos.: 1.2 7-12 mos.: 1.8 1-3 yrs.: 3.2 3-5 yrs.: 3.9 5-10 yrs.: 3.4 10+ yrs.: 6.7 (No tests of statistical significance were conducted because of the small numbers of cases involved.)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 3 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Horowitz (1978)	Cases were women, mean age 61 years, with endometrial cancer listed in the Yale Tumor Registry between July 1, 1974 and June 30, 1976; cases had to have endometrial carcinoma of Grade I or higher (Stage 0 "in situ" carcinoma was excluded). Controls were women with other gynecologic cancers listed in the Yale Tumor Registry between July 1, 1974 and June 30, 1976, matched for age and race to cases. Information on HRT use was obtained from hospital and clinic records.	119 cases (29% estrogen users); 119 controls (3% estrogen users)	Odds ratio 11.98 (4.02-47.73)	< 3.5 yrs.: odds ratio 0.8 (0.4-1.7) compared with gynecology controls; odds radio 0.7 (0.4-1.3) compared with community controls		
Horowitz (1978) (alternate method)	Cases were women, mean age 62 years, with endometrial cancer who underwent dilation and curettage or hysterectomy between January 1, 1974 and June 30, 1976. Controls were women with diagnoses other than uterine cancer matched for age and race to cases. Information on HRT use was obtained from hospital and clinic records.	149 cases (30% users); 149 controls (15% estrogen users)	Odds ratio (alternative method) 2.3 (1.26-4.25)			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 4 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use[a,b]
Wigle (1 978)	Cases were women aged 55 to 74 years with histologically confirmed endometrial cancer who first attended an Alberta, Canada cancer clinic during the period 1971 to 1973. Controls were women aged 55 to 74 years who attended the cancer clinic for any primary cancer other than breast, cervix, uterus, ovary, or other female genital organs. Information on HRT use and risk factors was gathered by questionnaire.	202 cases (47.2% estrogen users), 1,243 controls (26.3% estrogen users)	Any use, 2,2 (p< 0.01) Estrogen users was defined as users of hormonal replacement therapy or oral contraceptives.	1-4 years 1.8 (p< o 05) > 5 years 5,2 (p< 0,05)		Current use. 2.7 (p < 0,01) Past use. 2.0 (p< 0,01)
Jick (1979)	Cases were women 50 to 64 years of age who were members of Group Health Cooperative of Puget Sound, Seattle, Washington, who were diagnosed with endometrial cancer from January 1972 to June 1977. Controls were members of the same age that were hospitalized for other conditions at the same age as cases. Information was obtained from telephone interviews and clinic records,	67 cases (89.6% estrogen users); 74 controls (43.2% estrogen users)	Ever use: relative risk 11.2 (4,2 -21 .1)	Duration of use: O-4 years: 3.0 (0.5-14.9) 5-8 years: 36.0 (5.6-300.9) 9-12 years 63.0 (10,4-502.9) 13 years. 21.0 (4.6-107.9) Relative risk estimates were calculated by Grady (1995) from published crude data.	Dose: 0.3 mg CEE: 4.3 (1 .2-15 .6) 0.625 mg CEE: 7.1 (2,8-1 7.6) 1.25 mg CEE: (8.4 (2,0-36.5)	

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 5 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen us&[b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Antunes (1979)	Cases were all patients with endometrial cancer admitted to six of the 24 hospitals in the Greater Baltimore area from 1973 to February 1977. Cases were ascertained from hospital tumor registries, admissions records, and pathology records. Controls were female patients who were matched with cases for hospital, race, age, and date of admission, One set of controls were taken from hospital services other than gynecology, obstetrics, and psychiatry services. A second set of controls was taken from the gynecology service, Information was gathered through personal interviews, medical records, and pathologenic specimens.	451 cases (20% estrogen users); 446 controls from other services; 442 gynecology controls	Unadjusted relative risk 6.0 (3.7-9.7) compared with hospital controls Unadjusted relative risk 2.1 (1.5-NA) compared with controls from gynecology service Adjusted relative risk 5.5 (2.3-12.9) compared with " hospital controls Adjusted relative risk 2.4 (1 ,5-3.7) compared with gynecology controls	None: 1.0 <1 yr.: 2.2 (0,9-5,5) 1-5 yrs.: 2.9 (1 ,3-6.7) >5 yrs.: 15 (4,9-45)	<1 mg: 3,5 (1 ,6-7,6) 1-2 mg: 7,1 (2,8-18) >2 mg.: 3.7 (0,8-16)	

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 6 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Hulka (1980a)	Cases were all women who had received their initial therapy for endometrial cancer at North Carolina Memorial Hospital (NCMH) from 1970 through 1976; patients with carcinoma "in situ" were excluded. Cases were 60 years old, on average, at admission. Gynecology controls were women, average age 60 years, with intact uteri selected from the pool of all gynecologic admissions and consultations on surgical or medical services of the NCMH from 1970 through 1976 matched for age, race, and year of admission, and with intact uterus; excluded were women admitted to the gynecologic oncology service and women admitted primarily for curettage or endometrial biopsy. Community controls were a sample of women, average age 55 years, with intact uteri residing in a major referral area of NCMH, and matched for age and racial group. Sources of information included interviews and review of medical records.	256 cases (32.8% estrogen users); 224 gynecology controls (22.9% users); 321 community controls (27.1% users)	White women. 1.8 (0,9-2.5) compared with gynecologic controls; 1.4 (0.9-2.1) compared with community controls Black women: 0.7 (0.3-2.1) compared with gynecologic controls; 1.5 (0.4-5.1) compared with community controls	<3.5 yrs.: 0.8 (0.4-1.7 compared with gynecology controls; 0.7 (0.4-1 .3) compared with community controls >3.5 yrs.: 4.1 (1 ,8-9.6) compared with gynecology controls; 3.6 (1 .9-6.8) compared with community controls	<0,625 mg: 1.6 (NS) compared with gynecology controls; 2.3 (NS) compared with community controls >0,625 mg: 1.8 (NS) compared with gynecology controls, 1.4 (NS) compared with community controls	In comparison of cases to community controls, risk drops to that of non-users of estrogen after a 20-month estrogen-free interval; in comparison to the gynecology control group, excess risk disappeared 28 months after cessation of estrogen.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 7 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Hulka (1980b)	Cases were women, mean age 61 years, with endometrial cancer receiving their initial therapy at North Carolina Memorial Hospital (NCMH) between 1970 and 1976. Gynecologic controls were selected from patients admitted to the gynecology service and from patients receiving gynecologic consultations while inpatients on surgical or medical services of the NCMH during 1970 through 1976. Admissions to the gynecologic oncology service, women admitted for dilation and curettage, and women with a previous hysterectomy were excluded. Controls were matched for age, year of admission, and race with cases. Community controls were from a sample of women over 30 years old (mean age 56 years) residing in the major referral areas of NCMH, stratified by age and within racial group. All had intact uteri. Information was gathered from interviews and medical records.	256 cases (32.8% estrogen users), 224 gynecology controls (22.9% users), 321 community controls (27.1 % users)		Duration of estrogen use < 3,5 years: Stage 1A: 1.2 (NS) Stage 1B: 0.9 (NS) Stage 11: 0.7 (NS) Stage III-IV: 0.6 (NS) Grade 1. 1.0 (NS) Grade 2: 0.7 (NS) Grade 3: 0.6 (NS) invasion: myometrium and beyond. 0.5 (NS) Duration of estrogen use >3.5 yrs.: Stage 1A: 7.6 (p< 0,05) Stage IB: 1.6 (NS) Stage Il: 3.3 (p< 0,05) Stage III-IV 1.5 (NS) Grade 1 55 (p< 0,05) Grade 2: 19 (NS) Grade 3 2.9 (p< 0.05)	Estrogen strength=<O.625 mg. Stage 1A: 5.8 (p < 0,05) Stage IB-IV: 2.3 (NS) Grade 1: 4.0 (p< 0.05) Grades 2-3.2.5 (NS) invasion: endometrium: 5.2 (p< 0,05) myometrium and beyond: 2.1 (NS) Estrogen strength > 0.625 mg: Stage 1A: 8.5 (p< 0,05) Stages IB-IV: 1.5 (NS) Grade 1. 5.4 (p< 0,05) Grades 2-3. 2.0 (NS)	Estrogen-free interval > 6 me,, Stage 1A: 2.5 (NS) Stages IB-IV: 1.3 (NS) Grade 1. 2.2 (NS) Grades 2-3: 1.3 (NS) invasion: endometrium. 2.1 (NS) myometrium: 2.0 (NS) Estrogen-free interval < 6 months: Stage 1A. 8.8 (p < 0.05) Stages IB-IV: 2.1 (NS) Grade 1. 6.2 (p < 0,05) Grades 2-3. 2.3 (NS)

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 8 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use[a,b]
				invasion: only endometrium: 5.2 ($p < 0.05$) myometrium and beyond: 2.5 ($p < 0.05$) With long-duration estrogen use, the endometrial cancer risk is high for cancers that are Stage IA, Grade 1, and invading the endometrium only.	invasion: endometrium 5.5 ($p < 0.05$) myometrium and beyond: 2.3 (NS)	invasion: endometrium: 6.5 ($p < 0.05$) myometrium and beyond: 2.4 (NS)
Jelovsek (1980)	Cases were patients, mean age 59 years, with diagnoses of endometrial cancer at Duke University Medical Center (Durham, NC), 1940-1975, identified through the medical records and pathology files, as well as the office records of Duke physicians. One control patient was selected for each study patient from the general registration files of the medical records department (includes both outpatients and inpatients). Control patients were registered within one year at the date of diagnosis of cancer in the study patient, and matched for age, race, and parity; control patients were not hysterectomized. Information was gathered from medical records.	431 cases (12% estrogen users); 431 controls (6% estrogen users)	Odds ratio 2.4 (1.4-3.9) (unmatched)	6 mo.-3 yrs.: odds ratio 1.4 (0.6-3.5) 3 yrs.-5 yrs.: odds ratio 1.4 (0.3-6.5) 5 yrs.-10 yrs.: odds ratio 4.8 (1.6-14.5) > 10 yrs.: odds ratio 2.6 (1.1-5.9)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 9 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Salmi (1980)	Cases were all patients with endometrial cancer diagnosed and treated in the Department of Obstetrics and Gynecology at the University Central Hospital of Turku, Finland, from 1970 to 1976. Controls were women between the ages of 35 and 60 identified from Turku's continuing mass screening program for cervical and breast cancer. Women over 60 were identified from the National Population Registry. There were 585 controls, 282 of which were matched for age, height, weight, and social class. Information on HRT use was gathered by interviews.	318 cases (33% hormone users); 282 matched controls; 585 total controls (43.6% users)	Matched pairs analysis Any use of hormones. 0.6 (0.4-0.9) Use of hormones for gynecological conditions: 0.6 (0.4-0.9) Use of estrogen: 0.4 (0.2-0.7) Estrogen use was defined as use of 6 months or more. Estradiol only or combined with androgen. 0.3 (0.2-0.7) Estriol only. 0.4 (0.1-1 .0) Conjugated estrogens: 5.0 ($p < 0.05$) Other estrogens: 0.6 (0.2-1.4)			

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 10 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Stavraky (1981)	Cases were all new patients between 40 and 80 years of age with a diagnosis of endometrial carcinoma admitted to Victoria Hospital, London, Ontario between September 1976 and October 1978 for preoperative radiation. Two controls for each patient were selected from the hospital's daily patient register, one control was a woman with a gynecologic disorder, matched for age within.5 years; another control was a woman with a nongynecologic disease within the same age range; hysterectomized women were not included in control group. Information was gathered by questionnaire.	206 cases (58% estrogen users), 191 gynecologic controls (38% users); 199 nongynecologic controls (28% users)	unadjusted relative risk 2.4 (1 ,6-3.7) compared with gynecologic controls unadjusted relative risk 4,3 (2.7-6,7) compared with nongynecologic controls unadjusted relative risk for postmenopausal women only 2,3 (1 ,5-3,7) compared with gynecologic controls unadjusted relative risk for postmenopausal women only 4.8 (2.9-7.7) compared with nongynecologic controls adjusted relative risk[c] 1.5 (0.9-2.7) compared with gynecologic controls	All durations: unadjusted relative risk 2.9 (1 .6-5.1) adjusted relative risk 1.3 (0,5-3.7) Risk by duration of use among patients and gynecologic controls who presented with bleeding: unadjusted relative risk < 2 years: 2.3 (0.5-7,9) 2-4 years: 1,1 (0.5-2.5) 5-9 years: 4.1 (1 .4-10 .5) 1 O+ years, 11,0 (2.1-39.0) adjusted relative risk. O-4 yrs.: 0.7 (O 2-2,5) 5-10+ years: 2.3 (1 .8-8,4) Risk of endometrial cancer among patients and two control groups by duration of estrogen use 14,4 (5,0-41 .8) compared with nongynecologic controls	Gynecologic controls. <0,625 mg 1.9 (0.9-3.6) >0,625 mg 3.1 (1 ,5-6.3) Nongynecologic controls. <0.625 mg 2.9 (1 .4-57) >0.625 mg 6.4 (2.5-14,5)	Use <5 years duration Current users (use within past year). adjusted relative risk 1.3 (0,6-3,1) compared with gynecologic controls; 7,2 (2.6-20.3) compared with nongynecologic controls Past users (cessation of use > 1 year ago): adjusted relative risk 0.5 (0.2-1 .3) compared with gynecologic controls, 1,0 (0,4-2.5) compared with nongynecologlc controls

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 11 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
			adjusted relative risk[c] 4.8 (2.7-8.4) compared with non-gynecologic controls adjusted relative risk[c] for postmenopausal women only 1.5 (0.8-2.8) compared with gynecologic controls adjusted relative risk[c] for postmenopausal women only 4.2 (2,2-8,0) compared with nongynecologic controls Estrogen use was defined as use six months or more.	< 2 years, adjusted relative risk 0.7 (0.3-1.9) compared with gynecologic controls, 1.6 (0,6-4.3) compared with nongynecologic controls 2-4 years. adjusted relative risk 1.0 (0.4-2.2) compared with gynecology controls; 4.0 (1 .6-10 .1) compared with nongynecologic controls 5-9 years: adjusted relative risk 1.7 (0.7-4 1) compared with gynecologic controls; 5.3 (2.2-1 2.4) compared with nongynecologic controls 1 O+ years. adjusted relative risk 6.4 (2.1-19.3) compared with gynecologic controls,		Use >= 5 years duration: Current users. adjusted relative risk 4,3 (1 .9-9,7) compared with gynecologic controls, 11.3 (4.9-25.5) compared with nongynecologic controls Past use. adjusted relative risk 0.7 (0.2-2.7) compared with gynecologic controls, 2.3 (0.6-8.5) compared with nongynecologic controls

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 12 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Kelsey (1 982)	Cases were women ages 45-74 years old who were admitted from 1977 to 1979 to seven Connecticut hospitals with newly diagnosed endometrial cancer. Controls were other women in the same age group admitted to surgical services (except gynecology) of those hospitals at the same time as the cases. Information on HRT use was obtained by questionnaire.	167 cases (47% estrogen users), 903 controls (38% estrogen users)	Use >5 years: odds ratio 1.6 (1 .3-2,0)	Use <1 yr.: odds ratio 1.1 (no confidence intervals provided) 1-2.5 yrs.: odds ratio 1,0 2.6-5.0 yrs.: odds ratio 2.9 5.1-7.5 yrs.: odds ratio 4.3 7.6-10,0 yrs.: odds ratio 8.2 > 10 yrs,: odds ratio 2.7 (test for trend: p < 0,001)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 13 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen us&[b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
La Vecchia (1984)	Subjects were women admitted to university and general hospitals in the Greater Milan area between 1979 and 1983. Cases were diagnosed with endometrial cancer within the year prior to interview. Cases were between 33 and 74 years old (median age 60); 30 cases were below 50 years of age. Controls were women less than 75 years admitted for acute conditions unrelated to risk factors for endometrial cancer. Women with gynecological, hormonal, or neoplastic diseases or who had undergone hysterectomy were excluded from controls. Information was gathered by personal interview.	283 cases (25% estrogen users); 566 controls (17% users)	Relative risk 2.3 (1 .6-3.2) adjusted for body mass index and age	There was a significant trend of increasing risk with increasing duration of use (test for trend: p = 0.001). Age <55 years: <2 years use: 1,8 (0.9-3.6) >2 years: 5.1 (1 .5-17.1) (test for trend: p = 0.002) Age 55-64 years: <2 yrs,: 1.5 (0.8-2-6) >2 yrs,: 1,8 (0,7-4.5) (test for trend: p = 0.12) Age >= 65 years: <2 yrs.: 1,6 (0.7-3.5) >2 yrs.: 1,4 (0.4-5.4) (test for trend: p = 0.29)		

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 14 of 17)

Author	Description of cases and controls	Number of oases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Shapiro (1985)	Cases were women with endometrial carcinoma admitted to hospitals in Boston, MA; Philadelphia, PA; Baltimore, MD; Tucson, AZ; New York, NY; Kansas City, MO; San Francisco, CA; and London, Ontario; ages 50-69 years, with no history of other cancers. Controls were other female patients on medical, surgical, and orthopedic wards, ages 50-69 years, with no history of cancer, admitted for conditions judged not to be related to estrogen use. Patients were interviewed between September 1976 and December 1982.	425 cases (31 % estrogen users); 792 controls	Relative risk 3.5 (2,6-4.7) adjusted for age, body-mass index, and geographic area. Estrogen use was defined as use of conjugated estrogen, beginning at least two years prior to the date of interview.	<1 year: 0.9 (0,4-1 ,8) 1-4 years: 2.9 (1 .8-4.7) 5-9 years: 5.6 (3,4-9.3) > 10 years: 10 (5.9-18)		< 1 year since last use. < 1 yr. duration. — 1-4 yrs.: 2.1 (0.9-4.7) 5-9 yrs.: 6.3 (3.0-13) >10 yrs.: 12 (5,9-24) 1-4 years since last use: < 1 yr. duration: 0,6 (0.2-2,0) 1-4 years: 3.1 (1 .3-7,4) 5-9 years: 5.2 (2.1-13) > 10 years: 12 (4.8-32) 5-9 years since last use: < 1 yr. duration: 1,0 (0.3-3.5) 1-4 years: 4.0 (1 .4-12) 5-9 years: 6.3 (2,0-20) > 10 years, 3,7 (0.8-18)

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 15 of 17)

Author	Description of oases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
						> 10 years since last use: < 1 yr. duration: 1,2 (0.4-3.6) 1-4 years: 3.5 (1 ,4-8.3) 5-9 years: 4.1 (1 .1-15) > 10 years: —
Buring (1986)	Cases were white women, aged 40-80 years, who were admitted to the Boston Hospital for Women's Parkway Division with first diagnosis of endometrial cancer made between January 1970 and June 1975. Controls consisted of all white women, aged 40-80 years, admitted to the same hospital during the same period for nonmalignant conditions requiring surgery. Information was gathered from hospital and clinic records,	188 cases (39% estrogen users); 428 controls (17%. estrogen users)	Ever use: 2.4 (1 ,7-3,6) current use. 2.8 (1 ,8-4.2) (current use defined as use within the year before index admission)	< 1 yr.: 1,4 (no confidence interval provided) I-4 yrs.: 2.0 5-9 yrs.: 6.4 10+ yrs.: 7.6	0.3 mg, 0.625 mg: 2.7 (1 ,6-4.9) 1.25 mg, 2.5 mg: 3.8 (2.2-6.6)	< 1 yr.: 2,4 (no confidence interval provided) 1 + yrs.: 4.6 1-2 yrs.: 4.2 3-4 yrs.: 5.9 5+ yrs.: 4.5 An excess risk of endometrial cancer was noted to continue among estrogen users who had discontinued 5 or more years ago, although there were small numbers of former users.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 16 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Ewertz (1 988)	Cases and controls were women referred for radiotherapy at the Oncology Department II of the Finsen Institute, Copenhagen, Denmark. Cases were ages 44 to 89 years (mean age 66 years) and were identified between October 1977 and December 1978. Controls were patients with cervical cancer, from same hospital, matched for age at diagnosis. Data were derived from hospital records.	149 cases (56% estrogen users); 154 controls (21% estrogen users)	4.7 (2.9-7.7) ever users vs. never users			
Brinton (1993)	Cases were menopausal women, ages 20 to 74 years, newly diagnosed with endometrial cancer between June 1, 1987 and May 15, 1990 from seven hospitals in five areas of the United States. Population controls were matched to the cases for age, race, and residential area, identified by random digit dialing and HCFA data tapes. Information was gathered from home interviews.	300 cases (24% estrogen users); 207 controls (14% estrogen users)	Adjusted relative risk. 3.0 (1.7-5.1) Progestin alone: 1.8 (no confidence interval) Estrogens alone 3.4 (no confidence interval)	Both short- and long-term use elevated the risk of early stage tumors, but an effect on late-stage tumors was seen only for long-term use (relative risk 2.1 (0.7-6.4)).	Associations with dose were inconsistent although women who used low-dose preparations exclusively had the lowest risk. There were no striking relationships according to the type of estrogen or regimen used.	Although the highest risks were for recent estrogen users, persistent excess risks were seen even for those who had discontinued use 5 or more years ago.

TABLE G-1: HRT and Endometrial Carcinoma: Hospital-Based Case Control Studies (Page 17 of 17)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Jick (1993)	Cases were female members of Group Health Cooperative of Puget Sound, Washington, ages 50 to 64 with newly diagnosed endometrial cancer between 1979 and 1989. Controls were GHC members matched for age and length of membership in health maintenance organization to cases. Cases were identified from GHC's file of discharge diagnoses tumor registry. Information was gathered from pharmacy records and medical records.	172 cases (44% HRT users); 1,720 COntrols (40% HRT users)	Adjusted rate ratio: Current ERT users: 6.5 (3.1 -13.3) Current PERT users: 1.9 (0.9-3.8) Past ERT users: 1.0 (0.5-2.0) Past PERT users: 0.9 (0.3-3.4)	Estrogen alone: 3-4 years: adjusted rate ratio 1.9 (0.4-8.7) >5 years: adjusted rate ratio 22.0 (6.5-74.1) Estrogen and progesterone: >3 years: adjusted rate ratio 1,3 (0.5-3.4) There was insufficient data for women who had used estrogen and progesterone for more than 5 years.	Estrogen: 0.3 mg: 4.3 (1 .2-15 .6) 0.625 mg: 7.1 (2.8-17.6) 1.25 mg: 8.4 (2.0-36.5) Estrogen and progesterone: 0.3 mg: 1.8 (0.4-8.0) 0.625 mg: 1.6 (0.7-3.6) 1.25 mg: 5.4 (1 .0-30 .7)	
Levi (1993)	Cases were women below 72 years old who were diagnosed with endometrial cancer in the Swiss Canton of Vaud between 1988 and 1992, Controls were women of the same age hospitalized for acute conditions not related to cancer or HRT.	158 cases (38% HRT users); 468 controls (20% HRT users)	Risk-factor adjusted relative risk 2,7 (1 .7-4.1)	Duration of use: >5 years, 5,1 (2.7-9.8)		Recency of use: > 10 years since last use: 2.3 (1 ,2-4.5)

[a] 95 percent confidence intervals are shown in parentheses.
[b] Relationship is relative risk, unless stated otherwise.
c Adjusted for age, residence, number of pregnancies, education level, and menopausal status
KEY: HRT= hormonal replacement therapy; NS = not statistically significant

SOURCE: Off Ice of Technology Assessment, 1995

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 1 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Ziel 1975)	Cases were patients diagnosed between July 1, 1970 and December 31, 1974 with endometrial cancer at the Kaiser Permanente Medical Center in Los Angeles and reported to its tumor registry. Controls were identified from membership files of the Southern California Kaiser Foundation Health Plan population who live in vicinity of the Los Angeles facility. Two control subjects were selected for each patient and matched by age, area of residence, duration of Health Plan membership, and intact uterus. Information was gathered from review of medical records.	94 cases (57% estrogen users); 188 controls (15% estrogen users)	Relative risk 7.6 (4.3-13.4)	< 1 year: not enough data 1-4.9 years: 5.6 ($p < 0.01$) 5-6.9 years: 7.2 ($p < 0.01$) > 7 years: 13.9 ($p < 1x10^{-5}$)		
Mack (1976)	All cases of endometrial cancer occurring among residents of Leisure World (California) Retirement Community from 1971 to 1975 were compared to controls chosen from a roster of all women in the same community, matched for age and marital status. Information was gathered from clinic records, telephone interviews, and pharmacy records.	63 cases (89% estrogen users) 396 controls	Any estrogens: 8.0 (3.5-18.1) Conjugated estrogens: 5.6 (2.8-11.1)	1-11 mos.: 2.8 (no confidence interval) 12-59 mos.: 4.5 60-95 mos.: 9.3 96+ mos.: 8.8 dose ≤ 0.625 CEE 1-11 mos.: 6.6 12-54 mos.: 3.4 60-95 mos.: 6.0 96+ mos.: 4.8 dose > 0.625 CEE 1-11 mos.: 0.0 12-59 mos.: 29.8 60-95 mos.: 11.9 96+ mos.: 19.1	Dose ≤ 0.625 mg/day conjugated estrogens: 5.0 (no confidence interval provided) > 0.625 mg/day conjugated estrogens: 9.4	Estrogen-free interval before diagnosis: 0-23 mos.: 7.2 (no confidence interval) 24+ mos.: 3.4

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 2 of 7)

Author	Description of oases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
McDonald (1977)	Subjects were all cases of endometrial cancer among residents in Olmstead County, Minnesota over a 30 year period (1945 to 1974). Cases were 25 years of age and older. Four controls, age-matched and residents of Olmstead County, were selected for each case. Information was gathered from medical records.	145 cases (27% estrogen users); 580 controls (28% estrogen users)	All estrogens: 0.9 (0.6-1.4) Conjugated estrogens: 2.0 (1 .2-3.5)	All estrogens: all durations: 0.9 (0.6-1 .4) >6 mo. 2.3 (1 .4-3.6) Conjugated estrogens: all durations: 2.0 (1 .2-3.5) >6 me.: 4.9 (2.3-1 1.5) > 1 year: 5.3 (2.1-14.4) >2 years: 8.3 (2.9-29.9) >3 years: 7.9 (2.9-21 .2)	Dosage of conjugated equine estrogens: 0.625 mg/day: 1.4 (0.3-5.9) 1.25-2.5 mg/day: 7.2 (3.0-14.9)	
Weiss (1979)	Cases were all female residents of King County, Washington, aged 50 to 74 years with newly diagnosed endometrial cancer between January 1975 and April 1976. Cases were identified from the Cancer Surveillance System, a population-based tumor registry serving western Washington. Controls were white women aged 51 to 74 years from King County Identified from household surveys. Information on HRT use and risk factors was gathered through interviews,	322 cases (81 % ever users); 289 controls (34%. ever users)		Age-adjusted relative risk: 1-2 years 1.2 (0.4-3.7) 3-4 years: 5.4 (2.5-1 1,5) 5-7 years: 4.7 (2.6-8.4) 8-10 years. 11,7 (6.2-21 .8) 11-14 years. 24.2 (1 1,8-49,4) 15-19 years 102 (5.3-20,0) > 20 years, 83 (2.8-24.5)	Age-adjusted relative risk. <0.5 mg per day: 2.5 (1 .1-5,3) 0.6-1.2 mg per day: 8.8 (5.0-12.7) > 1.25 mg per day: 7.6 (5.0-1 1.6)	Time since last use: >8 years: 3.0 (0.9-10.6) 3-7 years: 3.8 (1 .5-9.5) 1-2 years: 5.3 (2.6-10.8) current use: 8.7 (6.4-1 1.8)

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 3 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Obrink (1981)	Swedish study comparing use of estrogens among 622 cases of endometrial cancer treated at Radiumhemmet (Stockholm) between 1974 and 1977 with estrogen use of the average female population, represented by a randomly selected sample of 1,866 age-matched controls. Progestin treatment was rare among cases and controls.	622 cases (19.27. estrogen users); 1,866 controls		6-36 months: 7.5% cases, 8.O% controls (NS) 37-72 months: 1 0.3% cases, 2.2% controls (p < 0.001) More than 6 years of treatment was uncommon.		
Spengler (1981)	Cases were newly diagnosed with endometrial cancer between April 1, 1977 and December 31, 1977, and were residents of metropolitan Toronto between 40 and 74 years of age. Cases were identified from the records of the pathology departments of 21 Toronto hospitals. Two age-matched controls were selected from the same neighborhood and type of dwelling as their respective case. Neighborhood controls were obtained by door-to-door canvassing which started at the fourth dwelling to the right of the case's residence and proceeded sequentially around the block or through the apartment building. No control had history of hysterectomy or cancer. Information was gathered by questionnaire and by review of hospital and clinic records.	88 cases (45% estrogen users), 177 controls (22% estrogen users)	Odds ratio 2.9 (1 .7-5,1) Odds ratio matched 3.2 (p= 0.0001) Relative risk (adjusted for age, obesity, age at menopause, nulliparity, and educational level) 3.7 (1 .8-7.6) Estrogen use was defined as use 1 or more months during or after menopause.	1-6 months: 1.4 (0.5-4.4) 7-24 months: 2.6 (1 .0-6,5) 25-60 months: 2.2 (0.7-6.5) >60 months: 8,6 (3.2-23.0)	Conjugated equine estrogens: <1 mg: 2.0 (0,9-4.6) >1 mg: 4.0 (1 .9-8.4) total: 3.0 (1 .7-5.3)	

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 4 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use[a,b]	Relationship of endometrial cancer to dose of estrogen[a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Henderson 1983)	Cases were white women from Los Angeles County with endometrial carcinoma diagnosed between January 1972 and December 1979, identified from a regional cancer registry; all cases were aged 45 years or less at diagnosis. Controls were white, age-matched, and selected from same neighborhood as cases. Information on HRT use and risk factors was gathered from telephone interviews.	127 cases (12% estrogen users); 127 controls (7% estrogen users)		< 2 yrs.: 1.38 (NS) > 2 yrs.: 3.13 (NS)		
Pettersson (1986)	Cases were women, mean age 63 years, newly diagnosed in 1980 and 1981 with endometrial carcinoma and living in the Uppsala, Sweden, Health Care region. Controls were age-matched, and from same county of residence as cases. Only a small number had used estrogen-progesterone therapy. Data was collected both by questionnaire and interview.	250 cases (20.1% estrogen users); 253 controls (15.8% estrogen users)	For treatment > 4 years duration. odds ratio 4.5 1.2-17.3)	Odds ratios for durations: < 12 months: 0.9 (0.4-1.8) 13-47 months: 1.1 (0.5-2.4) > 48 months: 4.3 (1.3-13.9)		

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 5 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]			Relationship of endometrial cancer to recency of estrogen use [a,b]
Lawrence (1989)	Cases were women ages 40 to 69 years from hospitals in upstate New York who had been diagnosed as having advanced-stage (stages 2-4) endometrial cancer in 1979-1981. Controls were selected from the files of licensed drivers maintained by the New York State Department of Motor Vehicles. Two controls were selected for each case, matched by county of residence and age. Information on HRT use was gathered through structured interviews.	84 cases (27% estrogen users); 168 controls (24% estrogen users)	< 1 year: odds ratio 0.84 (no confidence interval) 1-5 years: odds ratio 1.47 > 5 years: odds ratio 2.21	The risk of advanced endometrial cancer increased significantly ($p < 0.05$) with duration of use of estrogen pills. No significant association was found for any other variables or for interaction between longer estrogen use and dosage greater than 0.625 mg, continuous mode of administration, or recency interval (the time interval from the last use of estrogen to diagnosis). Despite a statistically significant correlation between duration of estrogen use and advanced-stage endometrial cancer, estrogen use actually contributed little to the risk of advanced-stage disease. Odds ratio=1.01 (1.00-1.03).	No significant association was found between dose and risk of endometrial cancer.	No significant association was found with recency interval and risk of endometrial cancer.

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 6 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use [a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Rubin (1990)	Results from Cancer and Steroid Hormone (CASH) Study, a multicenter study conducted in 8 areas of the United States (Atlanta, **GA;** Detroit, MI; San Francisco, CA; Seattle, WA; Connecticut, Iowa, New Mexico, and Utah). Cases were postmenopausal women 40 to 54 years of age who resided in one of the eight areas and who had an endometrial cancer diagnosed between December 1, 1980 and December 31, 1982. Controls were women with an intact uterus, matched for age and geographic area to cases. Information on HRT use was obtained through interview.	196 cases (24% estrogen users); 986 controls (14'%. estrogen users)	1.9 (1 .3-2.8) ever user vs. never user Estrogen use was defined as 3 months consecutive use of estrogen replacement therapy.	<2 yrs.: 1,3 (0.7-2,4) 2-5 years. 2.1 >6 years, 3.5	<0.625 mg per day, 1.2 (0,5-2.7) > 1.25 mg per day, 3.8 (1 .7-8.5)	**Time** since last use < 2 years all use. 1.9 (1 .2-3.2); duration <2 yrs.. 1.4 (07-3.0); duration >= 2 yrs., 2.4 (1 ,3-4.4) Time since last use 2-5 years: all use. 1.5 (0.8-3.1), duration <2 yrs.: 1.1 (0 4-3.3); duration >= 2 yrs.: 2.0 (0.8-4.9) Time since last use >= 6 years. all use. 2.7 (1.1 -6.4); duration <2 yrs.: 1.4 (0.4-5.2); duration >= 2 yrs., 5.4

TABLE G-2: HRT and Endometrial Carcinoma: Population-Based Case Control Studies (Page 7 of 7)

Author	Description of cases and controls	Number of cases and controls	Relationship of endometrial cancer to estrogen use[a,b]	Relationship of endometrial cancer to duration of estrogen use [a,b]	Relationship of endometrial cancer to dose of estrogen [a,b]	Relationship of endometrial cancer to recency of estrogen use [a,b]
Voight (1 991)	Cases were all women diagnosed with endometrial cancer between Jan. 1, 1985 and Dec. 31, 1987 who were residents of King County, Washington, and who were 40 to 64 years of age at diagnosis ; cancer cases were identified through the cancer surveillance system at the Fred Hutchinson Cancer Research Center. Controls were recruited by random telephone digit dialing; controls were nonhysterectomized women who were residents of King County. Information on HRT use was gathered through interviews.	158 cases (38% HRT users); 182 controls (27% HRT users)	Estrogen alone: O.R. 3.1 (1 ,6-5.8) Estrogen plus progesterone: O.R. 1.3 (0.6-2.8) Progestin use <10 days per month plus estrogen: O.R. 2,0 (0.7-5.3) Progestin use >= 10 days per month plus estrogen: O.R. 0.9 (0.3-2.4)	Estrogen only use 23 years: 5.7 (2.5-1 2.8) Estrogen use >3 years plus any use of progestin: 1.6 (0.6-3.9) Estrogen 23 years plus progestin <10 days per me,: 2.4 (0.6-9.3) Estrogen 23 years plus progestin >= 10 days per month: 1.1 (0.4-3.6)		

a 95 percent confidence intervals are shown in parentheses

b Relationship is relative risk, unless stated otherwise.

KEY: NS = not statistically significant,

SOURCE: Office of Technology Assessment, 1995.

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 1 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Gambrell (1979)	Participants were postmenopausal outpatients at Obstetrics and Gynecology Clinic, Wilford Hall USAF Medical Center, Texas. Duration of estrogen therapy ranged from 2.5 to 12 years. Recruitment between 1976-1977 was prospective, 1975 recruitment was retrospective.	8,170 patient-years (81% HRT use); 14 endometrial cancer cases	Endometrial cancer incidence (cases per 1,000 pt.-years). Estrogen alone: 6.8/1 ,000 PERT, 0.5/1 ,000 (p <0.01 compared to estrogen) progestin alone: 0/1 ,000 no therapy: 2/1 ,000 (NS compared to estrogen)	
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 review of death certificates. Information on descendants was gathered from medical records and family members.	2,270 white women (593 users, 1,677 nonusers)	Endometrial cancer deaths. Nonusers: 1 death from an unspecified genitourinary cancer. Users: 1 death from uterine cancer,	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 2 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Lafferty (1985)	Cohort members were postmenopausal women 45 to 60 years old followed at a single private practice in Cleveland, OH. All treated patients received conjugated equine estrogen 0.6 mg daily for three out of four weeks. Study was carried out between 1966 and 1981, and patients were followed for an average of 8.6 years. Patients were followed with physical exams twice annually.	61 estrogen-treated women, 63 untreated controls	One case of endometrial cancer occurred in untreated controls, and two in estrogen-treated women. No endometrial cancer deaths occurred in untreated controls and two deaths in estrogen-treated women. The difference in rates of endometrial cancer deaths were not statistically significant, but the population was very small.	
Gambrell (1986)	Participants were post-menopausal women seen at Wilford Hall USAF Medical Center (Texas) using various hormone regimens were compared to untreated women. Three years of retrospective data were gathered for 1972-74 from medical and pharmacy records and tumor registry. Women were recruited between 1975 and 1979, and followed until 1983. Information on HRT use and risk factors gathered at clinic visits.	2,905 postmenopausal women with 27,243 patient-years of observation between 1975 and 1983 (31 endometrial cancer cases).	No use: 245.5 endometrial cancer cases per 100,000 patient-years. Unopposed estrogen: 390.6 per 100,000 (NS vs. no use) Estrogen and progesterone: 49.0 per 100,000 (p <0,0001 vs. unopposed estrogen users) (p =< 0.005 vs. no use) Estrogen vaginal cream: 73.6 per 100,000 users (p <0,005 vs. unopposed estrogen users), None of the differences between the other groups were statistically significant,	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 3 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT [a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Stampfer (1986)	Subjects were members of the nationwide Nurses Health Study cohort. Cohort members were registered nurses ages 30 to 55 years old in 1976. Subjects of this study were cohort members who were free of cancer and had intact uteri. Information on HRT use and risk factors was gathered by questionnaire every two years, and deaths were identified through state vital statistics records. There was 114,896 person-years of follow-up among postmenopausal women in cohort.	96,356 women in cohort with intact uterus who were free of cancer at baseline (no information on number of postmenopausal), among postmenopausal women in cohort, there were 70 cases of endometrial cancer in 114,896 years)	Current use of postmenopausal HRT: 4.4 (2,2-7.1); Among past HRT users, there was an increased risk with increasing duration.	Current use and duration of use >5 years: 6.9 (3.6-13.2) Current use and duration of use <1 year. 3.5 (1 .2-10 .8)
Petitti (1987)	Subjects were participants in the Walnut Creek (California) Contraceptive Drug Study. Subjects were 18 to 54 at study initiation, and were recruited between December 1968 and 1972. All subjects received a complete history and physical at study entry. Through 1977, reformation was gathered from clinic visits and mailed questionnaires. From 1978 to 1983, information was gathered from the California Death Index and death certificates. Oral contraceptive users were excluded from this analysis.	3,437 never users of estrogen, 2,656 ever users of estrogen	Endometrial cancer deaths. nonusers: 1 users. 5 RR endometrial cancer death 2.6 (0.4-1 5.5)	

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 4 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Pagnini-Hill (1989)	Subjects were non-hysterectomized women, aged 44-100 years (73 median) at baseline from the Leisure World (California) Retirement Community, Subjects were recruited from June 1981 to January 1987. Of estrogen users, 99% had used unopposed estrogen. Average duration of follow-up was 4.6 years. Information was gathered by periodic questionnaires.	5,160 non-hysterectomized women	Risk ratio for endometrial cancer in users is 10 (p < 0,0001) compared with nonusers, No effect of dose on risk was found. The relationship between HRT use and incidence of endometrial cancer is reported in Henderson (1991) (Henderson, 1991),	Recency (years since cessation of estrogen), O-1 years. 25 (9,2-69) 2-7 years: 12 (no confidence interval) 8-14 years: 8.1 (non confidence interval) 15+ years: 5,8 (2.0-1 7) Duration of estrogen use,* < 2 years: 5.2 (no confidence interval) 3-7 years: 7.0 (no confidence interval) 8-14 years: 4 (no confidence interval) 15+ years: 20 (7,2-54)

*Paper also has table showing interaction of duration and years since cessation of therapy

TABLE G-3: HRT and Endometrial Carcinoma: Cohort Studies with Internal Controls (Page 5 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRP[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Henderson (1991)	Participants were residents of a Southern California retirement community (Leisure World), were almost entirely white, moderately affluent, and well educated. Subjects were recruited between June 1981 and January 1987. The resident's median age at study initiation in 1981 was 73 years. Information was gathered by periodic questionnaires and review of local county death certificates. Virtually all HRT users took unopposed estrogen. Reported here are the results of 7.5 years	8,881 postmenopausal women	Relative risk endometrial cancer death: 3.0 (no confidence interval provided) in ever users vs. never users of estrogen. The relationship between use of HRT and endometrial cancer incidence in this cohort is described in Pagnini-Hill (1989) (Pagnini-Hill, 1989),	

[a]95 percent confidence intervals are shown in parentheses
b Relationship is relative risk, unless stated otherwise.

KEY: NS = not statistically significant; O.E. ratio = observed to expected ratio; PERT = estrogen/progestin combination therapy

SOURCE: Office of Technology Assessment, 1995

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 1 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRP[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Hammond (1979)	Participants were diagnosed between 1940 and 1969 with diseases related to estrogen deficiency and followed for at least 5 years by the Duke University Obstetrics and Gynecology Service (Durham, NC). Expected rates of endometrial cancer were obtained from the Third National Center Survey for the Atlanta (Southeastern United States) area; 95.5% Of estrogen users received conjugated estrogens. Data on ERT use was obtained from hospital and clinic records.	301 "hypoestrogenic" patients who received ERT; 309 hypoestrogenic patients never receiving estrogen, 14 patients developed endometrial cancer	O.E. ratio 9.3 (4.7-16.7) in white women receiving estrogen: 1.1 (0.3-3.9) in white women not receiving estrogen All patients who developed adenocarcinoma of the endometrium during estrogen therapy had received this compound for at least five years.	
Vakil (1983)	Study examined the incidence of endometrial cancer in a cohort of women, 32-62 years of age, receiving estrogen treatment for menopausal symptoms among the patients of 20 gynecologists in the metropolitan Toronto area. Incidence rates in the cohort were compared to two control groups: the age-specific endometrial cancer incidence rates of the female populations of Ontario and of Saskatchewan. Estrogen therapy was begun between 1960 and 1970, and subjects were followed for up to 17 years	1,483 postmenopausal women	Relative risk of endometrial cancer in ever users 1.3 (no confidence interval provided	

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 2 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRF[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use [a,b]
Hunt (1987)	This is the same cohort as described in Hunt (1990) (Hunt, 1990). Cohort members were British women receiving hormone replacement therapy recruited at 21 menopause clinics. Subjects were recruited prospectively between 1978 and 1982, and retrospectively before 1978; nearly equal proportions were recruited retrospectively and prospectively. Most cohort members were aged 45-54 years at recruitment. Thirty-six percent of cohort had undergone hysterectomy, 2-2.5 times the proportion in the British population. Mean duration of follow-up was 67 months. Cancer registry rates for England and Wales were used for determining expected incidence.	4,544 British women receiving HRT (43% PERT users)	O.E. ratio of endometrial cancer is 2.84 (1 ,46-4.96) for current users of at least 1 year duration compared with expected incidence. No deaths from endometrial cancer occurred in the cohort. The relationship of HRT use to endometrial cancer death are reported in Hunt (1990), below.	Latency (time since first use): O-4 years. O.E. ratio 2.11 (0.57-5.39) 5-9 years. 3.03 (1.1 1-6.60) 10+ years, 5,71 (0.64-20.63) There was evidence of a rising trend in O.E. ratio with interval since first use, although the trend does not reach statistical significance.

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 3 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Ettinger (1 988)	Subjects were female members of Kaiser Foundation Health Plan, San Francisco, CA, all who had filled at least 2 prescriptions for an oral estrogen preparation and were aged at least 53 years in 1986. Estrogen users were menopausal women whose estrogen therapy was begun within three years of menopause and was used regularly for at least 5 years. Nonuser controls were women who had undergone spontaneous (nonsurgical) menopause, were identified from pharmacy records of health plan and were matched for age and length of membership in health plan. Mean age for estrogen users was 67 years, mean age of nonusers was 68.8 years. Clinical material was obtained from 1965 to 1980.	181 estrogen users, 220 nonusers controls	Risk ratio for endometrial cancer is 7.7 (2.4-24.5) for users compared with nonusers. Endocarconima developed in 9.9% of users compared with 1.4% of nonusers.	

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 4 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT [a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use [a,b]
Persson (1989)	Cohort members were women age 35 years or older who had been prescribed estrogens for the treatment of menopausal problems in the Uppsala health care region of Sweden during April 1977 to March 1980, identified through prescription records. Compliance, sociodemographic data, and lifetime exposures to estrogen and progesterone were assessed by a mailed questionnaire to 735 randomly selected members of the cohort. In addition, characteristics of all women with endometrial cancer were assessed by questionnaires. Cases of endometrial cancer were identified from a cancer registry and medical records. Expected outcome in the cohort was determined from age-specific incidence rates of endometrial cancer in the region in the same years. Pathologic specimens from all endometrial cancers and pre-malignant lesions in the cohort and the background population were reviewed. Average observation period	23,233 women on estrogens (133,373 person-years); 74 cases of endometrial cancer and 33 pre-malignant lesions	All HRT users: 1.4 (0.4-2.1) estrogen alone. 1.4 (1.1 -1 .9) estrogen and progestin: 0.9 (0.4-2.0)	Duration of estrogen use: estrogen alone. <6 mos.: 1.1 (0.5-2,5) 7-36 mos.: 1.4 (0,8-2.4) 37-72 mos.: 1.2 (0.6-2.2) >73 mos., 1,8 (1,1 -3.2) estrogen and progestin: <6 mos.: O (0,0-1 2.7) 7-36 mos.: 1.4 (0.5-3.6) 37-72 mos.: 1.2 (0.3-5.5) >73 mos.: O (0,0-456.1) Endometrial cancer and pre-malignant lesions estrogen alone. <6 mos.: 0,9 (0,4-2,1) 7-36 mos.: 1.6 (1 .0-2.5) 37-72 mos.: 1.6 (1 .0-2.6) >73 mos.: 2,7 (1 ,8-4,2) estrogen and progestin: <6 mos.: 0,9 (0.2-4.3) 7-36 mos.: 1.6 (0.7-3.5) 37-72 mos.: 0.9 (0.2-4.1) >73 mos.: O (0.0-211 8)

TABLE G-4: HRT and Endometrial Carcinoma: Cohort Studies with External Controls (Page 5 of 5)

Author	Description of cohorts	Size of cohort	Relationship of endometrial cancer to use and dose of HRT[a,b]	Relationship of endometrial cancer to duration, recency, and latency of HRT use[a,b]
Hunt (1990)	This is the same cohort as described in Hunt (1987) (Hunt, 1987). Subjects were women recruited from 21 menopause clinics around Britain; all had received at least 1 year continuous treatment with hormonal replacement therapy before recruitment, All subjects were interviewed at recruitment. Most subjects were age 45 to 54 at first use of HRT. Mean duration of HRT use was 66.9 months; 59& were current estrogen users. The observed mortality was compared to the expected rates in the female population of England and Wales.	4,544 long term users of HRT (43% PERT users)	Observed endometrial cancer deaths. O expected endometrial cancer deaths: 2,70 (taking into account uterine status) O/E ratio: 0.00 (0.00-0.97) The previous report, Hunt (1987), however, noted an elevated risk of incident endometrial cancer (see above)	

[a] 95 percent confidence intervals are shown in parentheses.
b Relationship is relative risk, unless stated otherwise

KEY: NS = not statistically significant; O.E. ratio = observed to expected ratio; PERT = estrogen/progestin combination therapy,

SOURCE" Office of Technology Assessment, 1995