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Hormones in the Etiology and Prevention of Breast and Endometrial Cancer*

R. DON GAMBRELL, JR., MD, Augusta, Ga

ABSTRACT: Since the incidence of endometrial cancer among estrogen-treated women at Wilford Hall Air Force Medical Center was not increased as reported by others, a prospective study was begun in 1975. With this data base, the cases of breast and endometrial cancer in estrogen and oral contraceptive users were reviewed. The incidence of mammary malignancy in postmenopausal estrogen users (141.0:100,000) was lower than that of the untreated women, ie, nonhormone users (342.3:100,000) ($P \leq .01$). The incidence of breast cancer in the estrogen-progestogen users (67.3:100,000) was significantly lower than that of the untreated women and than that expected from the Third National Cancer Survey (188.3:100,000) and the National Cancer Institute (NCI) data (229.2:100,000) ($P \leq .01$). Oral contraceptives also decreased the risk of breast carcinoma, since the incidence in users (10.3:100,000) was significantly lower than expected in this age group according to both the Third National Cancer Survey (53.3:100,000) and the NCI data (57.3:100,000) ($P \leq .01$). Unopposed estrogen replacement therapy increased the incidence of endometrial cancer to 410.8:100,000, but progestogen added to estrogen therapy significantly decreased this incidence to 68.1:100,000 ($P \leq .0001$). The estrogen-progestogen users also had a significantly lower incidence of endometrial carcinoma than the untreated women (258.3:100,000) ($P \leq .005$). Oral contraceptives, particularly the combination pill with estrogen and progestogen in each tablet, are protective against adenocarcinoma of the endometrium. The incidence of endometrial cancer apparently increased in premenopausal women during our study from 10.9:100,000 women in the first five years to 41.9:100,000 during the last two years as birth control pill use declined from 8,693 users in 1975 to 5,563 users during 1981, primarily in women over the age of 35.

ATTEMPTS HAVE BEEN MADE for many years to associate hormones, particularly estrogens, with breast and endometrial cancer. Since estrogens influence the growth of normal breast tissue, it is paradoxic that some patients with metastatic carcinoma of the breast respond to endocrine ablative surgery or antiestrogen therapy, while others may have remission with estrogen therapy. The incidence of breast cancer increases throughout the female life span and will strike one in 11 women in the United States.[1,2] Breast cancer is not only the most frequent malignancy in women (27%), but is also the leading cause of death from malignancy in women (19%) in the United States.[3] The American Cancer Society estimates 115,000 new cases of breast carcinoma were diagnosed in our country during 1983 and that 38,000 women died of it during that year. Speculation has arisen that any carcinogenic potential of birth control pills may not be detectable for ten years or more. However, long-term studies of large numbers of women have failed to incriminate either estrogen replacement therapy or oral contraceptives for any significantly increased risk of breast malignancy.[4-9]

It is now accepted that unopposed estrogen therapy increases the risk of endometrial cancer in postmenopausal women. Several retrospective studies since 1975 indicate that the risk of endometrial cancer from estrogen replacement therapy is increased from 1.7 to 20-fold.[10-13] There is also sufficient evidence from both the United States and England to indicate that opposing estrogen therapy with cyclic progestogens will prevent most endometrial cancers.[14-18] Since the incidence of endometrial cancer among estrogen-treated women at Wilford Hall USAF Medical Center was not increased as reported by others, a prospective study was begun in 1975. With this data base of hormone usage, the cases of breast and endometrial cancer in estrogen and oral contraceptive users at this institution were reviewed and comprise the basis for this report.

MATERIAL AND METHODS

A prospective study was begun in 1975 to determine the incidence of breast and endometrial cancer in postmenopausal women using various hormone regimens. A postmenopausal hormone survey card was initiated at the first visit and updated at each subse-

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quent visit. Information obtained included age, parity, blood pressure, weight, and history of hysterectomy with or without adnexal surgery. Hormone therapy, if any, was recorded, including type, dosage, how taken, and for how many years. Age at menopause and age of initial estrogen treatment were listed. A total of 5,563 postmenopausal women was registered in the study from 1975 through 1981. Data on the use of oral contraceptives for the seven years from 1975 through 1981 were obtained from computerized pharmacy records, based upon the number of birth control pills stocked and dispensed to patients.

The patients with breast and endometrial cancer were identified from the tumor registry. These records include narrative summaries, hospital chart cover sheets, operation reports, pathology reports, tumor board decisions, radiotherapy records, Southwestern Oncology Group (SWOG) chemotherapy protocols, and copies of all follow-up visits. Once a patient is entered into this registry, outpatient records are coded so that copies of all pertinent records are forwarded for inclusion. In addition, semiannual or annual questionnaires are mailed to all patients for current status after the initial therapy and patients are seen at least annually for a minimum of ten years. Wilford Hall United States Air Force Medical Center is the major US Air Force hospital for the San Antonio, Texas, area, so the patient population consists of female personnel on active duty, and wives and other dependents of military personnel, including retired personnel from that area. Statistical analysis of the data was performed by Harry Davis of the Systems and Computer Services, Medical College of Georgia, using the test for significance of difference between two proportions and the analysis of variance followed by Tukey's hsd (honestly significant difference) procedure.

RESULTS AND DISCUSSION

Exogenous Hormones and Breast Cancer

During the seven years of prospective study from 1975 through 1981, 53 postmenopausal women from the patient population at Wilford Hall USAF Medical Center were found to have breast carcinoma. There were 5,563 patients registered for a total of 37,236 patient-years of observation, an overall incidence of breast cancer of 142.3:100,000 women per year (Table 1). The lowest incidence of mammary malignancy was observed in the estrogen-progestogen users, eight patients diagnosed with breast cancer during 11,895 patient-years of observation for an annual incidence of 67.3:100,000 women. During 15,606 patient-years of observation, there were 22 breast cancers in the estrogen users, for an incidence of 141.0:100,000. With 18 carcinomas of the breast during 5,258 patient-years of observation, the incidence in the untreated women was 342.3:100,000. The expected incidence of breast cancer in this age group, according to the Third National Cancer Survey,[1] is 188.3:100,000, and, for ages 55-59, according to the National Cancer Institute Surveillance, Epidemiology and End Result (SEER) data,[2] is 229.2:100,000. The Third National Cancer Survey was conducted just before our study and the NCI SEER data was reported toward the end of our study.

TABLE 1. Incidence of Breast Cancer at Wilford Hall USAF Medical Center: 1975-1981

Therapy Group	*Patient-Years of Observation*	*No. Patients With Cancer*	*Incidence (per 100,000)*
Estrogen-progestogen users	11,895	8	67.3
Unopposed estrogen users	15,606	22	141.0
Estrogen vaginal cream users	3,130	3	95.8
Progestogen or androgen users	1,347	2	148.5
Untreated women	5,258	18	342.5
Total	37,236	53	142.3

The incidence of breast cancer in the estrogen-progestogen users (67.3:100,000) was significantly lower than that of the untreated women (342.3:100,000) and from that expected from the Third National Cancer Survey and the NCI SEER data ($P \leq .01$). The difference between the estrogen-progestogen users (67.3:100,000) and the unopposed estrogen users (141.0:100,000) was not significant, but does indicate a trend ($P \leq .08$). The incidence of breast carcinoma in the estrogen users (141.0:100,000) was significantly lower than that of our untreated group (342.3:100,000) ($P \leq .01$); however, it was not significantly different from that of the Third National Cancer Survey and the P value was $\leq .05$ compared to the NCI SEER data. The incidence of breast cancer in the estrogen vaginal cream users (95.8:100,000) was significantly lower than that of the untreated group (342.3:100,000), but not significantly different from that of either the Third National Cancer Survey or the NCI SEER data.

The concept of adding progestogens to estrogen replacement therapy was introduced at Wilford Hall USAF Medical Center in 1971. Figure 1 compares the number of women treated with estrogen and estrogen-progestogen with the incidence of breast cancer for the ten years from 1972 through 1981. With increased estrogen use, from approximately 1,320 patients in 1972 to 3,940 in 1975, there was no increase in the incidence of mammary malignancy. The apparent decline in the incidence of breast cancer from 189.4:100,000 in 1972 to 143.4:100,000 during 1975 was not statistically significant, but with progestogen use increasing from approximately 9.1% of the estrogen users in 1972 to 51.1% of the estrogen users during 1981, a significant decrease in the incidence of breast cancer occurred in the ninth and tenth years of study, with the incidence decreasing from 183.8:100,000 in 1978 to 104.2:100,000 during 1980 and 110.4:100,000 in 1981.

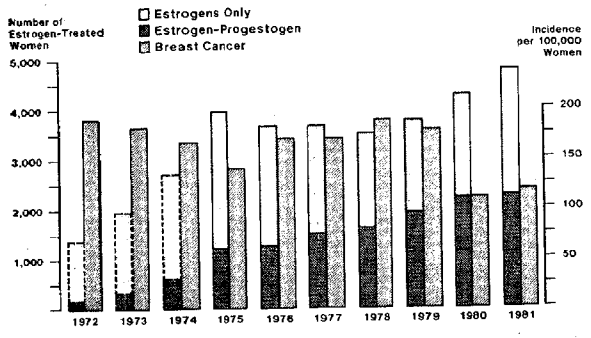

FIGURE 1. Comparison of the number of estrogen and estrogen-progestogen users with the incidence of breast cancer from 1972 through 1981. Dotted lines for estimated data from computerized pharmacy records; solid lines for data from prospective study.

It took seven years of prospective study and ten years of increasing progestogen use to reveal the protective effect upon the breast of adding progestogen to estrogen replacement therapy. There is no evidence that unopposed estrogen therapy increases the risk of breast cancer and, in fact, our study found a slightly significant decreased incidence of breast cancer in patients who used estrogens only. Hoover et al[4] observed an insignificantly increased risk of breast cancer (relative risk [RR] = 1.3) from postmenopausal estrogen use. In a later study from the same patient population, a decreased risk of breast cancer was found in the estrogen users by Bland et al.[19] Hammond et al[16] found four cases of breast cancer among 301 estrogen-treated women followed up for five or more years and four cases in the 309 untreated women. Only two studies[5,6] have observed any significantly increased risk of mammary malignancy from estrogen therapy. In neither was the risk increased in the total population, but rather in subgroups of estrogen users. In the ten-year double-blind study of Nachtigall et al,[15] four breast carcinomas were detected in the 84 placebo users and none in the 84 estrogen-progestogen users, which was statistically significant ($P \leq .05$).

Endogenous Hormones and Breast Cancer

Breast cancer is a multifactorial disorder with genetic considerations, endocrine relationships, oncogenic factors such as viruses, and environmental conditions such as chemical carcinogens. An estrogen window hypothesis has been proposed, in that unopposed estrogens with progesterone deficiency may provide a favorable state for induction of breast cancer by carcinogens in a susceptible mammary gland.[20] In a long-term follow-up of patients treated for infertility, those with progesterone deficiency had a 5.4 times greater risk of premenopausal breast cancer than women in the nonhormone group (those whose infertility was caused by other factors).[21] Another study of long-term progesterone deficiency observed an increased risk of postmenopausal breast cancer.[22]

Chronic anovulation increased the risk of endometrial cancer fivefold, and the RR of breast cancer after the age of 55 was 3.6. If the increasing incidence of breast cancer by age is closely examined, the role of female sex steroids becomes somewhat clarified (Fig 2).[1,2] The greatest increase in breast cancer is between the ages of late 30s and early 50s. At this time in a woman's life production of estrogens from the ovaries is declining as menopause approaches. More important is the fact that more women become anovulatory in the premenopausal years, resulting in an abrupt cessation of the cyclic progesterone levels that had been present throughout the reproductive years. The incidence of breast cancer continues to increase throughout the postmenopausal years, when estrogen levels are lower but not absent; however, few postmenopausal women, if any, produce progesterone. If unopposed estrogens were the cause of breast cancer, the incidence of this malignancy would peak in the 50s and 60s and decline thereafter, as does the incidence of endometrial cancer. Whatever the role of female sex steroids as cofactors or predisposing factors for mammary malignancy, progesterone deficiency seems to be more important than unopposed estrogens.

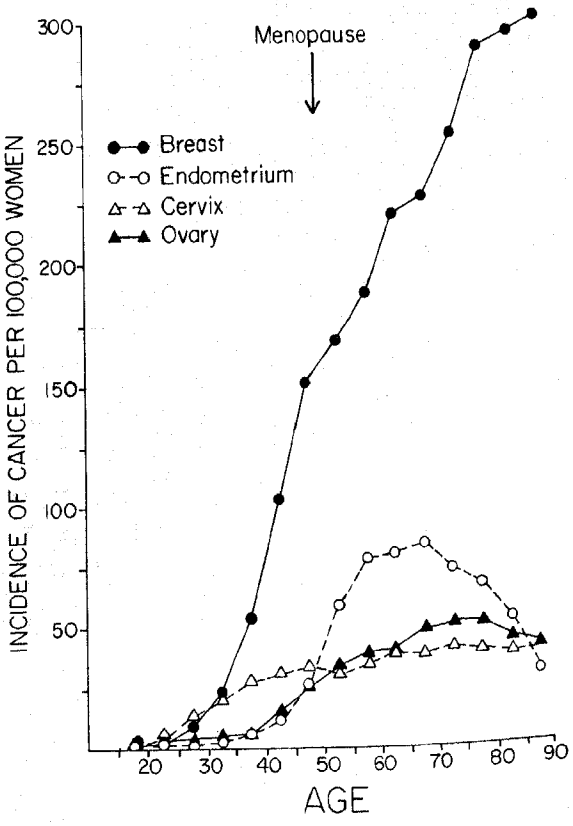

FIGURE 2. Incidence of breast, endometrial, cervical, and ovarian cancer in women according to age (from the Third National Cancer Survey data[1]).

Oral Contraceptives and Breast Cancer

Sixty-three premenopausal women with breast cancer were diagnosed at Wilford Hall USAF Medical Center from 1975 through 1981. A negative history of hormone use was obtained form 39 of these 63 patients (61.9%). Twenty-four women in this group were either using oral contraceptives when the mammary malignancy was detected or gave a history of their use. Duration of use varied from three months to 15 years and 19 patients had discontinued use from three months to 15 years before detection of the breast cancer. The number of patients using oral contraceptives during the seven years is shown in Table 2. There was a trend away from prescribing pills with a higher estrogen dosage (>50 μg) toward those containing small amounts of estrogen (50 μg or less). During the seven years there was a decline in oral contraceptive use by 26%, from 8,693 users in 1975 to 5,563 users during 1981, although the clinic population increased.

The incidence of breast cancer only among the patients currently using oral contraceptives could be calculated, since it was unknown how many patients from our clinic population had formerly used birth control pills. There were five women using oral contraceptives at the time breast cancer was diagnosed during 48,659 patient-years of observation, for an annual incidence of 10.3:100,000 (Table 3). Five other patients had used birth control pills until three to 14 months before detection of breast cancer. Including these five patients, the incidence of mammary malignancy was less that 20.6:100,000 women per year. Including all 24 women with any history of oral contraceptive use, the incidence of breast cancer was less than 49.3:100,000. All three of these rates are lower than the expected incidence in this age group, which is 53.3:100,000, according to the Third National Cancer Survey conducted just before our study.[1] These rates are also lower than those of the NCI SEER study (57.3:100,000), reported toward the end of our study.[2] The incidence of breast cancer in the current oral contraceptive users (10.3:100,000) was significantly lower than expected from both the Third National Cancer Survey and the NCI SEER data ($P \leq .01$).

Several epidemiologic studies have found either no increased risk of breast cancer in anovulant users or lower rates of malignancy in those taking birth control pills.[7-9] In the Walnut Creek study,[7] the incidence of breast cancer in the *ever* oral contraceptive users ages 18 through 39 was 25:100,000 compared to 55:100,000 in the *never* users (RR = 0.5). At all ages, including women to age 64, the incidence of mammary malignancy was 131:100,000 in the *ever* users and 114:100,000 in the *never* users (RR = 1.2), a difference that was not statistically significant. In the Royal College of General Practitioners study,[8] the incidence of breast cancer was 47:100,000 in the *ever* users compared to 39:100,000 in the control subjects (RR = 1.2). In the recent Centers for Disease Control (CDC) study,[9] the RR for *ever* users was 0.9, and women whose first use was more than 15 years earlier and who had used oral contraceptives for 11 years or more had an RR of 0.8. It is unfortunate that none of the epidemiologic studies separated their *ever* users into current users and past users. If they had, they might have obtained a decreased risk of breast cancer in current oral contraceptive users similar to the findings in our study.

Estrogen Replacement Therapy and Endometrial Cancer

Studies were performed at our institution from 1975 through 1981 primarily to determine the incidence of endometrial cancer in postmenopausal women receiving various hormone therapies. Adenocarcinoma of the endometrium was diagnosed in 28 patients during 20,560 patient-years of observation for an overall incidence of 136.2:100,000 women per year (Table 4). The largest group of patients, the estrogen-progestogen users with 11,753 patient-years of observation, had eight adenocarcinomas for an annual incidence of 68.1:100,000. The highest incidence of endometrial cancer was observed in users of unopposed estrogen, ten adenocarcinomas during 2,434 patient-years of observation for an incidence of 410.8:100,000. Nine untreated women were found to have adenocarcinoma of the endometrium during 3,484 patient-years of observation, an incidence of 258.3:100,000, the second highest observed. The difference between the estrogen-progestogen users (68.1:100,000) was highly significant ($P \leq .0001$, RR = 0.2). Not only did the estrogen-progestogen users have a significantly lower incidence than the unopposed estrogen users, they also

TABLE 2. Oral Contraceptive Use at Wilford Hall USAF Medical Center: 1975-1981

Year	*No. of Users*
1975	8,693
1976	7,566
1977	6,376
1978	7,236
1979	6,848
1980	6,377
1981	5,563
Patient-years of observation	48,659

TABLE 3. Incidence of Breast Cancer in Oral Contraceptive Users at Wilford Hall USAF Medical Center: 1975-1981

Oral Contraceptive Use	*Patient-Years of Observation*	*Mean Age (Range)*	*Patients With Cancer*	*Incidence (per 100,000)*
Current use	48,659	36.6 (35-39)	5	10.3
Use within one year	>48,659	36.6 (31-44)	10	<20.6
Any past history	>48,659	40.9 (31-53)	24	<49.3
Third National Cancer Survey (1975)		(35-39)		53.3
National Cancer Institute SEER (1980)		(35-39)		57.3

had a significantly lower incidence of endometrial cancer than the untreated women (258.3:100,000) ($P \leq .005$, RR = 0.3). The estrogen vaginal cream users also had a significantly lower incidence of endometrial carcinoma (50.6:100,000) than did the oral estrogen users ($P \leq .05$). The differences between the other groups were not statistically significant, although the difference between the progestogen or androgen users with no cancers during 913 patient-years of observation and the estrogen users did indicate a strong trend in that direction ($P \leq .06$).

Figure 3 compares the number of estrogen users and the number of estrogen-progestogen users with the number of endometrial cancers each year for the ten years from 1972 through 1981. With estrogen use increasing from approximately 1,000 postmenopausal women in 1972 to 2,700 by 1975, there was no increase in the number of endometrial cancers: six in 1972, five in 1973, and seven each in 1974 and 1975; however, with progestogen use increasing from 10% of the estrogen users in 1972 to 97.7% of the estrogen users during 1981, the number of endometrial cancer cases decreased from seven in 1975 to three or four each year during the next five years, and finally down to two cases in 1981.

Other studies from both the United States and abroad have confirmed the efficacy of adding progestogen to prevent adenocarcinoma of the endometrium.[15-18] Initially, a regimen of five to seven days of progestogen was prescribed monthly, but, soon after our prospective study began, we realized that this was not sufficient to prevent all endometrial cancers, so the duration was increased to ten days. Continuing studies have demonstrated that even ten days of progestogen monthly is insufficient since four cases of cancer have occurred with this duration of therapy. I concur with the recommendations of Whitehead et al[18] from England that the minimal duration of cyclic progestogens should be 13 days each month. During the reproductive years, the human corpus luteum produces progesterone for 13 to 14 days during the 28-day menstrual cycle. It is only logical, therefore, that progestogens be prescribed to estrogen-treated postmenopausal women for at least 13 days during a 30- or 31-day period.

TABLE 4. Incidence of Endometrial Cancer at Wilford Hall USAF Medical Center: 1975-1981

Therapy Group	*Patient-Years of Observation*	*No. Patients With Cancer*	*Incidence (per 100,000)*
Estrogen-progestogen users	11,753	8	68.1
Estrogen users	2,434	10	410.8
Estrogen vaginal cream users	1,976	1	50.6
Progestogen or androgen users	913	0	—
Untreated women	3,484	9	258.3
Total	20,560	28	136.2

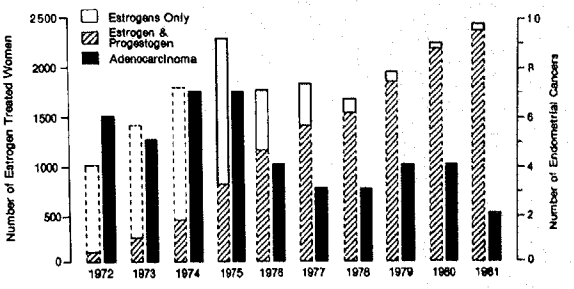

FIGURE 3. Comparison of the number of estrogen and estrogen-progestogen users with the number of endometrial cancers from 1972 through 1981. Dotted lines for estimated data from computerized pharmacy records; solid lines for data from prospective study.

Endogenous Estrogens and Endometrial Cancer

Not all postmenopausal women need estrogen replacement therapy, since many produce sufficient endogenous estrogens to remain asymptomatic and prevent the metabolic changes of later life. Within this group, however, may be those in need of progestogen therapy to prevent endometrial hyperplasia that may lead to cancer. During the reproductive years, estradiol secretion by the ovary constitutes the major source of estrogen production. In addition, both the ovaries and adrenal glands secrete androstenedione, which is then peripherally converted to estrone. When ovarian estradiol production diminishes at menopause, the principal source of estrogens is the peripheral conversion of adrenal androstenedione to estrone.[23] Two factors can increase this endogenous estrogen production: (1) increased production of androstenedione, and (2) increased peripheral conversion of it to estrone. Although the amount of androstenedione produced by normal postmenopausal women is 50% of that of premenopausal women, the percentage conversion of androstenedione to estrone in postmenopausal women is 150% of that in premenopausal subjects. The amount of androstenedione converted to estrone is further increased by aging, obesity, liver disease, and several other factors. This observation provides some insight into how predisposing factors, such as obesity, liver disease, and nulliparity, are related to endometrial cancer. The observation also explains why some postmenopausal women remain asymptomatic and are not affected by the metabolic changes of estrogen deficiency in later life, such as osteoporosis, atherosclerosis, and atrophic vaginitis.

In our study the second highest incidence of endometrial cancer was in the untreated women. Most of these postmenopausal women were not given estrogen therapy because they were asymptomatic and many showed near normal estrogen effect on the vaginal hormonal cytology. Many were obese and nulliparous, but not all had demonstrable predisposing factors. These postmenopausal women produce little,

if any, progesterone, so they need to be identified and treated with a progestogen to prevent adenocarcinoma of the endometrium. The progestogen challenge test should be administered to all postmenopausal women with an intact uterus, including estrogen-treated patients and asymptomatic women undergoing annual evaluation, by prescribing a progestogen daily for 13 days.[17] If there is a positive response as manifested by withdrawal bleeding, the progestogen should be continued for 13 days each month for as long as withdrawal bleeding follows. If there is no response, it is recommended that the progestogen challenge test be repeated annually.

Oral Contraceptives and Endometrial Cancer

If progestogens are protective in postmenopausal women, both estrogen-treated and those with increased endogenous estrogens, why were several cases of endometrial cancer reported during the mid-1970s among oral contraceptive users? Including three cases from Wilford Hall USAF Medical Center, 42 adenocarcinomas of the endometrium have been associated with birth control pills, principally the sequential type.[24-28] The sequential oral contraceptives contained very high dosages of estrogens (up to 100 μg of ethinyl estradiol), taken for 21 days with only five days of progestogen. As shown in our postmenopausal studies, five days of progestogen was insufficient to produce complete endometrial shedding, especially since the sequential birth control pill contained such a high dosage of estrogen. As a result of these studies, sequential pills were removed from the market in 1977 and there should be no additional endometrial cancers from these agents.

In 1975 10 to 13 million women in the United States were using oral contraceptives, and most were under 40 years of age. The annual incidence of endometrial malignancy is 21:100,000 women of all ages and ≤1:100,000 in women under the age of 40. If there were 10 million women under age 40 using birth control pills and the incidence was 1:100,000 per year, the expected number of 100 cases per year was more than three times the number reported during the past nine years (Table 5). It has been suggested that combined agents may afford protection against and the sequential pills may predispose toward endometrial cancer. A more logical conclusion is that the combination pills are protective from adenocarcinoma of the endometrium and the sequential contraceptives afforded less protection, as confirmed by the Walnut Creek contraceptive study[7] in which the risk of endometrial cancer was significantly decreased in *ever* users of birth control pills (RR = 0.6, 95% confidence interval, 0.3-0.9). In the CDC study, *ever* users of combined oral contraceptives were only half as likely to have adenocarcinoma of the endometrium as those who never used the pill.[29] This effect was much greater among nulliparous than parous women and may persist for ten years after cessation of birth control pill use.

I am concerned about the trend away from oral contraceptive use since there are so many side benefits, particularly for older premenopausal women. During the first five years of our study (Table 3), there were four cases of endometrial cancer in premenopausal women, including the three patients on sequential pills, for an incidence of 10.9:100,000. During 1980 and 1981, as more women discontinued oral contraceptive pills, particularly after age 35, the incidence of premenopausal adenocarcinoma of the endometrium increased to 41.9:100,000 (RR = 3.8). Other benefits from birth control pill use, in addition to decreased risk of endometrial and breast cancer, include less benign breast disease, fewer ovarian cysts and carcinomas, and less anemia, pelvic inflammatory disease, ectopic pregnancy, rheumatoid arthritis, endometriosis, and dysfunctional uterine bleeding.

The major complication in pill users over age 40 is myocardial infarction, in which there is an additive adverse effect from oral contraceptive use and smoking. The mortality from myocardial infarction in smoking users of oral contraceptive pills over age 40 varies from 19.2:100,000 (RR = 2.3) in the Walnut Creek study,[7] to 63.4:100,000 (RR = 4.2) in the Royal College of General Practitioners' study,[8] to 78.7:100,00 (RR = 2.5) in Jain's study.[30] However, the mortality in nonsmoking users of oral contraceptive pills after age 40 varies from 6.4:100,000 to 16.1:100,000 (RR = 1.4 to 3.3). Consideration should be given to continuing birth control pills in nonsmoking women beyond the age of 40, since the benefits outweigh the risks. Smoking women should be encouraged to stop smoking so they can also reap the side benefits of oral contraceptive pills.

CONCLUSIONS

Estrogen replacement therapy does not increase the risk of breast cancer and may possibly afford some protection. Adding progestogens to estrogen therapy significantly reduces the risk for mammary malignancy, and therefore should be given even to hysterectomized women for ten to 13 days each month. Unlike endometrial cancer, it may be that breast cancer is not diminished by progestogens alone so

TABLE 5. Incidence of Endometrial Cancer in Oral Contraceptive Users in the United States

	No. Users Under Age 40	*No. Users All Ages*
Oral contraceptive (OC) users in mid-1970s	10,000,000	13,000,000
Incidence of endometrial cancer	1:100,000	21:100,000
Expected cancers in OC users (per year)	100	273*
Reported cancers in OC users (8 years)	28	42

*Based upon 10% of endometrial cancers occurring before age 50 and few women using oral contraceptives beyond age 50.

consideration should be given to combination estrogen-progestogen replacement therapy for postmenopausal hormone therapy. Most studies list pregnancy, lactation, and increased parity as potentially protective against breast cancer. Oral contraceptives, by simulating pregnancy, especially with long-term use simulating increasing parity, may exert a protective mechanism against subsequent carcinoma of the breast. Therefore, birth control pills should be encouraged for younger women desiring family planning. For all women with intact uteri, progestogens should be added to estrogen replacement therapy for 13 days each month to reduce the risk of adenocarcinoma of the endometrium. The progestogen challenge test should be administered to asymptomatic postmenopausal women not requiring estrogen therapy and, if withdrawal bleeding results, the progestogen should be continued for 13 days each month for as long as withdrawal bleeding follows. Oral contraceptives should be encouraged for family planning since *ever* use reduces the risk for sebsequent endometrial cancer. Consideration should be given to continuing birth control pills in nonsmoking women past the age of 40 because the benefits, in addition to preventing endometrial cancer, probably outweigh the risk of cardiovascular disease.

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