ORAL CONTRACEPTIVES: RELATION TO MAMMARY CANCER, BENIGN BREAST LESIONS, AND CERVICAL CANCER

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Since the discovery and development of the first oral contraceptive by our laboratories (1), over 2000 articles have appeared on oral contraceptives, their components, and related subjects. Reviews summarizing general properties or discussing specific aspects of oral contraceptives have been published. The limited space available precludes an additional general survey of organ systems which may respond to oral contraceptives, and the more specific subject of the relationship of these compounds to mammary cancer, benign lesions of the breast, and cervical cancer was therefore chosen for review. The presentation is in part a critical discussion rather than an encyclopedic review.

INTRODUCTION

The oral contraceptives presently employed consist of an estrogen and progestin, administered in combination or sequentially; progestins may be given alone either orally or intramuscularly. Studies on estrogens and cancer are of particular interest, as for years it has been thought by some that estrogens may cause cancer, a concept that developed from some clinical data and from experimental studies performed chiefly in mice and rats. It has been difficult to obtain a positive effect of estrogen in other animal species, and clinical data to date have failed to demonstrate that estrogens cause cancer in women. However, because of the possible effect of estrogens, there has been considerable interest in the relationship of oral contraceptives to breast and cervical cancer. The properties of progestins differ from those of estrogens, and in certain biological systems a progestin may block or counteract the actions of an estrogen. It is therefore necessary to consider the effects of estrogens and progestins separately and their action when given in combination.

MAMMARY CARCINOMA

Cancer of the breast is the most common cause of death from cancer in women of reproductive age. Since it is known that estrogens cause growth of mammary gland tissue in women, and since mammary cancer is rare in men, it was logical for researchers to explore the possible role of estrogens in the development of breast cancer, even though many of the clinical concepts relative to breast cancer and hormones have rested on an uncertain foundation. For example, it was reported in 1896, and it has been taught and practiced since then, that ovariectomy will induce remission in many young women with advanced breast cancer (2). There are other reports of a similar effect, it being presumed that a favorable result was due to the elimination of ovarian estrogen secretion. Other investigators [cf Ravdin et al (3)] failed to find a beneficial effect of ovariectomy. To investigate this question further, a randomized prospective study of the value of ovariectomy as an adjunct to radical mastectomy for the treatment of operable carcinoma of the breast in premenopausal women was undertaken; the investigation found no evidence to indicate that prophylactic ovariectomy affected recurrence of the disease or survival rate (3).

It is probably correct to state that mammary cancer does not occur in the undeveloped gland, and to the extent that hormones are necessary for the development of the mammary gland they become a factor in the etiology of breast cancer. Despite the acceptability of this generalization most investigators agree that estrogens are not in themselves carcinogenic. There is evidence, which is beyond the scope of this review, that the presence of estrogens and progesterone provides only the background for the possible action of mammary tumor virus, prolactin, or genetic factors.

Experimental Studies

In 1932 Lacassagne (4) reported that in an inbred strain of mice with a high natural incidence of mammary cancer in the female, the administration of estrogen increased the incidence of mammary carcinoma in *male* mice. This and similar studies led to the fear that estrogens may cause breast cancer in women. Both genetic factors and the transmission of a "milk factor" are important in determining whether or not female mice of certain strains have a low or high spontaneous incidence of breast cancer. As shown by Bittner in 1936 (5), nursing mothers with the high spontaneous incidence of breast cancer transmit a milk factor or mammary tumor virus that plays an important role in inducing the high tumor rate in the female offspring. In high tumor strains of mice that possess the milk factor, estrogens will increase the incidence of breast cancer in male but not in female mice. Conversely, various studies demonstrate that in inbred strains of mice with a low spontaneous incidence of breast tumors and without the milk factor, the administration of estrogen does not increase the incidence of breast tumors in either male or female mice. Estrogens may increase the incidence of breast cancer in the rat but not in some other species of animals. Perhaps significantly, estrogen has not caused mammary cancer in the rhesus monkey, a finding which correlates with the absence of a demonstrable carcinogenic effect in women.

EFFECT OF ESTROGENS Earlier studies on the effect of estrogen on the incidence of mammary carcinoma in male and female mice and the relationship of this response to the strain of mouse and the absence or presence of the mammary tumor virus have been reviewed (6–9). Mestranol and ethinyl estradiol, the estrogens used in oral contraceptives, do not increase the incidence of mammary cancer in male or female mice from a strain (Carworth CF-LP) with a low spontaneous incidence of breast cancer (10). Using the RIII strain and F_1 (C3H X RIII) mice, which are high tumor strains, Rudali et al (11) observed mestranol to increase tumor frequency in male but not in female mice. Estrogens may increase the incidence of mammary adenocarcinoma in female rats, but the effect is an inconstant one and is not obtained in all studies (7, 10, 12).

Little information is derived from rabbits as this species is not used for chronic toxicity studies; one mammary adenocarcinoma was observed to develop in an estrogen-treated animal, but such may have been a chance finding (13). Estrogens have not produced mammary cancer in the guinea pig (8), and the administration of mestranol to dogs for 5 years did not have an adverse effect on the mammary gland (14).

The prolonged treatment of monkeys with estrogen has not resulted in mammary cancer. Pfeiffer & Allen (15) treated 6 rhesus monkeys for more than 2 years, 3 for more than 3 years, and 3 for over 4 years without inducing breast cancer. Geschickter & Hartman (16) administered estradiol or estrone to 6 rhesus monkeys for 13 months to 2 years and to 3 monkeys for more than 7 years; the treated animals showed, as expected, ductal hyperplasia and metaplasia and acinar dilation, but mammary cancer did not occur. In the extensive studies of Wazeter et al (14) mammary gland lesions were not observed in monkeys treated with mestranol for 5 years.

EFFECT OF PROGESTINS Progesterone has been variously observed to have no effect on, to increase, or to decrease mammary tumor incidence in mice (8). Norethynodrel has been reported to increase the number of mammary adenocarcinomas in female A/J and C3H/HeJ mice (17). Norethynodrel or ethynodiol diacetate did not exert a carcinogenic effect in male or female CF-LP mice (10). Various progestins are being studied in the dog and monkey (18).

EFFECT OF ORAL CONTRACEPTIVES Studies in mice have demonstrated that oral contraceptives (*a*) do not increase the incidence of breast cancer in female mice from inbred strains with a high spontaneous incidence of breast cancer and (*b*) do not increase the incidence of breast cancer in male or female mice from strains with a low spontaneous incidence of breast cancer (10, 19–23).

Low or moderately high doses of oral contraceptives do not increase the incidence of breast cancer in male or female rats (10, 24, 25). High doses of oral contraceptives may increase tumor incidence in some but not all groups of treated male and female rats (10). Several studies demonstrate that norethynodrel with mestranol does not increase the incidence of breast cancer in rats pretreated with dimethylbenzanthracene or methylcholanthrene [cf Drill (10)].

Sichuk et al (26) observed that administration of an oral contraceptive to male hamsters did not induce breast cancer.

Oral contraceptives are being studied in the beagle dog, but because of the markedly different reproductive cycle in this species, their sensitivity to certain progestins, and the type of tumor which commonly occurs, it is doubtful that the results obtained will have relevance to the effects that may occur in women. Mammary lesions have occurred in some studies with oral contraceptives, but the lesions have been difficult to interpret and there is disagreement among pathologists as to whether the change is benign or malignant (18). Mammary nodules occurred in both control and treated animals, and spontaneous regression is frequently seen in both groups. In dogs treated with two oral contraceptives for five years there was no significant difference in the number of palpable nodules between control and treated animals (10).

It was reported that 1 of 6 rhesus monkeys receiving norethynodrel with mestranol died from an infiltrating duct carcinoma of the mammary gland during the 18th month of treatment (27). That this is a chance association is shown by the absence of similar effects in other studies. Kar and co-workers (28) administered the same compound cyclically to 14 prepuberal rhesus monkeys for a period of 90 days to 3 years; 2 animals were treated for 2 years and 2 for 3 years. A cyclic withdrawal bleeding occurred regularly and breast development was promoted; obvious mammary gland lesions or death from mammary cancer did not occur in any of the treated animals. Drill et al (29) reported that the administration of Enovid-E® or Ovulen® to groups of 16 monkeys at 1, 10, or 50 times the human doses for five years did not lead to the development of breast nodules or death from breast cancer.

Clinical Studies

EFFECT OF ESTROGENS A review of clinical studies did not demonstrate that the use of estrogens increased the incidence of breast cancer in women (10). Although treatment was for prolonged periods of time, the majority of women treated were menopausal or postmenopausal and over 50 years of age. However, this should not be considered an objection as the effect of a real carcinogen will be related to the duration of treatment and time of follow-up rather than to the age at which treatment was started.

In the recent report of Burch et al (30) no statistically significant increase in breast cancer was observed in 737 women treated with estrogen for a total of 9869 woman-years. Fechner (31) found 13 of 240 women with breast cancer to be using estrogens; the estrogen did not produce distinct morphologic alterations or alter the proportion of different types of breast cancer. Examination of statistical data from various sources does not demonstrate an increase in mortality from breast cancer during the period when large numbers of women have been using estrogen (10), and in a retrospective case-control study (32) and a hospital survey (33) there was no association between the use of estrogens and the occurrence of breast cancer.

EFFECT OF PROGESTINS Treatment with norethynodrel (34), norethindrone (35), medroxyprogesterone acetate (36), or norethisterone acetate (37) may produce

objective remission in patients with mammary carcinoma. Zanartu et al (38) studied the development of mammary gland nodules in 3350 women receiving intramuscular medroxyprogesterone acetate or chlormadinone acetate for contraception; some also received estrogens. The study involved a total of 124,300 months of experience, or 9233 woman-years of treatment. During the test period ten breast nodules were detected, two of which were carcinomas. The number of cases found did not differ significantly from the calculated expected number (10).

EFFECTS OF ORAL CONTRACEPTIVES Since mammary cancer is the most common type of cancer observed in women of reproductive age, cases may be expected to occur by chance at the same time that oral contraceptives are used. Hertz (39) has emphasized that oral contraceptives should be studied for prolonged periods of time, since there is a long latent period, averaging ten years or more following exposure to known carcinogens before the ultimate carcinogenic response is obtained. The problem is that women using oral contraceptives for family planning are likely to interrupt therapy from time to time making it difficult to obtain data on large numbers of women using oral contraceptives for long periods of time. However, if a substance is carcinogenic a positive response should be expected in a proportion of individuals treated for 0–5 and 5–10 years; evaluation of such data and related studies does not demonstrate that oral contraceptives increase the occurrence of breast cancer or cause breast cancer [cf Drill (10)]. Fechner (40) did not find evidence for an increase in incidence of cancer, observing that since the introduction of oral contraceptives the frequency of breast cancer in women less than 35 years of age has remained at 4.4% of all breast cancers in his hospital population. Prechtel & Seidel (41) demonstrated that the use of the antiovulants did not increase the incidence of dysplasia or carcinoma of the mammary gland (Table 1). Similar results are provided by the recent report of Kay (42) who found no difference in the incidence of malignant neoplasm of the breast between women using oral contraceptives and a control untreated group.

In other studies mammograms made before and during the use of oral contraceptives did not demonstrate any increase in pathological findings (43), and a retrospective case-control study (44) and a hospital survey (45) do not reveal an association between the use of oral contraceptives and the occurrence of breast cancer.

BENIGN BREAST LESIONS

Benign breast lesions occur spontaneously in some species of animals and in women. Fibroadenoma is the most common type of benign breast tumor found in young women and breast nodules related to fibrocystic disease are frequently observed in premenopausal women.

Experimental Studies

EFFECT OF ESTROGENS The administration of ethinylestradiol or mestranol does not increase the incidence of mammary gland adenomas in male or female mice (46).

Table 1 Effect of oral contraceptives on frequency of mammary fibroadenoma and carcinoma in biopsy specimens from women age 15 to 45[a]

	Control group	Oral contraceptive users
Number of women	557	233
Fibroadenoma	27%	26%
Carcinoma	8%	6%

[a]Data from Prechtel & Seidel (41).

EFFECT OF PROGESTINS The incidence of mammary gland adenomas in male or female mice is not increased by administration of low, medium, or high doses of norethynodrel or ethynodiol diacetate (46). In male rats low doses are without effect, but the middle and high dose of norethynodrel and the high dose of ethynodiol diacetate increased the number of benign mammary tumors in male rats; none of the doses of either progestin produced any increase in incidence of benign mammary tumors in female rats (46).

Mammary gland nodules may be observed in untreated control dogs and in dogs receiving progestins (18). Benign mixed mammary tumors can be produced by the administration of progesterone (47, 48). The administration of megestrol acetate or chlormadinone acetate to dogs, particularly at high doses, also induces benign mixed mammary tumors and nodular hyperplasia (48, 50). One dog receiving chlormadinone had an adenocarcinoma, which may represent a spontaneous lesion (50). It should be emphasized that the benign mixed mammary tumor, a tumor that commonly occurs in the dog, is rarely seen in other domesticated animals, in other commonly used laboratory animals, or in humans, and this canine tumor is not the histological counterpart of the human fibroadenoma (49). The sensitivity of the dog to progesterone and certain progestins (51) and the type of tumor which occurs makes it unlikely that the results obtained in this species will offer predictability for effects in women.

There is a paucity of data on breast lesions in the rhesus monkey, but it appears that mammary nodules, usually transient in nature, may occur in untreated animals (18, 52). Nelson & Shott (52) reported that 2 of 20 control monkeys had multiple palpable breast nodules; excision and examination of one nodule demonstrated nodular hyperplasia. In contrast to the results obtained in the dog, preliminary evaluation shows that the administration of chlormadinone acetate to monkeys has not resulted in the occurrence of mammary nodules (18).

EFFECT OF ORAL CONTRACEPTIVES Oral contraceptives, administered in low, medium, or high doses, do not increase the incidence of mammary gland adenomas in male or female mice (46). Heston et al (23) did not obtain an increase in mammary tumors in any of five strains of mice, including the highly susceptible C3H strain, receiving three different dose-levels of Enovid®. Tumor incidence was not increased in male rats receiving low or medium doses of oral contraceptives; an increase

occurred in one of five high dose male groups, but no increase in tumor incidence was observed in female rats at any dose level (46).

Preliminary data on oral contraceptives used clinically does not indicate that these substances have a specific effect on the occurrence of mammary nodules in the dog or monkey (18). There was no significant difference in the number of mammary nodules between control and untreated groups of dogs or monkeys receiving Enovid-E or Ovulen for five years (10).

Clinical Studies

EFFECT OF ESTROGEN Fibrocystic disease is common in the premenopausal woman (53, 54) and may also occur in the postmenopausal woman treated with estrogens (55). Gray (55) found 22 cases of breast cysts in 1001 postmenopausal women receiving estrogens. Examination of breast tissue from 43 women taking estrogens for menopausal symptoms or replacement therapy revealed two of the patients with typical fibroadenomas (31). The other 41 patients had fibrocystic disease that did not differ from control patients except for a slight increase in epithelial hyperplasia, which the author judged to be insignificant. Also a retrospective case-control study did not show any association between estrogens and benign breast lesions (56).

EFFECT OF PROGESTINS Zanartu et al (38) evaluated medroxyprogesterone acetate and chlormadinone acetate as contraceptives, administering them intramuscularly every 2, 3, or 6 months to 3,350 women for 110,556 months of study (9213 woman-years). Estrogen was also given for 7 to 10 days each calendar month to induce withdrawal bleeding in women with amenorrhea, but the number of women in the study receiving estrogen is not stated. Eight women developed benign breast nodules during the study, 6 of whom had also received estrogen on occasion; 2 had chronic mastitis, 1 a fibroadenoma, and 5 had transient nodularities diagnosed as adenosis or cystic disease. The incidence of benign and transient lesions experienced in this large prospective study is not out of line with what may be expected in untreated women.

EFFECT OF ORAL CONTRACEPTIVES Fibroadenomas are the most frequent benign breast tumors found in young women and may therefore be expected to occur by chance in women taking oral contraceptives. Instances of fibroadenomas in women using oral contraceptives have been reported (55, 57, 58). Wiegenstein et al (59) noted that 12 of 67 women (18%) with adenofibromas had multiple lesions and believed it significant that 11 of the 12 had received oral contraceptives. However, Oberman (60) stated that their conclusion regarding the association of the adenofibromas and the pill seemed inappropriate, as multiple lesions occur in women not using such contraceptives. Oberman & French (61) described 79 women who had had adenofibromas excised before the use of oral contraceptives; 15 (19%) of the women had multiple adenofibromas, resulting in an incidence almost identical with that reported by Wiegenstein et al (59). Daniel & Mathews (62) also found the fibroadenomas to be multiple in 25% of 90 females, 12 to 21 years of age.

A series of carefully conducted studies by Prechtel (63) and Prechtel & Seidel (41, 64) have demonstrated that the use of oral contraceptives does not increase the frequency of mammary gland fibroadenomas observed at the time of surgery or in biopsy specimens (Table 1). Fechner (65) evaluated 4019 breast biopsies taken between the years 1952 and 1969, finding that the incidence of fibroadenoma, expressed as the percentage of all conditions for which surgical operations on the breast were done, was virtually identical for the years preceding the use of oral contraceptives and in the years during which oral contraceptives were used. Lastly, retrospective case-control analysis (44, 56) and a hospital survey (45) revealed no association between benign breast lesions and oral contraceptives.

Three reports emphasized the degree of epithelial proliferation present in their cases of fibroadenomas in women using oral contraceptives (55, 57, 58). However, the occurrence of increased epithelial growth is known to occur in women not using oral contraceptives, and more detailed studies do not demonstrate a difference between users and nonusers of oral contraceptives (41, 63–67).

CERVICAL CANCER

Next to breast cancer, cervical cancer is the most common cause of mortality in women of reproductive age. The etiology of cervical cancer is not known. Various studies have shown that the most important factors, some of which are interdependent, related to a higher frequency of cervical cancer are (*a*) sexual intercouse at an early age, (*b*) early marriage, (*c*) pregnancy in early reproductive years, (*d*) multiple sex partners and multiple marriages, (*e*) higher incidence of vaginal and pelvic infections, and (*f*) low socioeconomic status (68–70). These data suggest that the etiologic factor or factors are transmitted by sexual intercourse.

The cervix, being one of the reproductive organs, shows changes in secretory and mitotic activity in response to the cyclic output of ovarian hormones and to exogenous steroid administration. There is no known relationship of the steroid hormones to the pathogenesis of cervical cancer. Interest in estrogens derives chiefly from the finding that estrogen may increase the occurrence of cervical cancer in mice, an effect apparently not obtained in other species of animals. Consistent with the concepts discussed is the fact that cervical cancer is almost nonexistent in Catholic nuns. The disease is uncommon among Jews; this has led to the hypothesis, as yet unproven, that male circumcision, smegma, and other factors of penile hygiene are of etiologic importance. Some reports, but not all investigators, have observed a relationship between herpes virus type 2 and cervical cancer.

Whatever the cause of cervical cancer, the pathological process does occur in young women, and it is generally accepted that it progresses from cervical dysplasia to carcinoma in situ and finally invasive carcinoma. The peak frequency of dysplasia occurs in the 20–29 age group. Thus, clinically, the evaluation of oral contraceptives can be made at several different levels such as on the prevalence of suspicious and abnormal Papanicolaou smears or on the frequency of dysplasia and carcinoma in situ.

Experimental Studies

EFFECT OF ESTROGENS The administration of estrogens to various strains of mice has been observed to increase the occurrence of cervical cancer (8). In large scale studies in mice, treated as previously described (46), mestranol did not induce cervical carcinoma at any of the doses employed. With ethinyl estradiol three cervical carcinomas occurred in the high dose group, but none were obtained in the middle or low dose groups.

In their review of 1959 Gardner, Pfeiffer & Trentin (8) list only one study with estrogen in the rat; one cervical lesion, a uterine-cervical papilloma, was found in a group of ovariectomized rats receiving estrone (71). McKinney et al (24) did not obtain cervical cancer in rats given ethinyl estradiol. Cervical cancer has not been reported in the rabbit, guinea pig, or hamster treated with estrogens (cf 8).

The administration of estrogen to monkeys produces cervical squamous metaplasia, but cervical cancer does not occur even after treatment for prolonged periods of time (15, 72, 73).

EFFECT OF PROGESTINS Treatment of mice and rats with norethynodrel or ethynodiol diacetate [see Drill (46) for treatment schedule] did not result in cervical carcinoma.

EFFECT OF ORAL CONTRACEPTIVES Dunn (74) reported the occurrence of histological changes in uterine cervix, diagnosed as early cancer or infiltrating cancer, in all of six BALB/c mice treated with Enovid for 518–721 days; similar lesions were not present in five controls. This observation was not confirmed by the more extensive study of Heston et al (23), using 163 controls and 157 treated mice of the same strain. Heston et al state, "while we observed the lesions she described, we were unable to draw a clear line of distinction between them and those in the controls." The number of such lesions was increased in the high dose group, but not in the low or middle dose groups; grossly identified tumors did not occur. In the C3HfB, A, or C57BL strains of mice there was no increase in the occurrence of cervical lesions when Enovid was administered at three different dose levels (23). Treatment of Cf-LP mice with three different doses of Enovid, Enovid-E, Ovulen, Demulen, or Metrulen [protocol as previously described (46)], did not result in the occurrence of cervical carcinoma; one animal had a fibrosarcoma.

Cervical cancer did not occur in rats receiving ethinyl estradiol with megestrol acetate (24), Norlestrin (25), or in rats treated with different dose levels of Enovid, Enovid-E, Demulen, or Ovulen [see Drill (46) for treatment schedule].

Clinical Studies

CERVICAL CANCER AND AGE Before the era of oral contraceptives it was known, but not generally recognized, that a significant percentage of cases of cervical carcinoma occur in young women. As early as 1919 Peterson (75) observed that 5.1% of 406 cases of cervical cancer occurred in women between 20 and 30 years of age. A similar frequency is given in other studies for women age 30 or below, as

follows: 9.9% (76); 7.4% (77); 3.9% (78); 6.8% (79). Kyriakos et al (69) have recently reported 59 cases of cervical cancer occurring in women age 30 or less. Representative data on the frequency of invasive cervical cancer in young women and the increase in frequency with age are as follows: at age 25 or less, 0.6% (80); less than 30 years of age, 5.1% (81) and 4.6% (82); under age 35, 25% (83); below the age of 40, 25% (82) and 24.6% (84).

Although uncommon, invasive cervical cancer may also occur in women age 20 or less (85). In women age 15–19 Parker (82) found seven cases (0.69%) of carcinoma in situ and one case (0.06%) of invasive cervical cancer, and eight cases in women under the age of 21 have recently been reported (86). Among 3000 women screened, Ferguson (87) found 167 teenagers with class III to V smears; of 120 subjected to tissue diagnosis there were 43 cases of dysplasia, 16 cases of intraepithelial carcinoma, 1 case of superficial invasion, and 1 case of invasive carcinoma.

MORPHOLOGIC EFFECTS OF STEROIDS ON CERVIX Pregnancy, estrogens, progesterone, and oral contraceptives produce histological changes in the cervix. These changes are benign, although at times they may resemble and be confused with early carcinoma.

Atypical hyperplasia of cervical epithelium, varying from mild to severe, may be produced by either exogenous or endogenous estrogen (88). The histological changes may at times closely resemble those of carcinoma in situ, but there was no evidence that the changes were directly related to cervical carcinoma; similar atypical epithelial changes occurred in women during pregnancy and in newborn infants and seemed to be related to the high estrogen level present in these conditions. Maqueo et al (89) observed that many of the cervical changes occurring during pregnancy and after prolonged progestin therapy were present in a lower incidence in women using oral contraceptives. Carbia et al (90) did not observe precancerous lesions; the histological changes that occurred in the uterine cervix during the use of oral contraceptives were similar to those of normal pregnancy.

Endogenous estrogen may also result in adenomatous hyperplasia (88), and atypical reactions of the endocervical epithelium, variously called atypical endocervical hyperplasia, adenomatous hyperplasia, polypoid hyperplasia, or even reversible cancer, have been observed in women taking oral contraceptives (91–97). Although the changes are benign, the hyperplasia may at times be sufficiently atypical to be confused with early adenocarcinoma.

EFFECT OF ESTROGENS There are reports in the medical literature on the occurrence of cervical carcinoma in women using estrogens but the number of such cases is numerically insignificant. In view of the widespread use of estrogens various investigators have examined mortality statistics without finding an increase in mortality from cervical cancer during the period estrogens have been employed (9).

Geist & Salmon (98) did not obtain a case of genital cancer in 206 women receiving estrogens for 6 months to 5½ years, and concluded in 1941 that there "appears to be no evidence to justify the fear that carcinoma of the genital tract may result from the therapeutic use of estrogens." In 120 postmenopausal women treated

cyclically with estrogen for an average of 5 years there were no cases of cervical cancer (99). Wallach & Henneman (100) observed one case of carcinoma in situ among 292 women receiving estrogen for an average of 5.1 years. Wilson (101) treated women with estrogen for 14 months to 27 years (1852 patient years) without obtaining one case of genital cancer. In an extensive study Gordan (102) treated 220 postmenopausal women with estrogen for 1545 woman-years. Because of the number of patients, their advanced age, and the number of years at risk, 18 cancers were normally expected; only 6 were obtained and none were cervical carcinomas.

EFFECT OF PROGESTERONE Hertz & co-workers (103) observed that parenteral progesterone produced visible and palpable evidence of remission in 11 of 17 patients with cervical carcinoma. Similar studies have apparently not been conducted with any of the newer and orally active progestins.

CASES OF CERVICAL CANCER DURING USE OF ORAL CONTRACEPTIVES Clinical trials of oral contraceptives have been conducted without cases of cervical cancer being observed. In other clinical studies cervical cancer has been observed at the same time that oral contraceptives were employed (104–108). During a study of oral contraceptives Diddle et al (109) observed the occurrence of 2 cases of dysplasia, 6 of carcinoma in situ, and 1 case of early invasive carcinoma, but the number of cases in which the lesion was present before treatment is not known. Courey & Powell (110) report 16 cases of cervical cancer in situ in women age 22 to 45 who were not taking oral contraceptives, compared to 6 cases of cervical cancer in situ in women age 22 to 45 taking oral contraceptives. They also observed 9 cases of cervical cancer in the control group and no cases of cervical cancer in women using oral contraceptives. Unfortunately, prevalence rates cannot be calculated as the population in the reproductive age range is not given.

The occurrence of carcinoma of the cervix during the use of oral contraceptives is not unexpected, as cervical cancer will occur independent of the chance use of any medication. Although the cases that have occurred at the same time that oral contraceptives were being used do not indicate an adverse effect, it is obvious that more definitive data must be examined before any conclusion can be reached.

PAPANICOLAOU SMEARS AND ORAL CONTRACEPTIVES Initial data on oral contraceptives and the Papanicolaou smear have been reviewed (1), and more recent studies (111–125) involving larger numbers of women are summarized in Table 2. Examination of the prevalence rates does not indicate an adverse or toxic effect of the oral contraceptives. In comparing the prevalence rate for suspicious and malignant cervical smears between a control population and users of oral contraceptives it should be noted that there are differences in the characteristics of the groups which are present to some extent in each of the studies listed. The variables encountered may at times favor the control group or the treated group. Thus, if oral contraceptives are without a beneficial or detrimental effect on the cervical smear it may be expected, on the basis of chance alone, that the prevalence rate in women using oral contraceptives will be below the control rate about 50% of the time and above the control rate in about 50% of the studies. As seen in Table 2 the prevalence rate in

Table 2 Prevalence rate for suspicious and malignant cervical smears (Class III, IV, and V) (Percentage per 100 smears or patients)

Reference	Population	Control screening	Oral contraceptives
Tyler (111)	649	0.6[a]	
	1,004		0.4[a]
Tyler (112)	2,510	1.24	
	6,746		0.77
Pincus (113)	2,786	3.62	
	657[b]	1.97	
	2,850		1.30
	3,403		0.94
Garcia et al (114)	4,538	2.98[a]	
	1,346		2.67[a]
	306		2.29[a]
Attwood (115)	500	2.00	
	490		2.25
Wied et al (116)	19,325	0.51	
	1,628		0.43
Liu et al (117)	200	0.0	
	1,000		1.88
Andelman et al (118)	2,999	0.37	
	2,395		0.50
Topp & Meissner (119)	—	0.6–0.8	
	1,746		0.7
Soost (120)	32,046	2.9[c]	
	1,031		1.15
	2,881		0.97
Ayre et al (121)	100,000[d]	1.50	
	1,020[e]		2.64
Chai et al (122)	30,834	0.63	
	4,164		0.34
Kline et al (123)	17,724	1.0	
	2,296		2.0
Bibbo et al (124)	127,731[c]	1.64	
	2,624[f]	3.80	
	18,380		2.92
Miller (125)	2,394	0.66	
	2,394		0.58

[a] Class IV and V smears.
[b] Used only foams.
[c] Includes women of higher age levels.
[d] From private physician's offices.
[e] From one Planned Parenthood Clinic.
[f] Used only IUD.

women using oral contraceptives is slightly below the control value for 8 of the measurements, is between control rates in 2 studies, and is slightly above the control rate in 4 studies. No conclusion can be reached regarding the data of Liu, as the control population is too small to be significant.

Pincus & Garcia (126) compared the rate of development of Grade III to V Papanicolaou smears between 708 women using vaginal contraceptives or intrauterine devices and 873 women using oral contraceptives; all had negative smears before the use of contraceptives. Although exposure to oral contraceptives was longer, the cumulative incidence rate of abnormal smears was lower in women receiving oral contraceptives than in those using intravaginal foams, jellies, or intrauterine coils. Dougherty (127) notes that the medical literature indicates an expected ratio or prevalence rate to annual incidence rate of about 2:1. In his study with oral contraceptives the ratio was approximately 1, indicating the possibility of a change in incidence. However, the more extensive experience of Laurie & Korba (108) does not confirm his finding, as the incidence during use of oral contraceptives did not differ significantly from that reported in the literature.

Miller (125) evaluated the use of oral contraceptives in a community of 83,170 people; the female population between the age of 15 and 49 numbered 16,926, of whom 11,476 had cytological examinations. Of the women examined, 2394 were using an oral contraceptive, and a control group of 2394 women was selected by randomly pairing each patient on therapy with a patient of the same age. The patients were not matched for parity or other means of control, but the author states there were no differences between the test and control groups in regard to those factors and conditions known to be associated with an increased incidence of carcinoma of the cervix. There was no difference in the incidence of suspicious or malignant smears between the control and treated groups of women age 15–49 or when the prevalence rate was analyzed by 5-year age groups.

CERVICAL DYSPLASIA AND ORAL CONTRACEPTIVES Cervical dysplasia is usually considered a precancerous lesion that may revert to normal or may progress to carcinoma in situ. The percentage of women showing progression or regression will vary considerably depending on factors such as the duration of follow-up, the type of interim treatment, and the severity of the dysplasia (128, 129). Richart & Barron (130) estimated the median transit time to carcinoma in situ for all dysplasias was 44 months, ranging from a median of 86 months for patients with mild dysplasia to 12 months for a patient with severe dysplasia.

Ayre & co-workers (131) did not observe a carcinogenic effect of norethynodrel with mestranol when it was administered to patients with dysplasia, and later reported (121) regression of cervical dysplasia during treatment with this contraceptive. In the study of Soost (120) 5 of 6 class III smears were observed to revert to normal during continued use of oral contraceptives. Kline et al (123) reported that 19 of 45 women with atypical smears showed reversion to normal; of the 19 reversions, 12 were in women who continued oral contraceptives. It was reported (132) that the frequency of dysplasia in conization samples from women taking oral contraceptives was increased in young women but not in older women, but the review of

Haller (133) did not confirm
increased in any of the age groups. Fuertes et al (134) compared changes in the Papanicolaou smear between 4846 women using oral contraceptives and 4788 women using vaginal contraceptives. They concluded that there was no significant difference in the pattern of progression and regression of cervical cytology between the groups and that "oral contraceptives do not aggravate the conditions which lead to development of premalignant lesions in the uterine cervix."

Several studies have shown that neither the prevalence rate nor the incidence rate for cervical dysplasia is altered by the use of oral contraceptives. Data on the normal age-specific prevalence rate for cervical dysplasia in women of reproductive age are given by several authors (124, 135). Soost (120) found 6 class III smears among 1031 women taking oral contraceptives, giving a prevalence rate of 5.8 cases/1000 women, which is at or below the normal prevalence rate. In the extensive study of Bibbo, Keebler & Wied (124) the prevalence rate for dysplasia in users of oral contraceptives is not different from that of the two control groups (Table 3).

Stern (135) reports the normal age-specific annual incidence rate for cervical dysplasia in women age 20–49, for the years 1955–1959, to be 1.1 cases per 1000 women. Behrman (136) found 2 cases of dysplasia in 1359 women treated receiving oral contraceptives for an average of 1.7 years; the calculated average incidence rate of 0.86 cases per 1000 women per year is in the normal range. In a retrospective case-control study the use of oral contraceptives for an average of 20 months did not affect the risk for developing cervical dysplasia (137).

CERVICAL CARCINOMA IN SITU Studies on the prevalence rate for cervical carcinoma in situ in women using oral contraceptives are summarized in Table 4.

Melamed et al (138) found that the age-specific prevalence rates were higher in an oral contraceptive-treated group than in a control group of women using a diaphragm. They concluded that the small but significant difference
may be attributed to an increased rate in women using oral steroids or a decreased rate for women using the diaphragm. Various comments (139–143) made regarding the problems present in the study of Melamed and co-workers emphasize the difficulties encountered when a comparison of rates is attempted, difficulties that will be present to some degree in all studies of comparative prevalence rates.

Table 3 Prevalence rate for cervical cancer [Data from Bibbo, Keebler & Wied (124)]

	Control groups		
	IUD only	No IUD or oral contraceptive	Oral contraceptive users
Number of women	2,624	127,731	18,380
Dysplasia	3.12%	1.15%	2.31%
Cancer in situ	0.57%	0.35%	0.57%
Invasive cancer	0.11%	0.14%	0.04%

Table 4 Prevalence rate for cervical carcinoma in situ based on smears or biopsy

Reference	Population	Prevalence rate (Number/1000) Control	Oral contraceptives
Soost (120)	3,912	—	0.26
Melamed et al (138)	6,809[a]	3.8	
	27,508		6.6[b]
Chai et al (122)	30,834[c]	1.68	
	4,164[d]		0.96
Bibbo et al (124)	127,731[e]	3.5	
	2,624[f]	5.7	
	18,380		5.7
Miller (125)	2,394	2.1	
	2,394		0.84

[a] Control group used diaphragm.
[b] Includes data from women before using oral contraceptives.
[c] Nonfamily planning clinic.
[d] Family planning clinic.
[e] Includes women of higher age levels.
[f] Control group used intrauterine device.

In the study of Melamed et al (138) the prevalence rate for carcinoma in situ in women using oral contraceptives is approximately twice that of women using a diaphragm at the time of the first comparison. The first comparison made includes women who have just chosen a contraceptive method as well as women who have used the selected method. As most of the women used the oral contraceptive for less than one year and based on the average time required for the disease to progress from dysplasia to carcinoma in situ it would seem that most, if not all, cases of carcinoma in situ present at the first comparison had existed before the use of a contraceptive and that the resultant ratio of two most likely is more representative of a "control" ratio. The ratio does not change with the duration of treatment as might be expected if the treatment were having an effect. Stern, Clark & Coffelt (144) have shown that the frequency of dysplasia in women selecting the pill versus the diaphragm can vary twofold even before the chosen contraceptive is employed, and they suggest that such prior differences in susceptibility may explain the findings in the Melamed study. This twofold control variation is a factor to be considered even though it is not a constant occurrence (145). Shulman & Merritt (146) have demonstrated that during a period of 26 months there is a change in the percentage of smears with atypical cytology between women choosing the oral contraceptive and those selecting the intrauterine device. The time trend showed that for 8 to 10 months the intrauterine device rates were slightly lower, for 10 to 12 months the oral contraceptive rates were somewhat lower, and for 6 to 8 months the rates were about equal. Lastly, it should not be expected that the group receiving oral con-

traceptives will always show a prevalence rate below that of the control group; based on chance alone, and in the absence of any effect of oral contraceptives, it may be expected that approximately 50% of the time treated values will be either above or below control values.

The recent studies of Chai et al, Bibbo et al, and Miller do not demonstrate an increase in the prevalence rate for carcinoma in situ in women using oral contraceptives (Tables 3, 4). Carcinoma in situ was not increased in women taking Anovlar, as there was only one case observed in 67 women treated for 4–6 years (147). Laurie & Korba (108) found that the frequency of biopsies positive for carcinoma in situ in women receiving oral contraceptives was similar to that found in untreated populations. Miller (125), comparing 2394 women receiving oral contraceptives with 2394 control women, did not find any age-specific effect of treatment. Miller's patients had used oral contraceptives for an average of 49.1 months, whereas only 1931 women in Melamed's study are listed as using oral steroids for more than 3 years.

In two retrospective case-control studies there was no demonstrated association between the use of oral contraceptives and the occurrence of cervical cancer in situ (137, 148). In the study of Worth & Boyes (148) the mean interval between first use of oral contraceptives and entry into the study was 2.9 years for women age 20–24 and 5.3 years for women age 25–29.

INVASIVE CANCER Bibbo, Keebler & Wied (124) found that the prevalence rate for invasive cervical cancer in 18,380 women using oral contraceptives was less than that observed in control patients (Table 3). In a case-control study no association was demonstrated between the use of oral contraceptives and the occurrence of cervical cancer (149).

SUMMARY

The results of experimental studies on the relationship of estrogens and oral contraceptives to mammary lesions demonstrate that the type of response obtained depends largely on the species and strain of animal that is employed. A variety of clinical studies has failed to demonstrate that estrogen can cause mammary cancer; this lack of effect correlates with the results obtained in various studies in animals. Similar relationships exist for oral contraceptives, and the clinical data show good agreement in demonstrating that the contraceptive steroids do not have a tumorigenic effect on the human mammary gland.

Estrogen can increase the occurrence of cervical cancer in certain strains of mice, but apparently this effect is not observed in other species of animals, including man. The preponderance of data to date shows that oral contraceptives do not adversely affect the occurrence of abnormal Papanicolaou smears, cervical dysplasia, cervical cancer in situ, or invasive cervical cancer.

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