Role of Exogenous Female Hormones in Altering the Risk of Benign and Malignant Neoplasms in Humans

David B. Thomas

Fred Hutchinson Cancer Research Center, Seattle, Washington 98104

Abstract

The epidemiological and clinical evidence for various forms of exogenous estrogens altering the risk of neoplasms of the female genital system, breast, and liver are reviewed and evaluated. It is virtually certain that in utero exposure to diethylstilbestrol can cause clear cell adenocarcinomas of the vagina and cervix. There is strong evidence that various estrogens given for treatment of menopausal symptoms can cause endometrial carcinoma and that sequential oral contraceptives probably also do so. Oral contraceptives very probably reduce the risk of both cystic disease and fibroadenoma of the breast and increase the risk of liver cell adenomas. Studies to date do not provide consistent and convincing evidence that any form of exogenous estrogen alters the risk of cancers of the breast or ovary or that oral contraceptives alter the risk of cervical neoplasia or focal nodular hyperplasia of the liver, although recent reports suggest that continued vigilance is warranted. Specific topics requiring further epidemiological investigation are suggested.

Introduction

Exogenous estrogens have been administered to endocrinologically competent females at 3 crucial periods of life. Developing fetuses were exposed in utero when their mothers were treated with synthetic estrogens for threatened abortion. Large numbers of women receive estrogens, as well as progestogens, in the form of oral contraceptives during their potentially reproductive years. Many women receive estrogens at the end of the normal reproductive period of their lives for treatment of menopausal symptoms. Each of these 3 sources of exogenous estrogens has been implicated in the development of one or more neoplasms of the breast, female genital system, or liver, and the purpose of this paper is to review critically the evidence for these reported causal associations.

Clear Cell Adenocarcinomas of the Vagina and Cervix

From the early 1940's through the 1950's, the synthetic nonsteroidal estrogen DES was used to treat an estimated 0.5 to 2 million women in the United States for threatened abortion (57). Beginning in 1966, some women who were exposed in utero at that time developed clear cell adenocarcinomas of the vagina and cervix during or within a few years of puberty (33). Evidence that these neoplasms were caused by the prenatal DES exposure is considerable. Clear cell adenocarcinomas of the vagina were virtually unknown and those of the cervix were extremely rare prior to the late 1960's (26, 32, 84), and the reported number of cases increased yearly from that time through the mid-1970's (32). This increase paralleled the increase in the use of DES during the 2 previous decades. Nearly 90 to fully 100% of the cases of vaginal clear cell adenocarcinomas in various reported series (23, 26, 32) and more than two-thirds of those with the disease arising in the cervix (32) were found to have been exposed to DES in utero. In contrast, the proportion of normal women at the same age as the cases who had in utero DES exposure was found to be extremely low. These clear cell adenocarcinomas, which are undoubtedly of Müllerian origin, developed only in women who were exposed before the 18th week of gestation (32), at a time in which critical events in the embryonic development of the female genital tract occur. In addition, the carcinogenic response to in utero exposure to DES is highly specific; non-Müllerian tissues are not affected, as indicated by the observation that such exposure does not appear to alter the risk of carcinomas of the ovary, testis, upper or lower urinary tract, or breast or of sarcomas of the prostate, uterine corpus, or vagina (28, 29).

Although the available evidence suggests that prenatal exposure to DES is virtually a necessary factor for the development of clear cell adenocarcinomas of the vagina or cervix, it is not a sufficient one. The absolute risk of developing these tumors, if exposed, is actually quite low (31, 44). Estimates range from 14 to 140 cases per 100,000 women by the age of 24. On the other hand, 82% of 280 women exposed to DES in utero were found to have vaginal adenosis (the occurrence in the vagina of glandular epithelium of Müllerian origin, resembling that of the endometrium, endocervix, and oviducts) (51). It is from these lesions that the clear cell adenocarcinomas presumably arise. Although the latent period for the development of the tumor is long (average, 17.4 years), the tumors tend to occur within a narrow age range, from about the time of puberty to the early 20's (32). This suggests that unknown factors operative at about the time of puberty determine which DES-exposed women with adenosis develop clear cell adenocarcinomas. Elucidation of these factors should be the subject of future research.

Endometrial Carcinoma

The evidence that exogenous estrogens given around the time of menopause have caused an increase in the risk of endometrial cancer is nearly as strong as that for the relationship between in utero DES exposure and clear cell adenocarcinomas of the vagina and cervix. In the United
States the incidence of this neoplasm changed little with time from the 1930's to 1970, but since then it has increased dramatically, in some areas at a rate of about 10% per year (91). This increase follows by less than 10 years a marked increase in the use of p.o. administered estrogens for treatment of menopausal symptoms (27). The increase is greatest in women most likely to receive estrogens for menopausal symptoms, i.e., those between 55 and 70 years old who are white and are of high socioeconomic status (3).

Eight case-control studies of the relationship between exogenous estrogens and endometrial cancer have been conducted (18, 25, 38, 48, 54, 76, 97, 98). The results are summarized in Table 1. Two studies do not show a relationship. In the study by Wynder et al. (97), very few study subjects in either group had used estrogens; therefore it is not surprising that an association was not detected. In the study by Dunn and Bradbury (18), the controls were women with postmenopausal bleeding and a diagnosis of atrophic endometrium. Since such women may bleed because they are on estrogens, they are an unsuitable control group; it is likely that an overestimate of the prevalence of estrogen use in women without endometrial cancer has been provided, and this in turn would result in a spuriously low estimate of the risk of endometrial cancer in estrogen users relative to nonusers.

The other 6 case-control studies show a strong association between estrogens and endometrial cancer. The association is evident for conjugated estrogens, "any" estrogens (a high proportion of which are conjugated), and also for other forms of exogenous estrogens. A number of these studies also show an increased relative risk with duration of estrogen use (25, 48, 54, 98) and strength of preparations taken (24, 48, 54), and one study showed a diminution in risks with the passage of time from cessation of use (48). Also, cyclic use was found to increase the risk less than did continuous use (54). The association has persisted after re-reading of histological slides have now shown that neither the increase in incidence (79) nor the results of case-control studies (24) can be explained on this basis.

The relationship of exogenous estrogens to endometrial cancer has been confirmed in one prospective study: women with breast cancer who received hormone treatment that consisted largely of nonsteroidal estrogens had an increased risk of uterine cancer (34). In addition, a number of women with gonadal dysgenesis who have been treated with DES have developed endometrial cancer at a relatively early age (17, 53, 66, 75); in contrast only one woman with this condition who had not received estrogens is known to have developed endometrial cancer, and this occurred at age 79 (17).

There is also now some evidence that sequential oral contraceptives may be associated with carcinoma of the endometrium. Asymptomatic women using these agents have been found to have a high prevalence of atypical adenomatous endometrial hyperplasia, which may be a precursor to carcinoma (46), and a number of case reports of young women with endometrial carcinoma who have used sequential oral contraceptives have appeared in the recent literature (15, 40, 45). More convincingly, two-thirds of 30 women in a registry for endometrial cancer in young women taking oral contraceptives were found to have taken sequential preparations; by contrast only about 10% of all users of oral contraceptives in the United States have used sequential agents (74). It is interesting that, compared to endometrial cancer cases who have used combined oral contraceptives or who were nonusers, those who had used sequential agents tended more frequently to have tumors with clear cell features. Also, the results from some of the studies of menopausal estrogens, a lower proportion of the cases who were sequential oral contraceptive users than nonusers had a history of obesity.

The evidence for a causal association between exogenous estrogens and endometrial cancer is thus very strong.

Table 1

Casual ic studies of the relationship of exogenous estrogens to endometrial carcinoma

<table>
<thead>
<tr>
<th>First author</th>
<th>Date of publication</th>
<th>No. of cases</th>
<th>Type of estrogen</th>
<th>Relative risks of users</th>
<th>Minimum use of estrogen users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen (38)</td>
<td>1954</td>
<td>&lt;72</td>
<td>Any</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Wynder (97)</td>
<td>1966</td>
<td>112</td>
<td>Any</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Dunn (18)</td>
<td>1967</td>
<td>55</td>
<td>Any</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Smith (76)</td>
<td>1975</td>
<td>317</td>
<td>Any</td>
<td>&gt;4.5</td>
<td></td>
</tr>
<tr>
<td>Ziel (98)</td>
<td>1975</td>
<td>94</td>
<td>Conjugated</td>
<td>7.6</td>
<td>13.9</td>
</tr>
<tr>
<td>Mack (48)</td>
<td>1976</td>
<td>63</td>
<td>Conjugated</td>
<td>8.0</td>
<td>5.6</td>
</tr>
<tr>
<td>McDonald (54)</td>
<td>1977</td>
<td>145</td>
<td>Conjugated</td>
<td>5.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Gray (25)</td>
<td>1977</td>
<td>205</td>
<td>Conjugated</td>
<td>3.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Any women who had at one time or another used oral contraceptives.*
The statistical association is too high and has been replicated under too many different circumstances to be easily explained by selection bias or some unknown confounding factor. A dose-response has been well documented, various forms of exogenous estrogens have been implicated, and risk has been shown to decrease with cessation of exposure. Finally, the association is biologically plausible because estrogens stimulate endometrial proliferation, untreated women with endogenous estrogen deficiencies rarely develop the disease, and women with conditions characterized by excessive or noncyclic endogenous estrogens, such as ovarian secreting tumors, polycystic ovaries, and obesity, are at increased risk.

Ovarian Tumors

Evidence for a causal relationship between menopausal estrogens and ovarian tumors is quite meager. At least 3 case-control studies have failed to show a higher proportion of estrogen users among women with ovarian cancer than among unaffected women (1, 93, 96), although the proportion of estrogen users in the controls in some of these studies was so low that it is unlikely that an increased risk associated with estrogen use could have been detected. Also, the possible relationship of exogenous estrogens to specific histological types of ovarian cancer was not investigated in these studies.

Two prospective studies of women show an increased risk of ovarian cancer in women treated with estrogens (7, 36). Both are based on small numbers of cases, but the ratio of observed to expected cases is high. The first study (36) was a follow-up investigation of women treated with conjugated equine estrogens for more than 6 months by a single practitioner. Eight ovarian cancer cases developed in the study group compared to slightly more than 3 that would be expected if the study group had had the same risk as women in Connecticut or in the areas covered by the Third National Cancer Survey. Three women who had also received DES in addition to conjugated equine estrogens developed ovarian cancer, compared to an expected number of 0.1. This suggests that DES might be particularly carcinogenic for the ovary, which is supported by the preliminary results of the second prospective study (7). This is a follow-up study of women who participated in a randomized trial of DES for treatment of threatened abortion in the 1950's. Four women in the treatment group, but only one in the placebo group, have developed ovarian cancer.

There is some evidence that unlike other epithelial tumors of the ovary, the relatively rare clear cell and endometrioid tumors may be of Müllerian origin (72, 73). These tumors are more strongly associated with marital status than are the other histological types (92) and may thus have a different etiology, although other epidemiological features of the various histological types of ovarian tumors have not been adequately studied. Like endometrial cancer the incidence of these 2 types of ovarian cancers has increased in several areas of the United States since 1970, following a rise in consumption of exogenous estrogens for use at menopause (90).

There has been one case report of multiple paraovarian cysts with columnar epithelium intermingled with clear cells occurring in a 13-year-old girl who was exposed to DES in utero (20), suggesting that in utero DES may cause clear cell tumors to develop in remnants of Müllerian tissue in the ovary, as well as in the vagina and cervix.

The effect of oral contraceptives on risk of ovarian cancer has not been adequately investigated, although studies of the problem are under way. Rigorous epidemiological studies of the possible relationship of both oral contraceptives and other forms of exogenous estrogens to various histological types of ovarian tumors should be conducted.

Cervical Squamous Dysplasia and Carcinoma

Cervical squamous dysplasia and carcinoma tend to occur in women of childbearing age, and there has been considerable concern as to whether oral contraceptives alter a woman's risk of these conditions. This has proved to be an exceedingly difficult problem to study. Variations in incidence rates over time and from one population to another are virtually impossible to interpret, let alone relate to use of oral contraceptives, because of variations in the proportion of women who have had Papanicolaou smears. Another difficulty is that carcinoma of the cervix is probably caused, at least in part, by a venereally transmitted carcinogenic agent, and neoplastic diseases of the cervix have been related to age at first intercourse and to a number of indices of sexual promiscuity or multiple partners (42). Some studies indicate that women who choose to take oral contraceptives also tend to exhibit some of these traits. Users of oral contraceptives could, therefore, develop cervical neoplasia at a higher rate than do nonusers, simply because of their sexual behavior and not because of the steroidal hormones used for contraception. In support of this, 2 studies have shown that choosers of oral contraceptives had a higher prevalence of squamous dysplasia than did choosers of other forms of contraception (60, 77). Epidemiological studies of the relationship between oral contraceptives and cervical neoplasia must therefore be designed and analyzed to account for this problem of potentially confounding variables.

Three types of studies of the relationship of oral contraceptives to cervical neoplasia have been conducted. These are prevalence, case-control, and prospective studies. In prevalence studies the proportions of oral contraceptive users and nonusers that are found at screening to have cervical neoplasia are compared. The results of at least 5 such studies have been published (6, 55, 56, 83, 94). Two of the 5 showed a higher prevalence of cervical neoplasia in oral contraceptive users than in nonusers (55, 56). Melamed et al. (56) found a higher prevalence of carcinoma in situ in users of oral contraceptives than in diaphragm users, and Meisels et al. (55) found a higher prevalence of squamous dysplasia in oral contraceptive users than in nonusers who participated in a community screening program. However, the results of neither of these studies can be given much credence. The findings of the Melamed study are questionable because the behavioral characteristics of diaphragm users render them an unsuitable comparison group (even though an attempt was made to control for a number of potentially confounding variables) and because the dia-
phragm could be protective against a venereally transmitted carcinogen. The Meisels study considered only one confounding variable, age at first coitus, and no attempt was made to control for any indices of sexual promiscuity or for age.

Table 2 summarizes the results of 5 case-control studies of oral contraceptives and cervical neoplasia (11, 61, 69, 80, 95). The last 2 columns of the table indicate whether some index of age at onset of sexual activity and of multiple sexual partners was considered in the data analysis. The first 4 studies did not show a statistically significant association between either squamous dysplasia or carcinoma and oral contraceptive use. The recent study by Ory et al. (61) shows a positive association between oral contraceptives and both squamous dysplasia and carcinoma \textit{in situ}, and the relative risk of both conditions was found to increase with duration of use. These associations persisted after adjusting for age at first birth, age, parity, and marital status. However, no index of multiple partners was considered.

The results of this study are also questionable for another methodological reason. Study subjects were restricted to women who had had at least 2 normal Papanicolaou smears prior to the abnormal or additional normal one that rendered them eligible for inclusion in the study as cases or controls, respectively. If users of oral contraceptives who are destined to develop a cervical neoplasm are more likely to have multiple Papanicolaou smears than are such women who are not users of oral contraceptives, then restricting the study group to women with multiple smears would result in a case group that has more users of oral contraceptives than cases in the general population. This selection bias would result in a spuriously high relative risk. It is not unreasonable that such inadvertent biased selection of cases could have happened in this study. Women with gynecological symptoms such as vaginal discharge or itching may well be at increased risk of cervical neoplasia and, if using oral contraceptives, they could indeed be more closely monitored and, hence, could be more likely to have multiple Papanicolaou smears than if not on oral contraceptives.

Two prospective studies provide incidence rates of cervical neoplasia in users and nonusers of oral contraceptives. Vessey et al. (86) found the incidence of carcinoma \textit{in situ} to be no different for users of oral contraceptives and intrauterine devices. More recently, Peritz et al. (64) reported the incidence of both carcinoma \textit{in situ} and squamous dysplasia to be greater in oral contraceptive users than in nonusers and to increase with duration of use. This relationship persisted after adjustment for 8 potentially confounding factors, although no direct indices of sexual promiscuity or age at first intercourse were taken into account.

A third prospective study involved measuring the incidence of carcinoma \textit{in situ} in oral contraceptive users and nonusers who had squamous dysplasia (78). After 7 years of follow-up, the probability of developing carcinoma \textit{in situ} in this high-risk group was 0.30 for oral contraceptive users and 0.05 for nonusers. Although this 6-fold difference in rates is impressive, it is based on small numbers of women with carcinoma \textit{in situ}, and possible differences between oral contraceptive users and nonusers with respect to age at first intercourse and degree of sexual promiscuity again were not determined.

In summary, the most recent case-control and prospective studies have shown that the risk of both squamous dysplasia and carcinoma \textit{in situ} increases with duration of use of oral contraceptives and that women with squamous dysplasia develop carcinoma \textit{in situ} at a greater rate when using oral contraceptives. Although none of these 3 studies adequately accounted for possible differences in the sexual behavior of oral contraceptive users and nonusers, these findings cannot be ignored. It is also possible that oral contraceptives do increase the risk of cervical neoplasia and that they had not been used long enough by a sufficiently large number of women for an adverse affect to become manifest by the time that the earlier studies with negative results had been conducted. Additional studies that adequately measure sexual promiscuity and age at onset of sexual activity must be conducted, despite the difficulties in collecting and obtaining permission to collect this kind of sensitive information.

**Benign Breast Tumors**

There is strong evidence that oral contraceptives reduce the risk of benign breast diseases. At least 7 case-control studies of these conditions and oral contraceptive use have

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**Table 2**

<table>
<thead>
<tr>
<th>First author</th>
<th>Date of publication</th>
<th>Neoplastic condition</th>
<th>No. of cases</th>
<th>Relative risk</th>
<th>Age at 1st sex</th>
<th>Multiple partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas (90)</td>
<td>1972</td>
<td>Cancer \textit{in situ}</td>
<td>104</td>
<td>0.58</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Boyce (11)</td>
<td>1972</td>
<td>Dysplasia</td>
<td>105</td>
<td>1.24</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive and \textit{in situ} cancer</td>
<td>196$^a$</td>
<td>1.23$^b$</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Worth (95)</td>
<td>1972</td>
<td>Cancer \textit{in situ}</td>
<td>310</td>
<td>1.15$^b$</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sandmire (69)</td>
<td>1976</td>
<td>Invasive and \textit{in situ} cancer</td>
<td>76</td>
<td>0.53$^b$</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ory (61)</td>
<td>1977</td>
<td>Dysplasia</td>
<td>854</td>
<td>1.37$^b$</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer \textit{in situ}</td>
<td>147</td>
<td>1.67$^b$</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

$^a$ Exact number not clear from publication.

$^b$ Values calculated from data in published report.
been undertaken (9, 41, 58, 63, 65, 70, 88), the results of which are summarized in Table 3. All but the study by Nomura and Comstock (58) show the relative risk in users of oral contraceptives to be less than 1, and the first 5 show a diminution in risk with increasing duration of use.

The first 6 studies in the table are hospital based; both cases and controls were women who were admitted to participating hospitals. The Nomura study utilized all cases diagnosed in Washington County, Md., during a defined period of time, and the controls were drawn from a census of that county. If one were dealing with a condition like breast cancer than is sufficiently serious ultimately to bring a high proportion of all women in the population with the disease to medical attention, then the method of control selection used by Nomura would be the most appropriate. However, benign breast diseases are not such conditions, and women with them who have been put on oral contraceptives by a physician may well be more likely to have their condition diagnosed than are women not on oral contraceptives. Pill use among the cases in all 7 studies may thus have been overestimated. This would tend to cause a spurious increase in the observed relative risks. However, in all but the Nomura study this tendency was compensated by the utilization of controls who, like the cases, had already entered the medical care system and thus were more likely to have used oral contraceptives than were healthy women in the general population.

As shown in the middle portion of Table 3, the protective effect of oral contraceptives appears to be particularly strong for cystic diseases of the breast, although, as indicated in the lower portion of the table, 3 of 4 studies do show oral contraceptives to reduce the risk of fibroadenoma. As shown in Table 4, protection against both fibroadenoma and cystic disease has also been observed in 3 prospective studies (59, 67, 86).

Recent data from the prospective study of the Royal College of General Practitioners (68) show the incidence rates of benign breast disease to be inversely related to the amount of progestogen in the preparations used, and 4 case-control studies (10, 58, 65, 70) have failed to show menopausal estrogens (which have no progestogen) to be protective against benign breast disease (Table 5). These observations suggest that it is the progestational component of oral contraceptives that is responsible for their protective influence. However, at variance with this is the observation from the case-control study of Kelsey et al. (41) that only sequential oral contraceptives protect against cystic disease or fibroadenomas. This finding is based on

Table 4

<table>
<thead>
<tr>
<th>Type of benign breast disease</th>
<th>Incidence/1000 woman yr</th>
<th>Minimum yr of use by long-term users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long-term users</td>
<td>Non-users</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>Ory (59)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cystic disease</td>
<td>Ory (59)</td>
<td>1.3</td>
</tr>
<tr>
<td>All types</td>
<td>Vessey (87)</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>RCGP (67)a</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*a* RCGP, Royal College of General Practitioners.

Table 5

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of cases</th>
<th>Relative risk in ever users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sartwell (70)</td>
<td>1048</td>
<td>1.03</td>
</tr>
<tr>
<td>Boston Collaborative Drug Surveillance Programme (10)</td>
<td>52</td>
<td>0.97</td>
</tr>
<tr>
<td>Nomura (58)</td>
<td>317</td>
<td>2.50</td>
</tr>
<tr>
<td>Ravnihar (65)</td>
<td>497</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*a* An ever user is any woman who has at one time or another used oral contraceptives.

Table 3

<table>
<thead>
<tr>
<th>Type of benign disease</th>
<th>First author</th>
<th>No. of cases</th>
<th>Relative risks</th>
<th>Minimum yr of use by long-term users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ever usersd</td>
<td>Long-term users</td>
</tr>
<tr>
<td>All types</td>
<td>Ravnihar (65)</td>
<td>419</td>
<td>0.72</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Kelsey (41)</td>
<td>366</td>
<td>0.81</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Sartwell (70)</td>
<td>1048</td>
<td>0.99</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Vessey (88)</td>
<td>255</td>
<td>0.60</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Paffenbarger (63)</td>
<td>446</td>
<td>0.80</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>BCDSP (9)a</td>
<td>98</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nomura (58)</td>
<td>318</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Cystic disease</td>
<td>Sartwell (70)</td>
<td>306</td>
<td>0.85</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Ravnihar (65)</td>
<td>266</td>
<td>0.66</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Kelsey (41)</td>
<td>211</td>
<td>0.83</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Vessey (88)</td>
<td>117</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>Sartwell (70)</td>
<td>71</td>
<td>1.20</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>Ravnihar (65)</td>
<td>106</td>
<td>1.06</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Kelsey (41)</td>
<td>123</td>
<td>0.92</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Vessey (88)</td>
<td>86</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

*d* Any women who had at one time or another used oral contraceptives.

*b* Boston Collaborative Drug Surveillance Programme.
small numbers of users, however, and additional information from other studies is needed.

For reasons already given, the value shown in Table 5 of the relative risk of benign breast diseases in estrogen users that was calculated from the Nomura study (58) is probably too high. There is no other evidence that noncontraceptive estrogens increase the risk of benign breast conditions.

Women with benign breast lesions of various types have been shown to be at increased risk of breast cancer. In one series, women with lesions termed fibroadenoma, adenosis, fibrosing adenosis, and intraductal papilloma were at particularly high risk (43). Risk has also been related to the degree of atypia in the ductal linings, and, to a lesser extent, to the presence of apocrine metaplasia (8, 43). However, it is unknown whether oral contraceptives protect against benign breast diseases with the specific histological characteristics indicative of a high risk of breast cancer; therefore it cannot be inferred from the results of studies of benign breast diseases that oral contraceptives are protective against breast cancer.

Breast Cancer

The incidence of breast cancer increased gradually from 1960 and 1961 to 1970 and 1971 in both Britain and Connecticut (2) and more sharply in the United States between 1970 and 1974 (21). These increases, however, have been adequately explained by factors other than the use of oral contraceptives or estrogens for replacement therapy at menopause (2, 21, 87).

At least 9 case-control studies of breast cancer and oral contraceptives have been conducted, available results from 8 of which are summarized in Table 6 (9, 30, 41, 63, 65, 71, 86). None show a significant overall increase or decrease in risk of breast cancer in oral contraceptive users. This consistency of results is striking, considering the varied settings in which the different studies were conducted and the numerous methodological differences.

However, in the 2 studies that were restricted to relatively young women (41, 63) and provided information on fairly long-term use, users of contraceptives for more than 5 years had a relative risk of 1.7. Although this value does not differ significantly from unity in either study and in neither was there evidence of a consistent increase in risk with duration of use, these findings indicate the need for additional information on long-term users.

Only 2 studies (63, 87) provide information on relative risk of breast cancer in relation to time since initial use of oral contraceptives. Neither show a consistent change in risk with the passage of time. Analysis of data published by Vessey et al. (87) yields a relative risk of 0.87 after 8 years, and Paffenbarger (63) observed a relative risk of 1.1 after 6 years from first use. Information is needed on the risk of breast cancer after longer periods of time since initial exposure.

The Paffenbarger study (63) also showed that oral contraceptives were associated with an increased risk of breast cancer in parous women who first used them prior to the birth of their first child and in 15- to 39-year-old nulliparous women. These findings suggest that early use of oral contraceptives does not afford the protection against breast cancer that an early first birth provides (49, 81) and may increase the risk of breast cancer. This same study also showed women with a history of benign breast disease prior to use of oral contraceptives to be at increased risk of breast cancer.

There have been 3 prospective studies of oral contraceptives and breast cancer (59, 67, 87). They are shown in Table 7. The study of the Royal College of General Practitioners shows no relationship between oral contraceptives and breast cancer. The other 2 studies show a negative association, but in neither study is the relationship statistically significant. In the Ory study (61) the rate was the same in the risk of breast cancer that an early first birth provides (49, 81) and may increase the risk of breast cancer. This same study also showed women with a history of benign breast disease prior to use of oral contraceptives to be at increased risk of breast cancer.

Table 7

Prospective studies of the relationship of oral contraceptives to the risk of breast cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Incidence/1000 woman yr by use of oral contraceptives</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal College of General Practitioners (67)</td>
<td>0.36 (11)</td>
<td>0.34 (16)</td>
</tr>
<tr>
<td>Vessey (87)</td>
<td>0.18 (5)</td>
<td>0.44 (11)</td>
</tr>
<tr>
<td>Ory (59)</td>
<td>0.6 (22)</td>
<td>1.0 (115)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of cases.

Table 6

Case-control studies of the relationship of oral contraceptives to the risk of breast cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Type of control</th>
<th>No. of cases</th>
<th>Age of cases</th>
<th>Yr cases diagnosed</th>
<th>Relative risk ever users</th>
<th>Relative risk for long-term users</th>
<th>Minimum yr of use by long-term users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey (86)</td>
<td>Hospital</td>
<td>322</td>
<td>16-45</td>
<td>1968-74</td>
<td>0.89</td>
<td>0.94</td>
<td>2</td>
</tr>
<tr>
<td>Boston Collaborative Drug Surveillance Programme (9)</td>
<td>Hospital</td>
<td>23</td>
<td>20-75</td>
<td>1972</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paffenbarger (63)</td>
<td>Hospital</td>
<td>452</td>
<td>&lt;50</td>
<td>1970-72</td>
<td>1.1</td>
<td>1.7</td>
<td>8</td>
</tr>
<tr>
<td>Henderson (30)</td>
<td>Office</td>
<td>308</td>
<td>40-64</td>
<td>1971-73</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sartwell (71)</td>
<td>Hospital</td>
<td>284</td>
<td>20-73</td>
<td>1969-72</td>
<td>0.86</td>
<td>0.97</td>
<td>5</td>
</tr>
<tr>
<td>Kelsey (41)</td>
<td>Hospital</td>
<td>99</td>
<td>20-44</td>
<td>1971-73</td>
<td>1.35</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>Lilienfield b</td>
<td>Neighborhood</td>
<td>342</td>
<td>18-74</td>
<td>1973-75</td>
<td>1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ravnihar (65)</td>
<td>Hospital</td>
<td>254</td>
<td>1973-75</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>190</td>
<td>20-49</td>
<td>1972-74</td>
<td>0.91</td>
<td>0.86</td>
<td>2</td>
</tr>
</tbody>
</table>

* An ever user is any woman who has at one time or another used oral contraceptives.
b Personal communication.
for women who had used oral contraceptives for less than 2 years and for women who had used them for 2 or more years.

At least 7 case-control studies of noncontraceptive estrogens and breast cancer have been conducted (Table 8) (10, 13, 16, 30, 47, 65, 71), none of which shows a significant association between these preparations and mammary carcinoma. The study by Casagrande et al. (13) is small and the relative risk of 3.1, although impressive, is not statistically significant. Also, there is a possibility of selection bias, such as that described previously in relation to the Nomura study (58) of benign lesions. The study by Mack et al. (47) was conducted to examine the relationship of reserpine to breast cancer. A small relative risk in excess of 1 was noted for 4 classes of drugs in addition to estrogens, suggesting that selection bias may have been operative in this study, too.

Two prospective studies of noncontraceptive estrogens and breast cancer have been conducted (12, 35), results from which are summarized in the last 2 lines of Table 8. Methodological errors in the design and analysis of the Burch study (12) render the results questionable, and the relative risk of 1.2 is not statistically significant.

The study of Hoover (35) consisted of following up through the end of 1972 a total of 1891 women who had been given conjugated estrogens for menopausal symptoms between 1939 and 1960. Observed number of breast cancers in the study group were compared with expected numbers that were derived from incidence rates from the Second and Third National Cancer Surveys. Although the overall risk of breast cancer was slightly increased in the study group (relative risk, 1.3) and was of borderline statistical significance, the questionable appropriateness of the source of the expected numbers renders this finding difficult to interpret. More importantly, the risk increased with duration of follow-up. Risk did not appreciably increase until 12 years after initial use, after which time it approximately doubled. This observation is consistent with the long latent period that follows exposure to known carcinogens. No studies of oral contraceptives have provided data on risk of breast cancer so long after initial use, and this finding emphasizes the need for such information, particularly for sequential oral contraceptives.

The increase in risk was greatest in women who took the preparations of highest strength, but also in those who took their medication less frequently than daily, and risk was not related to duration of use.

This study also showed that the risk of breast cancer in women who developed benign breast disease after starting on estrogens was increased 7-fold. The risk was approximately doubled in women who had a history of benign breast disease prior to taking estrogens. These findings are consistent with Paffenbarger's observation (63) that oral contraceptives predispose women with benign breast disease to breast cancer.

The case-control study by Henderson (30) showed somewhat different findings relating risk of breast cancer to time since initial use of estrogens. The relative risk was actually observed to be less than unity in users less than 10 years after initial use, but it was greater than 1 for users 10 or more years after first use. This is what one would observe if estrogens delayed the development of preexisting breast cancer.

Additional information regarding the possible relationship of exogenous estrogens to breast cancer is obviously needed. Of particular interest is the effect of oral contraceptives on breast cancer risk after prolonged use, long after initial use, in women with various histological types of benign breast diseases and in young nulliparous women. The effects of sequential and combined preparations also must be assessed separately, as well as the influence of noncontraceptive estrogens.

Liver Tumors

In 1973 Baum et al. (4) reported a series of 7 women of childbearing age with hepatic adenomas, all of whom had taken oral contraceptives. This has been followed by numerous additional reports of cases and series of cases of benign liver tumors in users of oral contraceptives.

The lesions have been described by a variety of names, and no uniform histological classification has been

Table 8

<table>
<thead>
<tr>
<th>Type of study</th>
<th>First author</th>
<th>Type of controls</th>
<th>No. of cases</th>
<th>Yr during which breast cancer was diagnosed</th>
<th>Measure of estrogen use</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-based Case-Control</td>
<td>Sartwell (71)</td>
<td>Hospital</td>
<td>284</td>
<td>1969-1972</td>
<td>Ever</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Boston Collaborative Drug Surveillance Programme (10)</td>
<td>Hospital</td>
<td>51</td>
<td>1972</td>
<td>Ever</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Ravnihar (65)</td>
<td>Clinic</td>
<td>374</td>
<td>1972-1974</td>
<td>Ever</td>
<td>0.78</td>
</tr>
<tr>
<td>Population-based Case-Control</td>
<td>Henderson (30)</td>
<td>Office</td>
<td>100</td>
<td>1969-1972</td>
<td>Ever</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Casagrande (13)</td>
<td>Neighborhood</td>
<td>47</td>
<td>1972-1973</td>
<td>Ever</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Craig (16)</td>
<td>Population and neighborhood</td>
<td>134</td>
<td>1949-1967</td>
<td>Ever</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Mack (47)</td>
<td>Population</td>
<td>111</td>
<td>1971-1975</td>
<td>Ever</td>
<td>1.6</td>
</tr>
<tr>
<td>Practice-based Prospective</td>
<td>Burch (12)</td>
<td>None</td>
<td>19</td>
<td>1948-1973</td>
<td>≥5 yr</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Hoover (35)</td>
<td>None</td>
<td>49</td>
<td>1939-1972</td>
<td>≥6 mos.</td>
<td>1.3</td>
</tr>
</tbody>
</table>
adapted. It is likely, however, that 2 basic types of lesions have been observed (62). One is the hepatic cell adenoma, which is a highly vascular tumor composed of well-differentiated hepatocytes, and the other is focal nodular hyperplasia, which is probably the same entity as the liver hamartoma and consists of nodules of hepatocytes separated by fibrous trabeculae.

Formal studies of the relationship between these 2 tumor types and oral contraceptives are few, and most are not of rigorous design. The majority consist of collected series of cases that are either small in number or comprised only women who were selected for study because they had used oral contraceptives. Such studies are of little value in determining a causal relationship between liver tumors and oral contraceptives. Nonetheless, there is considerable evidence to suggest that hepatic adenomas are caused by oral contraceptives. The relationship of oral contraceptives to focal nodular hyperplasia is less clear.

Because these are both benign tumors, they are not usually reported to tumor registries or included in cancer surveys. Time trends in incidence rates are consequently unknown. However, a number of literature reviews and retrospective searches of hospital records (4, 5, 50) clearly indicate that hepatic adenomas were extremely rare prior to the report by Baum et al. (or before the widespread use of oral contraceptives). There were, however, many reports of focal nodular hyperplasia prior to the oral contraceptive era (37), and it is unclear whether the recent increase in the number of these reports reflects an actual increase in the occurrence of this tumor or merely an increase in the awareness of its existence and its possible relationship to oral contraceptives. Also, in a series of benign liver tumors from the Armed Forces Institute of Pathology (37), the female: male ratio in 130 patients with focal nodular hyperplasia was 2:1, with their ages ranging from 10 months to 75 years; in contrast, all 75 cases of hepatocellular adenoma were women and, although they ranged in age from 17 to 61 years, most were in their 20’s and 30’s. Reports of hepatic adenomas regressing after withdrawal of oral contraceptives (39, 52) are added evidence of a causal relationship between this tumour and steroidal contraceptives.

Vana et al. (85) have reported the results of a survey of liver tumors in hospitals accredited by the American College of Surgeons Commission on Cancer. Unfortunately, the response rate to this survey was low, use of oral contraceptives is unknown for a number of the cases, and the data are not adequately analyzed or presented. Results from this survey nonetheless support the hypothesis that hepatic adenomas are related to oral contraceptives: the frequency of benign liver tumors increased with age in nonusers of oral contraceptives but was highest in users from 26 to 30 years of age, this peak was evident for hepatic adenomas, and the relative risk increased with duration of use. In addition, oral contraceptives with mestranol were used much more frequently by the cases than by the controls.

Mestranol is dimethylated in the liver to ethinyl estradiol, and it has been suggested that the mechanism by which oral contraceptives cause adenomas is somehow related to this metabolic process (19).

On the other hand, oral contraceptives are known to reduce the flow of bile, and it has been hypothesized (22) that this is the mechanism by which oral contraceptives could cause tumor development; reduction in the bile excretion rate could result in an increase in the concentration of hepatic carcinogens of any origin in the liver.

Evidence that oral contraceptives are a cause of liver adenomas is thus quite strong, although rigorous studies of the problem have not been completed. Hepatic adenomas as a complication of oral contraceptive use are, however, extremely rare. No cases of adenomas or focal nodular hyperplasias were found in 2 large prospective studies of oral contraceptives in Britain, the combined experience of which was nearly 150,000 woman-years (89). The relationship of oral contraceptives to focal nodular hyperplasia has not been adequately substantiated.

There is also no convincing evidence that malignant tumors of the liver are caused by oral contraceptives. Case reports of hepatomas in users (14, 22, 82) could easily represent chance phenomena. On the other hand, such reports should be followed by formal epidemiological studies, and this has not been done.

Conclusions

Exogenous female hormones can alter the risk of neoplasms developing in certain hormone target organs or where such hormones are metabolized. It is a virtual certainty that in utero exposure to DES can cause clear cell adenomas of the vagina and cervix. Oral contraceptives very probably cause hepatic cell adenomas but reduce the risk of both cystic disease and fibroadenomas of the breast. There is also strong evidence that various forms of estrogens given around the time of menopause increase the risk of endometrial carcinoma, and sequential oral contraceptives may also be a cause of this neoplasm.

Studies to date do not provide consistent or conclusive evidence that any form of exogenous estrogens alters the risk of neoplasms of the breast or ovary or that oral contraceptives cause focal nodular hyperplasia of the liver or cervical neoplasia. However, some recent studies provide evidence to suggest that risk of these neoplasms may be increased, at least in some subgroups, by exposure to one or more forms of exogenous estrogens. Additional investigations are definitely warranted to provide the information necessary to make a balanced judgment as to the relative benefits and dangers of both oral contraceptives
and estrogens used at menopause. It has been well established that estrogens should not be administered to women during the first trimester of pregnancy.

References

D. B. Thomas

Role of Exogenous Female Hormones in Altering the Risk of Benign and Malignant Neoplasms in Humans

David B. Thomas

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