Estrogens as a Cause of Human Cancer: The Richard and Hinda Rosenthal Foundation Award Lecture

B. E. Henderson, R. Ross, and L. Bernstein

University of Southern California School of Medicine, Los Angeles, California 90033-0800

The concept that hormones can cause, i.e., increase the incidence of, neoplasia was first developed by Bittner et al. (1), based on experimental studies of estrogens and mammary cancer in mice. We have refined that concept into a hypothesis for a major role of estrogen and other hormones in the etiology of several human cancers (2). A key element of this hypothesis is that neoplasia is the consequence of excessive hormonal stimulation of a particular target organ, the normal growth and function of which are under hormonal control. The response of this end organ (e.g., endometrium, breast) to the proliferative effects of the hormone is a progression from normal growth to hyperplasia to neoplasia. In this model, hormones increase the incidence of neoplasia in the absence of outside initiators such as chemicals or ionizing radiation.

We have hypothesized three specific circumstances in which estrogen plays a role in this model of hormone-induced neoplasia. In the first two circumstances, which relate to the breast and the endometrium, estrogens themselves act as the stimulatory hormones, increasing the frequency of mitotic activity in the target organ. As rare consequences of this estrogen-induced proliferation, malignant phenotypes develop due to errors in the mechanics of cell division (e.g., DNA copying errors, chromosomal translocations, etc.) (Fig. 1).

We believe that breast cancer risk is determined primarily by the total cumulative exposure of breast tissue to bioavailable estrogens and the associated cumulative mitotic activity. Although a related mechanism applies to endometrial cancer, the critical exposure in the endometrium is not estrogen per se but that fraction of estrogen which is unopposed by the modifying influences of progesterone. The primary prevention of these two estrogen-induced neoplasms probably will come not from control of exposure to classical exogenous initiators but from modification of factors which directly affect the secretion, tissue binding, and availability of estrogen itself over a woman's entire lifetime.

We have recently hypothesized a second mechanism by which estrogens can increase the incidence of neoplasia; in this situation, estrogens alter the normal embryological development of primitive germ cells (Fig. 2). Unlike breast and endometrial cancer, in germ cell tumor development there is no ongoing proliferation of cells leading to a rapid transition to neoplasia. Instead estrogens cause developmental arrest of fetal germ cells, which then remain dormant until puberty, rather than developing further or regressing. At puberty, gonadotropins from the pituitary stimulate proliferation of both the normal and "dormant" estrogen-arrested cells. Stimulation of the latter cells can produce a germ cell neoplasm. This model resembles more closely the two-stage model of carcinogenesis of Knudson (3), with estrogen serving as the "initiator" and gonadotropins serving as the second stage "promoters."

Estrogen can be derived from both endogenous and exogenous sources. Endogenous sources in women include direct secretion of estrogens from the ovary, operative only during menstrual life, and peripheral conversion of adrenal-derived androgens to estrogen in fat cells. The primary exogenous source of estrogen during reproductive years is OCs, with hormone replacement therapy becoming the primary source thereafter. Until the 1970s, the use of DES in pregnancy provided a third important exogenous estrogen source during the childbearing years. Exposure to estrogens from exogenous sources can be measured directly in epidemiological studies, either through careful interviewing or by examination of medical and pharmaceutical records. Measurement of endogenous estrogen exposure often must be done indirectly. Ovarian activity is usually measured by evaluating the onset, cessation, timing, and regularity of menstruation and the timing and frequency of pregnancy and lactation. Adipose tissue sources are measured primarily by evaluating physical characteristics and dietary habits.

In the discussion which follows, we attempt to establish estrogen as a cause of several human cancers by describing the epidemiological evidence linking estrogen exposure from endogenous and exogenous sources to endometrial, breast, and germ cell tumor development.

Endometrial Cancer

The incidence of endometrial cancer rises rapidly until age 50 and thereafter increases at a much reduced rate. It has been shown by Pike (4) that this age-specific incidence curve is compatible with two straight lines of different slopes joining at the menopause. During the premenopausal period, our hypothesis suggests that the shape of this curve is entirely dependent on weight-related estrogen production and the use of estrogen replacement therapy. With loss of ovarian function at the menopause, the slope of the age-specific incidence curve decreases. In the postmenopausal period, our hypothesis suggests that the shape of this curve is entirely dependent on weight-related estrogen formation and the use of estrogen replacement therapy.

The importance of weight in determining the risk of endometrial cancer is well documented. The pioneering work of MacDonald et al. (5) demonstrated that adipose tissue is particularly rich in an aromatase enzyme that converts androstenedione to estrone. Estrone, in turn, can be converted to estradiol, the most biologically potent human estrogen. In addition, SHBG levels are lower in obese women (6), so that the amount of bioavailable estradiol (the portion not bound to SHBG) in obese women is higher than would be expected from the pe-
ESTROGENS AS A CAUSE OF HUMAN CANCER

Peripheral conversion of androstenedione to estrone alone.

Table 1 shows the relative risks of endometrial cancer associated with increasing weight in selected studies of postmenopausal and premenopausal women (7–10). The three studies selected for postmenopausal women are those with the largest numbers of cases and controls and all show at least a doubling of risk between the thinnest and heaviest women. There does not appear to be a weight beyond which risk does not increase further.

The relative risks for premenopausal women tend to be higher than those for postmenopausal women in comparable weight categories (Table 1). In our case-control study of women with endometrial cancer who were diagnosed before age 45 (7), we found a dramatic increase in risk with current (i.e., at diagnosis) weight, such that women who weighed 190 lb or more had nearly 20 times the risk of women who weighed less than 130 lb. A total of 63% of the cases weighed 150 lb or more compared to only 14% of the controls. Levels of bioavailable estradiol are not detectably higher in heavier premenopausal women than in nonobese women of the same age (11), because adipose tissue makes only a small contribution to the overall estrogen production in women with functioning ovaries. This fact suggests that the mechanism by which obesity increases the risk of endometrial cancer in premenopausal women is through the induction of anovulation and the ensuing progesterone deficiency. This is consistent with findings that amenorrhea, subnormal luteal phase progesterone levels, and irregular menstrual periods are all associated with obesity in premenopausal women (12–15).

Thus, although a woman with normal menstrual cycles will have endometrial proliferation for about 14 days each month, a woman with obesity and anovulation will have endometrial proliferation for a considerably longer time and an associated higher risk of endometrial cancer.

An important, although decidedly unplanned, “natural” experiment, demonstrating the importance of estrogen in the genesis of endometrial cancer, occurred during the early 1970s. Approximately 5–10 years earlier, oral conjugated equine estrogens became widely available as a form of ERT. There was a dramatic rise in the use of this form of ERT over an approximately 15-year period. By 1975, the first case-control studies were published which demonstrated high risks of endometrial cancer in users of this therapy (16–18). Additional studies were conducted in different populations using different methodologies; virtually all produced evidence of a strong association between ERT and risk of endometrial cancer, particularly in users of long-term, high-dose regimens. The role of exogenous estrogens as a cause of endometrial cancer is supported by the marked increase in risk observed after a relatively short duration of use of sequential oral contraceptive pills (7), which deliver an unopposed estrogen during most of the monthly cycle.

As potent as ERT and sequential OCs are as causes of endometrial neoplasia, these effects apparently can be mitigated by the simultaneous administration of progesterone or synthetic progestogens. By increasing the intracellular conversion of estradiol to the less active estrone and slowing the rate of translocation of receptor-bound estradiol to the nucleus, progestosterone effectively blocks the mitotic effects of estrogen (19, 20).

One clinical implication of this antiestrogenic effect of progestogens is the change in risk of endometrial cancer with the use of combination rather than sequential oral contraceptives (Table 2). A series of case-control studies has demonstrated that use of COCs leads to a 50% or greater reduction in endometrial cancer risk (Table 3) (7, 8, 21–24). The newer regimens of hormone replacement therapy follow a pattern not unlike that of sequential OCs, with an unopposed estrogen given early in the cycle followed by estrogen combined with a progestational agent, typically administered for the last 10 days of the cycle. This regimen attempts to reproduce the hormonal pattern of the normal menstrual cycle, albeit at lower levels of...
both estrogen and progesterone. One might predict that this method of hormone replacement therapy would only partially offset the increased risk of endometrial cancer associated with ERT by protecting the endometrium during part of the cycle when the progestogen is actually used. Daily use of combination estrogen-progestogen therapy, which would mimic the pattern of COCs and thereby presumably obviate the risk of endometrial cancer entirely, is not currently recommended. One reason for this is that synthetic progestogens are thought to offset the benefit from heart disease mortality accruing to users of ERT by negating the beneficial effects of ERT on lipid secretion and metabolism (25).

Breast Cancer

Less is known about the normal hormonal control of breast compared to endometrial epithelia. Nevertheless it appears that estrogen is the primary stimulant for breast cell proliferation. Menstrual and reproductive events are among the most important breast cancer risk factors. It is likely that the alteration in risk from these events is mediated by changes in estrogen secretion and availability. Prolactin, an important regulator of breast carcinogenesis in rats, may also play a role in human breast carcinogenesis. However, in humans prolactin does not appear to act as a primary mitogen but as a facilitator at the cellular level of the mitotic actions of estrogen (26). Although there are no definitive data on the role of progesterone in breast neoplasia or even on the regulation of growth of normal breast tissue, we have concluded that progesterone does not have a growth-mediating effect on breast tissue comparable to that on the endometrium. We base this conclusion, in large part, on the fact that COCs do not decrease the risk of breast cancer (27), as they so clearly do for endometrial cancer, and on the evidence that breast mitotic activity actually peaks during the luteal phase of the menstrual cycle (28), in marked contrast to the endometrium. The latter observation has suggested the possibility that progesterone itself may actually be a breast epithelial mitogen (96).

Among non-demographic factors, the most consistently documented risk factors for breast cancer are early age at menarche, late age at menopause, late age at first-term pregnancy, and weight (29). The age-specific incidence curve for breast cancer emphasizes the importance of menstruation in determining risk. The initial cases occur in early adulthood and the rate of increase in incidence then rises sharply with age to the time of the menopause, when it slows dramatically. The rate of increase in the postmenopausal period is only about one-sixth the rate of increase in the premenopausal period. This age-specific incidence curve appears, then, to be shaped in a major way by the effects of ovarian activity.

Early age at menarche has been demonstrated as a risk factor for breast cancer in most case-control studies (30). In general, an approximately 20% decrease in breast cancer risk results from each year that menarche is delayed. In a study of young women, we recorded not only age at onset of menstruation but also age when "regular" (i.e., predictable) menstruation was first established (31). For a fixed age at menarche, the establishment of regular menstrual cycles within 1 year of the first menstrual period more than doubled the risk of breast cancer, when compared to women with a 5-year or longer delay for menses to regularize (Table 4). Women with early menarche (age 12 or younger) and rapid establishment of regular cycles had an almost 4-fold increased risk of breast cancer when compared to women with late menarche (age 13 or older) and long duration of irregular cycles.

These observations suggested that regular ovulatory cycles increase a woman's risk of breast cancer (32) and supported results from an earlier study of circulating hormone levels in daughters of breast cancer cases and in age-matched daughters of controls. The daughters of the breast cancer cases, who as a group have at least twice the breast cancer risk of the general population, had higher levels of circulating progesterone on day 22 of the menstrual cycle than did the controls (33). This result was later confirmed by Trichopoulos et al. (34). Since cumulative estrogen levels are greater during the normal luteal phase than during a comparable period of a nonovulatory cycle (35), cumulative frequency of ovulatory cycles is an index of cumulative estrogen exposure (and, if progesterone is a breast tissue mitogen, of progesterone exposure as well).

Other supportive evidence for the concept that the cumulative number of ovulatory cycles, i.e., cumulative estrogen exposure, is a major determinant of breast cancer comes from the international studies of MacMahon et al. (36), who studied the frequency of ovulation in relation to age at menarche and number of years since menarche in girls ages 15 to 19 years, selected from several populations at varying risk of breast cancer. In all these populations, women with later menarche were more likely to have anovular cycles than women with early menarche, given the same number of elapsed years since menarche. Adjusting for years since menarche, the highest frequency of ovulatory cycles was observed in those populations with the highest breast cancer rates. Apter and Vihko (37) in a longitudinal study of 200 schoolgirls also found that those with early menarche establish ovulatory cycles more quickly than girls with later onset of menstruation. The average intervals from

<table>
<thead>
<tr>
<th>Age at menarche</th>
<th>Yrs from menarche to &quot;regular cycles&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>56</td>
</tr>
<tr>
<td>Controls</td>
<td>51</td>
</tr>
<tr>
<td>RR</td>
<td>3.7</td>
</tr>
<tr>
<td>13+</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>34</td>
</tr>
<tr>
<td>Controls</td>
<td>70</td>
</tr>
<tr>
<td>RR</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* From Henderson et al. (31).
menarche until 50% of cycles were ovulatory were 1, 3, and 4.5 years for girls with menarche before age 12, at ages 12–12.9, and at age 13 years and older, respectively.

In the same way in which early onset of menarche and regular ovulation equate with a greater cumulative lifetime exposure to estrogen and greater breast cancer risk, late occurrence of menopause and the extended exposure to ovulatory cycles at the end of menstrual life also increase risk of breast cancer. Women whose natural menopause occurs before age 45 have only one-half the breast cancer risk of women whose menopause occurs after age 55 (38). Artificial menopause, induced by either bilateral oophorectomy or pelvic irradiation, also markedly reduces breast cancer risk. This effect appears to be slightly greater than that of natural menopause (38).

Two of the earliest known and most reproducible features of breast cancer epidemiology were the decreased risk associated with increased parity and the increased risk of single women. MacMahon et al. (39) made a major advance in our understanding of the role of pregnancy in altering breast cancer risk through their analysis of an international collaborative case-control study. Single and nulliparous married women were found to have the same increased risk of breast cancer, which was approximately 1.4 times the risk of parous married women. Among married women in each country, parous women with breast cancer had fewer children than parous controls. MacMahon et al. clearly demonstrated, however, that this apparent protective effect of parity was actually due to a protective effect of early age at first birth. Those women with a first birth occurring before age 20 had about one-half the risk of nulliparous women or of women delaying their first birth until age 30 or later. After controlling for age at first birth, subsequent births had little influence on the risk of developing breast cancer. Women with breast cancer had fewer children overall, simply because they had their first child, on the average, at a much later age. Two studies in other populations (40, 41) have observed a small residual protective effect of an increasing number of births, and this suggests that there may be certain circumstances in which multiparity does offer some further protection. In a recent study in Shanghai, we observed that women with breast cancer had fewer children overall, whether spontaneous or induced, before the first full-term pregnancy did not have any protective effect. Recently, we found that a first-trimester abortion, occurring before age 20 had about one-half the risk of nulliparous women, an observation which has been replicated recently (46). In addition, we found that parous women had higher levels of SHBG and lower levels of free estradiol than their nulliparous counterparts (47).

Lactation has not been clearly established to either enhance or protect against breast cancer development. If the cumulative number of ovulatory cycles is directly related to breast cancer risk, a beneficial effect of long duration of nursing would be expected, because nursing results in a substantial delay in reestablishment of ovulation following a completed pregnancy. Because of a small proportion of mothers with a large cumulative number of nursing months, most previous epidemiological studies have not allowed for precise estimates of the effects of lactation on breast cancer risk. We recently completed a population-based case control study in China, a population in which long duration nursing is the norm. In that study a 30% reduction in breast cancer risk was observed for each 5 years of nursing experience.

There is a strong relationship between weight and breast cancer risk. The relationship is critically dependent on age. For women under age 50 there is little or no increased risk associated with increased weight, but by age 60 a 10-kg increment in weight results in approximately an 80% increase in breast cancer risk (48).

Whether this weight effect is one of excess weight (body fat) or weight per se is unclear. Contradictory results have been reported on whether, for example, Quetelet’s index (wt/heg) is correlated with breast cancer risk. Unadjusted weight appears to be as good an indicator of risk as any other function of weight and height.

Asian women have low breast cancer rates. It is widely believed that the relatively low fat diet of Asian women, vis-à-vis the high-fat diet of women in the United States and Europe, is responsible. However, the results of case-control and cohort studies attempting to link dietary fat with breast cancer have been largely negative (49, 50). It seems reasonable that any dietary contribution to international breast cancer rates is due not to a specific nutrient, e.g., fat, but to the amount of calories consumed and utilized. Excessive calorific intake in the presence of a sedentary lifestyle leads to excess weight, thereby increasing the risk of breast cancer. Support for this interpretation comes from a recent article by Albanes (51) which summarized an extensive number of animal experiments on the interrelationships of calorific and fat intake, weight, and mammary tumor incidence. He showed that, in the face of the limited physical activity of a laboratory animal, calorific intake was highly correlated with both weight and increased mammary cancer risk (Table 5). Fat per se was clearly unimportant in these studies.
outside of its contribution to total caloric intake.

OCs have been widely used since the early 1960s. There is now a substantial body of literature on the relationship between OC use and risk of breast cancer. We recently summarized the results of 16 case-control and 4 cohort studies (52), which provide convincing evidence that OCs, when used during most of a woman’s reproductive life, do not alter the risk of breast cancer. Likewise, most studies show little evidence of a trend of increasing risk with increasing duration of use.

However, if breast tissue mitotic activity is an important determinant of risk, some subgroups of women using COCs may be, under certain circumstances, at increased risk of breast cancer. These circumstances will be those in which the woman’s average breast tissue mitotic activity, when taking a particular COC, is greater than her average “normal” breast tissue mitotic activity.

The late adolescent and perimenopausal periods, when anovular cycles are common, would be expected to provide just the right circumstances for increased risk from the combination-type pill. Five studies have reported specifically on the use of combination oral contraceptives around the time of the menopause (53-57). All of these studies found some evidence of an elevated risk of breast cancer with such use, although the range of reported relative risks has been wide (Table 6).

We have reported that long-term COC use in the late adolescent period also carries with it a substantial increase in breast cancer risk (58). However, more recent studies have not totally supported our observations (59-63) (Table 7). In one (59), increased risk of breast cancer was confined to use before a first FFTP; in a second study in which cases and controls were matched on exact year of age and exact age at FFTP, risk was significantly associated with total duration of use and use before FFTP (60). In another, larger population-based study (61), no difference in risk whatsoever was reported for use at young ages or before FFTP. However, a Swedish study (62) found an increased risk with long-term COC use at an early age similar to that which we reported. Thus, it remains unclear whether COCs when taken at a young age alter the risk of breast cancer.

Most early studies of the possible effects of ERT on the risk of breast cancer were uncontrolled follow-up studies. The most credible of these studies was a cohort study conducted by Hoover et al. (63). Although they reported only a 25% excess of breast cancer in their cohort of menopausal estrogen users compared to the number expected based on general population rates (49 observed versus 39 expected), they did report a more substantial excess among women using high doses for a long time.

Early case-control studies that reported findings on menopausal estrogens and breast cancer were often limited by small numbers, by insufficient data on dose and duration of use, and by the definite possibility of bias. A new group of carefully conducted population- and hospital-based case-control studies have recently been published (64-75) (Table 8). Those studies which have used healthy population comparison groups provide evidence of an increased risk of breast cancer in long-term users. This increase is of the order of 50-100% in women using ERT for approximately 5-15 years, compared to nonusers. The results of these population-based studies contrast with results of those recent studies which have used hospital controls, which find no evidence of an increased risk overall or with long duration of use (Table 8). One possible explanation for this is that hospital controls have more contact with the health care system and are therefore more likely to use elective drugs than the population as a whole.

Based on the best available data, it seems sensible to conclude that long-term use of ERT in moderately high doses carries with it a sizable increase in breast cancer risk, that small doses for a short time convey no measurable increase in risk, and that the effects of smaller doses for long periods of time have not been adequately studied but are unlikely to be substantial.

---

**Table 6** Breast cancer risk and oral contraceptive use during the perimenopausal period

<table>
<thead>
<tr>
<th>First author</th>
<th>Ref.</th>
<th>Duration of use</th>
<th>Relative risk of current users compared to nonusers of following age at diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey</td>
<td>57</td>
<td>40-44</td>
<td>1.5</td>
</tr>
<tr>
<td>Jack</td>
<td>54</td>
<td>40-44</td>
<td>4.0</td>
</tr>
<tr>
<td>Royal College of General Practitioners</td>
<td>56</td>
<td>40-44</td>
<td>1.7</td>
</tr>
<tr>
<td>Brinton</td>
<td>53</td>
<td>40-44</td>
<td>1.3</td>
</tr>
<tr>
<td>Lipnick*</td>
<td>55</td>
<td>40-44</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* For Vessey’s study, age groups are 41-45, 46-50 years. Royal College of General Practitioners study presents data for upper age group as 45+.

**Table 7** Early oral contraceptive use and risk of breast cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Ref.</th>
<th>Subgroup</th>
<th>Duration of use</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pike</td>
<td>58</td>
<td>Use before age 25</td>
<td>1-24 mos</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25-48 mos</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49-72 mos</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73+ mos</td>
<td>4.9</td>
</tr>
<tr>
<td>McPherson</td>
<td>59</td>
<td>Use before FFTP</td>
<td>1-12 mos</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13-48 mos</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49+ mos</td>
<td>3.1</td>
</tr>
<tr>
<td>Meirik</td>
<td>60</td>
<td>Use before FFTP</td>
<td>-3 yr</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-7 yr</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8+ yr</td>
<td>4.4</td>
</tr>
<tr>
<td>Stadel</td>
<td>61</td>
<td>Use before FFTP</td>
<td>1-12 mos</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13-48 mos</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49+ mos</td>
<td>1.2</td>
</tr>
<tr>
<td>Olsson</td>
<td>62</td>
<td>First use before: Age 20</td>
<td>Any</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age 20-24</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age 25-45</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Compared to never use.

---
The combination of estrogen-induced anomalous development in utero leading to neoplastic consequences in the postpubertal period was initially suggested by the work of Herbst et al. (75) in describing the association between in utero DES exposure and vaginal adenocarcinoma. They showed that there was a greatly limited age range during which these neoplasms developed (approximately ages 15–29) and that the relevant exposure was always limited during the first trimester of the index pregnancy (75). Vaginal carcinomas develop from müllerian duct remnants that are induced by DES exposure to persist beyond early fetal life. These remain dormant during childhood and are activated at puberty.

Risk factors for testis cancer include age, cryptorchidism, race, and in utero exogenous estrogen exposure and may include maternal nausea and maternal obesity as well. Age-specific incidence rates of malignant germ cell tumors of the testis peak in early adult life (76). This pattern is reminiscent of the age-specific incidence of vaginal adenocarcinoma resulting from maternal DES exposure. This correspondence suggested to us a hypothesis for the etiology of testicular germ cell neoplasms that was based on in utero hormonal exposure.

Recently conducted epidemiological studies have reported relative risks of testis cancer of 3 to 14 for men with a history of a cryptorchid testis compared to those who experienced normal descent (77–83). A persistently undescended testis is often accompanied by other structural abnormalities. The testis is smaller and, histologically, tubule development and spermatogenesis are retarded. Sertoli cell development is delayed and there are abnormalities of the Leydig cells (84).

It is clearly not the abdominal location of the undescended testis that increases the risk of cancer in this gonad. After descent is achieved by surgical treatment, previously undescended testes retain a higher than normal risk of cancer (82, 85). Furthermore, the contralateral, normally descended testis of a cryptorchid testis compared to those who experienced normal descent (77–83) is another, sometimes intermediate, outgrowth for the subsequent lower incidence of testis cancer in black males (76), deserves mention because it may represent a slight variation of this “estrogen excess” hypothesis. In searching for an explanation for the protection afforded black males, we studied the hormone levels in maternal blood of black and white women during early pregnancy. After adjusting for length of gestation and sex of offspring, black women had testosterone levels that were fully 48% higher than those of white women during the early weeks of gestation (2-sided P = 0.0009). However, black women also had total estradiol levels that were 37% higher, free estradiol levels that were 30% higher, and SHBG levels that were 22% higher than those of white women, even though none of these results was statistically significant. These findings suggest the possibility that not only estrogen levels but also the testosterone levels in the circulating maternal blood are important factors in the development of the testis. The absolute excess of testosterone in the early gestational blood of black women, by providing a “protected” environment for testicular development and descent, is one possible explanation for the subsequent lower incidence of testis cancer in black male offspring. In rats, estrogen-inhibited testicular descent can be reversed by treatment with androgens (90).

There are similarities in the epidemiology of ovarian and testicular germ cell tumors. The ovarian tumors tend to have a peak incidence rate in the young adult age range and, as for testis cancer, these rates have been increasing (91). In a recent study, we observed a high risk of these tumors associated with maternal exposure to hormonal drugs during the index pregnancy (relative risk, 3.6, P = 0.018). Although we have limited our presentation to the evidence for a role of estrogen in the etiology of three types of human

---

### Table 9 Results of four case-control studies examining the association between maternal hormone use and testicular germ cell cancer in offspring

<table>
<thead>
<tr>
<th>First author Ref.</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative risk (95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson</td>
<td>79</td>
<td>6</td>
<td>5.0* (0.4–65.0)*</td>
</tr>
<tr>
<td>Schottenfeld</td>
<td>83</td>
<td>11</td>
<td>2.1 (0.9–10.3)</td>
</tr>
<tr>
<td>Depue</td>
<td>78</td>
<td>9</td>
<td>8.0 (1.3–49.0)</td>
</tr>
<tr>
<td>Moss</td>
<td>89</td>
<td>9</td>
<td>0.9 (0.3–2.6)</td>
</tr>
</tbody>
</table>

* Adapted from Walker et al.*
* Matched.
* Confidence limit determined from reported P value: [P(1) = 0.11].
* Refers to use of DES or other hormones to control bleeding.

---

neoplasms, there is substantial evidence for a similar mechanism, involving different mitogenic hormones, in the development of several additional human cancers, including those of the prostate, ovary, and thyroid (2). The focus of our discussion has been on epidemiology and prevention, but understanding the biological basis for hormone-induced neoplasms has important therapeutic implications as well. Progestogens have been used to induce regression of preexisting adenomatous hyperplasia, a precursor of endometrial carcinoma (92). In fact, progestogens can effectively treat carcinoma in situ of the endometrium (93), if not more advanced disease (94). The chemotherapeutic agent, tamoxifen, has evolved into an important mode of therapy for advanced breast cancer based on its antiestrogenic properties and has been suggested recently as a possible chemopreventive agent for high-risk women (95).

References

12. Rogers, J., and Mitchell, G. W. The relation of obesity to menstrual disturb
17. Rogers, J., and Mitchell, G. W. The relation of obesity to menstrual disturb
21. Rogers, J., and Mitchell, G. W. The relation of obesity to menstrual disturb
Estrogens as a Cause of Human Cancer: The Richard and Hinda Rosenthal Foundation Award Lecture

B. E. Henderson, R. Ross and L. Bernstein


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/48/2/246.citation

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.