

Endogenous Hormones as a Major Factor in Human Cancer¹

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Abstract

Hormone-related cancers account for almost 30% of all cancer cases in the United States. Data from animal experiments and from epidemiological and endocrinological studies in humans support the hypothesis that the individual hormones which control normal growth of target organs can also create the proper conditions for neoplastic transformation. The concept that hormones can cause, *i.e.*, increase the incidence of, human cancer is most developed for the four hormone-related cancers which are numerically the most important, namely, breast, prostate, endometrium, and ovary. Even for these sites, large gaps remain in our knowledge of the responsible hormones and the conditions which create the optimal opportunity for carcinogenesis. Although scanty, the available epidemiological evidence also suggests a hormonal role in the pathogenesis of testis cancer, thyroid cancer, and osteosarcoma. We believe that the primary prevention of all these cancers will probably depend on modification of the factors which affect the secretion and metabolism of the responsible hormones rather than on control of exposure to classical exogenous initiators.

Higginson and Muir (48) calculated recently that about one-third of male and two-thirds of female cancers are probably caused by environmental factors related to "life-style." This vague term life-style encompasses such factors as diet, sexual activity, and reproductive behavior. Hormone-related cancers (Table 1) figure prominently in this category of cancers affected by life-style. These cancers account for almost 30% of all cancer cases in the United States.

The concept that hormones themselves can cause, *i.e.*, increase the incidence of, neoplasia was developed by Bittner (10), Huggins (53), and Furth (31). Normal growth and function of each of these endocrine target organs are controlled by one or more steroid or polypeptide hormones (Chart 1), and in experimental animals, the incidence of neoplasia can be increased by excessive hormonal stimulation of the target organ. In this type of hormone-related neoplasia, there is a progressive transition from normal growth to hyperplasia to neoplasia (for review, see Ref. 31). The neoplasms produced are initially hormone responsive and dependent, but eventually, they become autonomous.

In this model, hormones can increase the incidence of neoplasia even in the absence of outside initiators, such as chemicals or ionizing radiation. In the course of cell division, DNA copying errors may lead to the genetic or epigenetic changes, possibly mutations or other chromosomal errors, necessary for neoplastic transformation (22). Clearly, the chances of such neoplastic change increase with increases in the frequency of cell division. We believe that the primary prevention of these

neoplasms will not come from control of exposure to classical exogenous initiators but from modification of the factors which directly affect the secretion and metabolism of the responsible hormones. Furthermore, since such hormones affect cell division rates of normal, hyperplastic, and even early neoplastic cells, understanding these factors should lead to effective intervention even late along the course of transition from normal functioning cells to hormone-responsive neoplastic cells.

It is the purpose of this article to review the evidence that endogenous hormones are important naturally occurring carcinogens in the sense discussed above, *i.e.*, they are substances that markedly affect the incidence of cancer. Each of the cancers listed in Table 1 will be discussed briefly. We will begin with endometrial cancer since the relationship between the involved hormones and this cancer is the most completely understood.

Endometrial Cancer

The importance of estrogen in the etiology of endometrial cancer has long been recognized, and our current understanding of the pathogenesis of the disease is summarized in Chart 2. Early studies of women with endometrial cancer demonstrated evidence of high estrogen, including ovarian stromal hyperplasia and a high vaginal cornification index (6, 111). The importance of estrogen is also suggested by studies in animals in which DES³ inoculation of rabbits and *p.o.* administration of estrone sulfate to mice have produced endometrial cancer (80, 94).

This estrogen excess hypothesis is also supported by the epidemiological observation that obesity is a major risk factor for endometrial cancer in postmenopausal women, since it has been shown that the level of circulating estrogen in such women is determined to an important degree by body weight (109). The reason for this is that plasma estrogen in the postmenopausal woman is largely derived by extraglandular conversion of androstenedione to estrone, and the rate of this aromatization increases with body weight since adipose tissue is particularly rich in the necessary enzymes (109). Estradiol is then derived from peripheral conversion of estrone (118). This last step is particularly important, since, although the concentration of estrone is 2 to 3 times that of estradiol in postmenopausal women, estradiol is more strongly bound to cytosol receptors in the endometrium, and, in fact, there is some evidence that estrone has no effect in the endometrium (39). The bioavailability of estradiol may be related to the concentration of SHBG in the serum, and recent results show that the SHBG concentration is lower in obese women (88). Thus, obese women not only have greater concentrations of circulating estrogens, but the estradiol may be more available to estrogen-responsive tissue.

The few published studies which directly measured plasma

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³ The abbreviations used are: DES, diethylstilbestrol; SHBG, sex hormone-binding globulin; DTH, dihydrotestosterone; TSH, thyroid-stimulating hormone.

Table 1

Age-adjusted annual incidence rates of hormone-related malignant neoplasms (United States Third National Cancer Survey, 1969 to 1971)

Ages were adjusted to 1970 United States population by Cutler and Young (21).

Site	Male	Female
Breast	0.7	73.8
Endometrium		20.2
Ovary		13.9
Testis	3.1	
Prostate	60.6	
Thyroid	2.1	5.0
Bone	1.0	0.7
Total	67.5	113.6
All sites	346.7	270.2

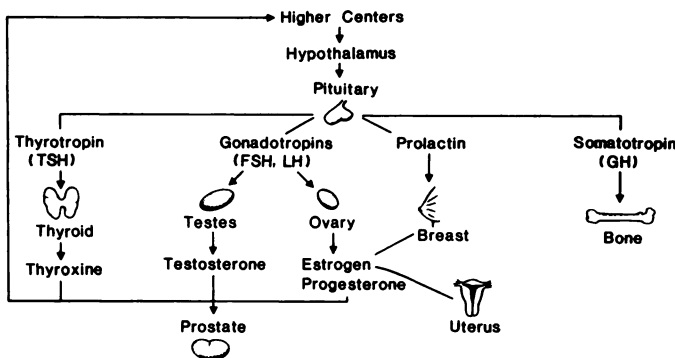


Chart 1. The pituitary hormones and their major target organs. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

estrogen levels in cases of endometrial carcinoma and controls showed increased levels in the cases (2, 8, 61, 71). In 3 of these case-control studies, the authors carefully considered whether the higher levels in cases were only a reflection of their relative obesity. Two of these studies concluded that it was (61, 71), but one found an excess in cases even after adjusting for differences in weight (8).

The estrogen excess hypothesis predicts, of course, that menopausal estrogen replacement therapy would increase the risk of endometrial cancer. Gusberg and Hall (40) published a series of 23 patients with endometrial cancer who had been taking exogenous estrogens for more than a year prior to diagnosis. Although this series was uncontrolled, the authors expressed the opinion that the pathological picture suggested an estrogen effect and concluded "that this hormone plays some role in the development of these tumors." In the past few years, numerous comparative studies, both case-control and cohort in design, have confirmed this opinion (72, 78, 110, 129). The risk ratios in such studies have been high, usually in the range of 3 to 8, and in most, increasing risk with increasing dose and duration of treatment has been apparent.

Progesterone and other progestins have profound effects on the endometrium and are therapeutically useful in treating both endometrial hyperplasia and carcinoma. Three distinct effects can be seen, 2 of which may be regarded as antiestrogenic: in the endometrial cells themselves, progestins increase the activity of the dehydrogenase that converts estradiol to the biologically less active estrone (114); and progestins decrease the concentration of estradiol receptors (52). The third effect of progestins is to cause differentiation of the endometrial cells

to a secretory state. For these reasons, there is considerably more endometrial mitotic activity in the follicular phase, during which circulating estrogen is unopposed by progesterone, compared to the luteal phase of the menstrual cycle. We would therefore predict that a high frequency of anovulatory cycles, during which time no progesterone opposes the circulating estrogen, would be a risk factor for endometrial cancer. Premenopausal endometrial cancer cases do show a higher frequency of anovulatory cycles, but the situation is confounded by the fact that this is commonly found in association with polycystic ovarian disease or obesity. A protective role for progestins is also supported by the increased risk of endometrial cancer in users of sequential oral contraceptives, with a high dose of unopposed estrogen for 3 of every 4 weeks (70), and the decreased risk in users of combined oral contraceptives, with estrogen and progestin given in combination throughout the cycle (62, 122).

One would predict that simultaneous administration of progestins with menopausal estrogen replacement therapy would drastically reduce the risk of endometrial cancer associated with such compounds. A common prescribing pattern for estrogen replacement therapy is 21 days of medication followed by 7 days of respite; it is not clear how much, if any, reduction in risk will result from taking progestins only during the 7-day respite.

Breast Cancer

The breast cancer risk factors of early age at menarche and delayed age at menopause indicate that ovarian activity is an important determinant of risk of this cancer and suggest a critical role for estrogens (36, 73). This is strongly supported by the extensive studies of the role of estrogens in the occurrence of mammary tumors in rodents (65, 76, 90, 127). Animal studies also strongly suggest that elevated levels of prolactin increase the risk of mammary cancer (124). In place of the estrogen excess hypothesis for endometrial cancer, an estrogen-prolactin excess hypothesis is thus suggested for breast cancer. This hypothesis proposes that the risk of breast cancer is essentially determined by the intensity and duration of exposure of breast epithelium to estrogens and to prolactin. Our current understanding of the pathogenesis of the disease is summarized in Chart 3.

The hormonal changes of puberty include increases in the circulating levels of estrogen and prolactin, both of which have important effects on breast epithelium. Early menarche could exert its increased risk simply by producing a greater number of menstrual cycles by a given age (119). The protective effect

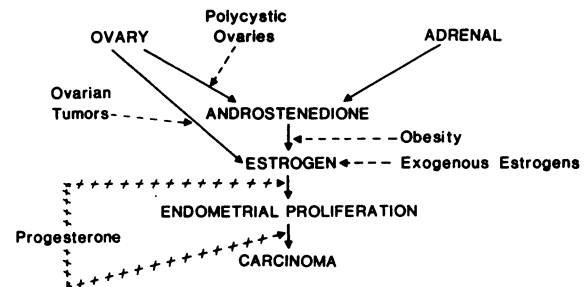
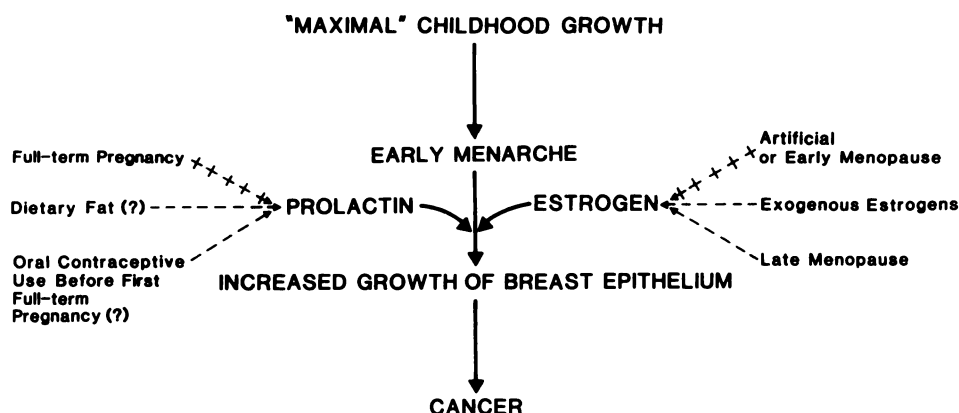


Chart 2. Sources of estrogen and factors influencing estrogen levels and endometrial proliferation. ---, positive effect; + + + +, negative effect.

Chart 3. Factors influencing estrogen and prolactin levels and breast tissue proliferation. - - -, positive effect; + + + +, negative effect.



of early menopause, whether natural or induced, would occur through reducing levels of circulating estrogen; the model would predict that menopausal estrogen replacement therapy would increase breast cancer risk if given over a long period of time in high doses. Studies strongly suggesting this effect of menopausal estrogens have been published recently (50, 57, 103). Factors contributing to elevated endogenous levels of estrogen would similarly be expected to elevate risk. Thus, increased body weight, by contributing to elevated endogenous estrogen levels as we discussed above, would elevate risk in postmenopausal women. This is clearly shown in the studies of de Waard *et al.* (24) and in the long-term follow-up study of the American Cancer Society (67).

A few studies of estrogen levels in premenopausal breast cancer patients and controls have been reported, England *et al.* (27) found a 15% average elevation of total plasma estrogens in a small study of 40- to 49-year-old patients. A similar increase was reported by Cole *et al.* (17) for total urinary estrogens in 73 premenopausal cases and 55 such controls. The only study of plasma estrogen levels in postmenopausal breast cancer cases and controls was also reported in the paper by England *et al.* (27). They studied estradiol levels in 25 cases and 25 controls and found that, on the average, the levels were 30% higher in cases; no data were given on the weight of these women. There have been several studies on urinary estrogens in postmenopausal cases and controls; most, however, included very few subjects. Data on total estrogens from 4 of the 5 studies (4, 13, 38, 77, 95) suggest increased levels of estrogen in the cases; weights of the women in these studies were also not given.

A number of studies of prolactin levels in breast cancer patients and controls have been reported. Many of these studies have had small numbers of patients and controls, and it is not always clear that the investigators have controlled carefully for the marked variation in prolactin levels that occurs during a 24-hr period. Nevertheless, of the 6 patient-control comparisons of premenopausal women we have found in the literature (16, 49, 74, 108), 5 showed higher levels in patients, and, on the average, the values for the breast cancer patients are elevated some 1.5- to 2-fold. The results of a similar study in postmenopausal women by Hill *et al.* (49) also showed a clear elevation of prolactin levels in United States white and Japanese breast cancer patients but not in South African black breast cancer patients when compared to controls. Other studies of postmenopausal women have not found such a difference (11, 64, 79, 83, 92), and probably no difference exists in the

postmenopausal years. As with all case-control hormone comparisons, it is, of course, possible that the differences observed are a consequence of the disease rather than a cause.

Treatment with reserpine is associated with markedly elevated serum prolactin values in the range typical of postpartum lactation. Such large elevations of prolactin in rodents would lead to greatly increased mammary cancer rates (81). Case-control studies clearly show this not to be the case in humans, although one cannot dismiss the possibility that there is a small increase in risk (56). It has been reported that the mitogenic effect of prolactin is mediated by elevating levels of estradiol cytoplasmic receptors (86). Translocation of these receptors to the nucleus requires estrogen. Thus, elevated prolactin levels in the postmenopausal period, when most reserpine is used, might have little mitogenic effect in view of the low levels of circulating estrogen.

The model suggests that the increased risk of breast cancer in family members of breast cancer cases may be partly mediated by higher levels of estrogens and prolactin. We tested this by comparing the plasma hormone levels of daughters of young breast cancer cases and daughters of controls and found some evidence of this (47, 96). The most striking difference between the 2 groups of nulliparous teenagers was obtained by considering the plasma level of estrogen (estrone plus estradiol) and of prolactin together. Urinary estrogens of teenage daughters of breast cancer patients have also been shown to be elevated in a recent study by Trichopoulos *et al.* (113), and Levin and Malarkey (66) found elevated mean 24-hr prolactin levels in daughters, mostly nulliparous, of breast cancer cases. Fishman *et al.* (29), however, did not find high values of estrogens or prolactin when they studied women with a mean age of 32 and a mean parity of 1.8 from breast cancer families.

Progesterone measurements from both our study and that of Trichopoulos *et al.* (113) suggest that the teenage breast cancer daughters were ovulating more frequently than were other girls of their age even after allowing for age at menarche. We would suggest that this is the reason for the elevated estrogens, and possibly prolactin, of the high-risk teenagers. If this is so, then the results of Fishman *et al.* (29) are not necessarily contradictory, since differences in ovulation frequency may well disappear with increasing age and, probably more importantly, after a pregnancy. Incidentally, our results and those of Trichopoulos *et al.* (113) provide no support for the idea that anovulatory cycles (unopposed estrogen) are a characteristic of women at increased risk of breast cancer as

has been proposed (107).

A major decrease in breast cancer risk may be achieved by early first full-term pregnancy (73). Cairns (14) has suggested that this protective effect is due to first full-term pregnancy terminating a hypothesized increase with age in the number of breast stem cells, and other permanent protective fundamental structural effects of first full-term pregnancy on breast epithelium are certainly possible. The estrogen-prolactin excess hypothesis suggests, however, that the protective effect of early full-term pregnancy could occur, at least in part, through permanently reducing prolactin levels (when the woman is not pregnant or actually lactating). This was suggested to us by the steady decrease in mean prolactin levels of women with age, noted by several workers (23, 116). We published some preliminary evidence that prolactin levels are lower in parous than in nulliparous women (97), and we have confirmed this finding by showing that nuns and their nulliparous sisters have early morning prolactin levels some 35% higher than do their parous sisters of the same age (128).

In a recent case-control study, we found that a first trimester abortion before the first full-term pregnancy was associated with a substantial increase in the risk of breast cancer (98). This dual effect of first pregnancy, an initial increase in risk followed by a long-term decrease in risk, offers one explanation for the observation that, if a woman delayed her first birth to her middle or late 30's, then she experienced a breast cancer risk greater than that of a woman who never had a child (73). Further work is clearly needed in this area.

Prostate Cancer

Although prostate cancer is currently the second most common cancer in United States males, little is known about the etiology of the disease. The principal growth-regulating hormones of the prostate are testosterone and its metabolite DHT (93, 126); a testosterone excess hypothesis for prostate cancer is therefore suggested, *i.e.*, that elevated levels of both testosterone and DHT over the course of many decades lead to prostate gland hyperplasia and carcinoma.

Two epidemiological observations suggest that increased levels of androgens may be involved in the pathogenesis of the disease. (a) Autopsy studies show that patients with cirrhosis of the liver have lower rates of prostate cancer than do controls of the same age (34), and alcohol depresses circulating testosterone levels (35). (b) Castration produces a palliative effect on advanced prostate cancer (54), and prostate cancer is seemingly unknown in castrates (51).

Perhaps the strongest piece of evidence in favor of this hormonal hypothesis is the observation by Noble (89) that testosterone alone can produce prostatic adenocarcinoma in rats. This finding is of particular importance since adenocarcinoma of the prostate has been particularly difficult to induce experimentally by any means. Other evidence is provided by the experiments of Brown *et al.* (12), who induced adenocarcinoma of the prostate in intact male rats parabiosed to castrated males or oophorectomized females following unilateral nephrectomy in both partners. Very high circulating levels of testosterone were demonstrated in the target male prior to tumor development.

Recently, Ghanadian *et al.* (33) found that prostate cancer cases had higher mean levels of serum testosterone than did

healthy controls of the same age. Prostate cancer cases in this study had a clear excess of high values. Seven of the 33 cases but only one of the 42 controls had serum testosterone levels greater than 30 nmol/100 ml. Ahluwalia *et al.* (1) also found significantly higher levels of serum testosterone in prostate cancer cases compared to age-matched controls in United States but not African blacks. Hammond *et al.* (42) did not find any differences in their case-control study, but they only had 11 cases of prostate cancer.

In the United States prostate cancer rates in white males are only one-half those in black males, and this difference is evident throughout adult life. The hormonal hypothesis would predict that black males should have higher testosterone and DHT levels. We know of no population study comparing testosterone and DHT levels in United States blacks and whites.

Until recently, it was widely believed that androgen production and serum testosterone levels decline with age, thereby complicating any hypothesis linking androgen excess to prostate carcinogenesis (117). However, the only study of healthy men which has controlled for factors that may affect testosterone secretion or metabolism (alcohol consumption, obesity, prostatic and testicular disease, and use of certain medications) showed no such decline with age for either circulating testosterone or DHT (43).

Besides androgens, estrogens and prolactin may also have a role in prostatic carcinogenesis. The idea that low levels of estrogen may increase the risk of prostate cancer is suggested by the fact that estrogen therapy produces palliation in advanced prostate cancer (54) and that the lower prostate cancer rate of persons with liver disease produced by excess alcohol consumption may be due to the liver disease producing hyperestrogenism (109). The presence of estrogen receptors has been demonstrated in human prostatic cancer (7). However, unlike androgen receptors, estrogen receptors are localized mainly in the stromal compartment of the prostate (18). Therefore, estrogens might be expected to have different effects on prostate tissue than do androgens. In animal models, prolactin appears to act synergistically with luteinizing hormone in controlling secretion of testosterone by the testes (41) and with androgens in stimulating prostate growth and function (63).

Epithelial Ovarian Cancer

A growth-regulating hormone excess hypothesis for this tumor differs in a fundamental way from the above hypotheses for cancer of the endometrium, breast, and prostate. In this case, the responsible hormones, namely, gonadotropins, are not directly stimulatory to the ovarian epithelial cells, but instead, the epithelial cells replicate after each ovulation to cover the exposed surface of the ovary. This indirect hormone excess hypothesis predicts that any respite from the normal cyclic gonadotropin stimulation of the ovary would be protective.

This hypothesis is supported by compelling evidence from a number of case-control studies showing that the risk of ovarian cancer progressively declines with each succeeding pregnancy (3, 15, 60, 87). This evidence has been extended recently in 2 ways: (a) our case-control study (15) in women under age 50 found that incomplete pregnancies were also protective; and (b) Newhouse *et al.* (87) and we both found that oral contraceptive use protected against the disease. The degree of protection from all 3 factors (*i.e.*, full-term pregnan-

cies, incomplete pregnancies, and oral contraceptive use) was simply proportional to the duration of their associated periods of anovulation.

The age-specific incidence curve of ovarian cancer can be brought into line with the familiar linear log-log plot of other nonhormone-dependent epithelial tumors (25) if ovarian age is considered as starting at menarche and proceeding at a reduced rate (roughly 30% of normal) during periods of anovulation, including the postmenopausal period (15).

No animal model for epithelial ovarian tumors exists. Castrated rodents with intrasplenic ovarian transplants have constant high levels of gonadotropins, and this does result in a very high rate of tumors in the transplanted ovaries (9, 58, 68). These tumors are, however, granulosa cell tumors of thecal, not epithelial, cell origin.

Testis Cancer, Thyroid Cancer, and Osteosarcoma

These 3 tumor types are numerically less important than are the hormone-associated carcinomas we have discussed so far. This is reflected by the few epidemiological studies that have been made of these sites. The scanty evidence available suggests, however, a hormonal role in the pathogenesis of each.

Testis. The gestational and early childhood periods are probably critical in the pathogenesis of testis cancer. This is suggested by the age-specific incidence curve of the disease, which shows a broad peak between ages 20 and 40 (Chart 4), and by the fact that the major known risk factor for cancer of the testis is cryptorchidism (46, 84, 85, 106). Failure of the testes to descend in the third trimester, *i.e.*, cryptorchidism, is probably caused by dysgenesis of the testes (105); this dysgenesis may be due to excessive free estrogen present in the first trimester of pregnancy, *i.e.*, at the time of differentiation of the external male sexual characteristics. This hypothesis is supported by several observations.

In utero exposure to exogenous estrogens in the form of DES and oral contraceptives can lead to cryptorchidism (19, 104). Similar effects occur in male offspring of pregnant animals given DES (91). In a recent case-control study, we found

evidence that both excessive nausea and vomiting and exogenous hormone use during the index pregnancy are risk factors for testis cancer (46). The etiology of nausea in pregnancy is not completely understood, but nausea is a common side effect of exogenous estrogen administration, and nausea in pregnancy may similarly be due to a temporary high level of free estrogen. This could come about by the rise of estrogen production early in pregnancy temporarily exceeding the rise in SHBG. Although the result was not statistically significant, a 2-fold increased risk of testis cancer following DES exposure *in utero* was also found by Schottenfeld *et al.* (106).

There is roughly a 7-fold increased risk of testis cancer in a person with cryptorchidism [a 12-fold increased risk in the affected testis and a 3-fold increased risk in the unaffected testis (46, 106)]. Cryptorchidism must partly predispose to testis cancer because of the defect itself, but the increased risk in the contralateral testis suggests that the increased levels of follicle-stimulating hormone (the hormone responsible for germ cell proliferation) associated with both unilateral and bilateral cryptorchidism (69, 115, 125) may lead to increased activity in the normal testis and hence to an increased risk of cancer. Microscopic examination of the contralateral descended testis in infants and young boys does reveal, however, defects similar to those found in the undescended testis (82). The difference in the rates of cancer in the 2 testes may therefore merely reflect a quantitative difference in frequency of the (unknown) precursor lesion.

Thyroid Cancer. The pituitary hormone TSH is the principal hormone regulating the growth and function of the thyroid gland (55), and we therefore suggest, following the same line of reasoning we have used above, a TSH excess hypothesis for thyroid cancer. This hypothesis is supported by the observation that growth of some thyroid cancers is dependent on TSH secretion so that suppression of TSH release by administration of thyroxine is often an effective treatment for thyroid carcinomas (20).

The hypothesis is also supported by experimental work. Sustained elevation of TSH induces thyroid tumors in rodents (5, 37), and the mechanism by which elevated TSH levels are achieved appears unimportant. Thyroid tumors have been produced by iodine-deficient diets, by blocking thyroid hormone synthesis, by administering TSH directly, and by chemical goitrogens.

Thyroid cancer is roughly 2.5 times more common in females than in males. The combined data from all cancer registries reporting to the International Agency for Cancer Research (26, 120) show, however, that under age 10, there were 43 thyroid cancer cases in girls and 37 in boys. This near equality changes abruptly around puberty so that the ratio of females to males is roughly 3 in the 10- to 19-year age group. The ratio remains at about 3 until the menopause in women when it begins to decline steadily, reaching 1.5 by age 65 (Chart 5). This suggests that sex hormones probably play a very important role in the development of thyroid cancer. The thyroxine-binding globulin level in normal females is 10 to 20% higher than in males (32), and in pregnancy, a 50% increase in the level of thyroxine-binding globulin results in a similar magnitude increase in TSH level (75). It therefore appears likely that TSH levels of nonpregnant normal females will be elevated above the level in males at some point in the menstrual cycle although not necessarily throughout the cycle. It has been claimed that there

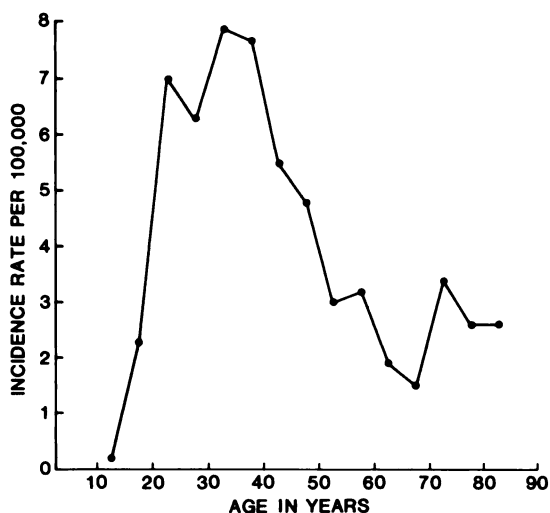


Chart 4. Age-specific incidence rates for cancer of the testis in white males. United States Third National Cancer Survey, 1969 to 1971 (21).

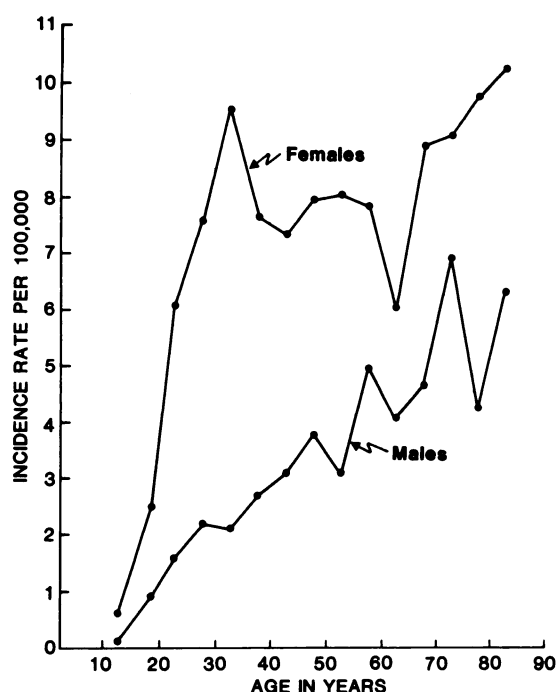


Chart 5. Age-specific incidence rates for cancer of the thyroid in whites. United States Third National Cancer Survey, 1969 to 1971 (21).

are changes in size and activity of the thyroid during the course of a normal menstrual cycle (101), and, if substantiated, this would also suggest transient changes in TSH levels. The reason for the sex differential in thyroid cancer incidence is, of course, very likely to be related to a similar or even more extreme sex differential in other diseases of the thyroid (101).

Data from most countries of the world show that the incidence of thyroid cancer increases steadily with increasing age in much the same way as do other epithelial cancers (26, 120). In the United States, this same pattern was evident up to the late 1930's, but by the 1950's, an early age peak was becoming evident (99, 123). The main reason for this uniquely United States pattern appears to be the use of radiation therapy for benign childhood conditions, a practice which was very common here from around 1930 to around 1960 (44). The relative risk for radiation-induced thyroid cancer appears to be independent of sex (45, 102), so that in absolute terms, females are more susceptible to radiation-induced thyroid cancer. The age distribution of occurrence in the infancy-irradiated series of Hempelmann *et al.* (45) again shows the pattern we described above, namely, equality of cancer rates in females and males until puberty and only thereafter a preponderance of female cases.

Osteosarcoma. The age-specific incidence curve of osteosarcoma peaks in the adolescent period and again in old age, but the disease rarely occurs in middle age. Epidemiological findings strongly suggest that the adolescent peak in incidence is associated with the pattern of childhood skeletal growth. Skeletal growth results from a combination of factors, but hormonal activity is a primary stimulus. Pituitary growth hormone, thyroid hormone, androgens, and estrogens are all involved. The excess growth hypothesis first proposed by Johnson (59), namely, that the incidence of osteosarcomas is simply a function of the amount of cellular activity in the bones,

explains most of the known facts about this tumor.

During the preadolescent period from about age 5 to 11, girls grow faster than boys, but their growth stops earlier so that, by the middle to late teenage years, males are considerably taller (112). The age-specific incidence curves for osteosarcoma follow the same pattern. In Los Angeles County, the osteosarcoma rates for girls up to about age 13 are roughly 30% higher than are the rates in boys, but after this age, the incidence rate for girls declines sharply while the rate for boys continues to rise. In the age group 15 to 24, the male rate exceeds the female rate by some 140%. Maximal skeletal growth precedes the adolescent peak in incidence by 3 to 4 years in each sex. The higher peak in men appears to simply reflect the greater overall size of men compared to women.

Osteosarcomas in adolescents occur most frequently in the epiphyses of long bones, sites of maximal bone growth (100, 121). Fraumeni (30) compared the height of children with osteosarcoma to that of children with other cancers and to national standards. The 2 comparisons gave similar answers. The average differences in height were quite small, but by expressing the data in relative risk terms, we found that the risk of osteosarcoma of children above the 75th percentile of height for age was 2.6 times the risk of children of average height. Children above the 97th percentile had 7.2 times the risk of children of average height. Blacks are known to have proportionately longer legs and arms than do whites despite similar adult height (28), and our data from Los Angeles County show that they have a higher rate of osteosarcoma under age 25 than do whites, all the excess being in long-bone tumors.

The excess growth hypothesis is also supported by clinical studies of osteosarcomas in older people, in whom the sarcomas often occur in conjunction with benign bone pathology, primarily Paget's disease (100, 121). The common denominator of these benign conditions appears to be excessive bone turnover, either as part of a reparative process or as part of the pathological condition itself.

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