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Relationship of Obesity to Blood Estrogens[1]

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Abstract

It has become conventional wisdom that estrogenic stimulation of breast tissue has something to do with the causation of breast cancer and that the reason obesity is a risk factor for breast cancer is that obese women are hyperestrogenized. However, it has been very difficult to demonstrate that excessive exogenous estrogen increases the incidence of breast cancer, that endogenous estrogen excess is present in breast cancer, or that obese women are hyperestrogenized. We have examined the last question by measuring 24-hr mean plasma estrone and estradiol levels in the midfollicular phase in 18 healthy, regularly cycling, very obese (53 to 218% above ideal weight) women and 16 regularly cycling, age matched, nonobese control women. Unlike obese men, the obese women showed no significant elevation of either estrone or estradiol. Their average estrone level was 72 compared with 64 pg/ml in controls; their average estradiol level was 65 compared with 57 pg/ml in controls. In the combined group (obese plus nonobese), there was a significant correlation of percentage of deviation from ideal weight with plasma estrone ($y = 63 + 0.12x$; $p < 0.05$) but not with estradiol. This correlation supports the current hypothesis that there is increased androstenedione → estrone conversion (*i.e.*, increased aromatase activity) in obesity. The reason plasma estrone levels are not significantly elevated in obese women is that the small amount derived from androstenedione is swamped by the much larger amount derived from ovarian secretion, which is apparently unaffected by obesity. Unless there is increased local formation of estrogens in the breast tissue of obese women, the absence of elevated plasma estrogens in them means that their breasts are not "seeing" increased estrogen levels. Thus, endogenous hyperestrogenization is unlikely to be a causative factor of breast cancer in obese women.

The facts that the normal female breast is responsive to estrogenic stimulation, that the growth of breast cancer may be accelerated by increased endogenous estrogen (as in pregnancy) or by administration of exogenous estrogen, and that breast cancer may regress when endogenous estrogen is decreased (by oophorectomy) or antagonized (by antiestrogens) have led to the concept that an increased level of endogenous estrogenic stimulation may be a major factor in the development of breast cancer (the "estrogen hypothesis"). It should be emphasized, however, that the background facts relate to already existing cancer; thus, the notion of a relationship of increased estrogen levels to the development of breast cancer represents a conceptual leap of considerable magnitude. To be sure, breast cancer can be produced in susceptible animals by the administration of estrogens, but there is no clear-cut evidence of increased estrogenicity in human female breast cancer (47), and the evidence that estrogen administration increases the incidence of human breast cancer is unconvincing (25, 44). Some workers (20) have reported increased estrogenicity in women at risk for familial breast cancer, but others (5, 15, 35) have not confirmed this finding. What I will discuss is the evidence for increased estrogenicity in obese women, who some workers (6, 11, 34) believe are at increased risk for breast cancer, although others (1, 46) disagree.

The simplest version of the "estrogen hypothesis" invokes an increase in the level of the primary estrogen, estradiol, but several more complex variants of the hypothesis have been proposed:

1. Excess of a particular estrogen metabolite may be the culprit. One version of this is the "estrone hypothesis" promulgated by Siiteri *et al.* (41), which was initially developed with respect to endometrial cancer and was later extended to breast cancer. This hypothesis was based on the notion that estrone is carcinogenic, while other estrogens are not. Since estrone formation is said to be increased in obese women (13, 18), the estrone hypothesis would account for an increase of breast cancer in these women. However, recent pharmacological studies (3, 16) have demonstrated clearly that both the estrogenic and carcinogenic effects of estrone are quantitatively and qualitatively essentially indistinguishable from those of estradiol or estriol; therefore the estrone hypothesis appears to be untenable at this time, regardless of whether estrone formation is indeed increased in obesity, a point to which I will return.

A second version of this variant is the "abnormal metabolite hypothesis" proposed by Dilman *et al.* (12), based on findings of increased urinary excretion of uncharacterized "estrogen metabolites" in women with breast cancer. Nothing further has been published in this area.

2. An imbalance between harmful estrogen metabolites (estrone and estradiol) and a protective estrogen metabolite (estriol) may be the culprit. This is the "estriol hypothesis," which is associated with Lemon *et al.* (31) and Cole and MacMahon (8). This variant too has been rendered untenable by the recent comparative pharmacological studies of estrone, estradiol, and estriol mentioned above, and Cole has abandoned it (7).

3. An imbalance between the harmful effects of estrogen and the protective effects of progesterone may be the culprit. The initial version of this variant was the "anovulation-luteal inadequacy hypothesis" proposed by Sherman and Korenman (40), which is based on evidence that women with a variety of risk factors for cancer have in common a high incidence of frequent or chronic anovulation and/or luteal inadequacy and therefore a subnormal progesterone/estrogen ratio. The existence of an increased incidence of anovulation and/or luteal inadequacy in women with breast cancer has been supported by the

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anatomical findings of Sommers (42) and Grattarola (17) and the hormonal data of Kodama *et al.* (28), Bulbrook *et al.* (5), and Cowan *et al.* (9), but has been put in doubt by the hormonal data of England *et al.* (14), Swain *et al.* (43), and Malarkey *et al.* (32).

A later version of this variant is the "estrogen window hypothesis" of Korenman (30), which proposes that an increased duration of either of the 2 normal periods of anovulation and therefore low progesterone/estrogen ratio (*i.e.*, the "windows"), namely, the few years just after menarche and the few years just before menopause, increases the risk of developing breast cancer. This hypothesis has been weakened by several items of epidemiological evidence, as summarized by me (47) and by Henderson *et al.* (21).

Both versions are weakened by the fact that no clear-cut antiestrogenic effect of progesterone can be demonstrated in the breast; indeed, it has been reported by Poel (38) that progesterone is cocarcinogenic for the rodent breast.

The special variants of the "estrogen hypothesis" aside, trying to ascertain whether there is an overall increase in estrogenicity in a particular group of women, such as those with breast cancer or those with obesity, brings us up against one of the central problems of endocrinology, namely, how to measure the level of hormonicity for any given hormone. Conceptually, the answer seems simple: one must measure the concentration of the final effector at the effector site. This, however, is of little help in practical terms since the final effector may not be known, and the effector site may not be accessible. At the practical level, 2 major approaches have been suggested: measurement of the production rate of a hormonal effector or its precursor; or measurement of the concentration of the effector in an accessible body fluid, normally blood. Although the latter approach seems more direct, "cleaner," and biochemically more logical, studies of production rate, which include all studies of urinary metabolite excretion and all radioactive tracer studies of precursor-to-product conversions, have been used extensively, on the basis of the tacit assumption that increases or decreases in production rate are mirrored, at least qualitatively if not quantitatively, by corresponding increases or decreases in effector concentration.

At this point, I want to emphasize that, unless the effector is synthesized within the target tissue, that tissue can have no way of "seeing" increased synthesis elsewhere in the body except through an increased concentration in body fluids (*e.g.*, blood). In other words, increased synthesis of a particular effector (*e.g.*, an estrogen) is biologically irrelevant to a distant tissue unless it produces an increase in concentration of the effector in the fluids bathing that tissue.

Are there in fact instances in which changes in the rate of production of a hormonal effector are not mirrored by corresponding changes in its blood level? There are, with respect to cortisol in dysthyroidism. Hyperthyroidism markedly increases and hypothyroidism markedly decreases the rate of cortisol production (19), but neither condition alters the prevailing blood levels of cortisol. Clinically, both hyperthyroid and hypothyroid patients are euadrenal, which confirms the primacy of blood concentration over production rate as a measure of hormonicity.

This brings us to the present issue. The putatively increased risk of development of breast cancer in obese women has been more or less tacitly ascribed to increased estrogenicity in these women. What is the evidence?

Several groups have reported increased rates of conversion of Δ^4-androstenedione to estrone in obese women (13, 18); it has also been reported that this conversion is increased in obese men (26). The increased conversion is generally attributed to an increased mass of adipose tissue, the presumed locus of the conversion, and this concept is supported by reports of a linear correlation between measures of the mass of adipose tissue and measures of the rate of conversion (13). The conversion is mediated by aromatase, which is the reason why aromatase inhibitors have achieved the current high level of interest in connection with breast cancer.

Is their increased conversion of Δ^4-androstenedione to estrone biologically relevant to increased estrogenicity in obese women and thus to an increased risk for breast cancer? As I have suggested above, there are 2 ways in which the increased conversion could be relevant, either by taking place within the breast and thereby raising the local intramammary concentration of effector estrogens or, if it takes place distantly in s.c. and omental adipose tissue, by raising the blood levels of effector estrogens. The first possibility has not been studied and cannot be ruled out. What about the second?

I have found reports from 6 laboratories concerning blood estrogen levels in postmenopausal obese women (2, 4, 10, 22, 23, 33, 36, 37, 45), and 2 reports concerning levels in premenopausal obese women (24, 29). My group has recently published the results of a third study in premenopausal obese women reporting data on 24-hr mean plasma estrone and estradiol levels (48). Four of the groups that studied postmenopausal women (2, 4, 36, 37) found no significant elevation of blood estrone or estradiol levels in obese women. One group (45) reported increases in both hormones; Judd's group (10, 22, 23, 33) reported a correlation between estrone and estradiol levels and the degree of obesity, but the values in the obese subjects were not outside the range of values in the nonobese subjects. With regard to premenopausal women, the reports of Kopelman *et al.* (29) and Kaufman *et al.* (24) agree that there is no significant elevation of plasma estrone or estradiol in obese women.

The studies by my group (comprising Drs. Gladys Strain, Jacob Kream, Joseph Levin, John O'Connor, David Fukushima, and myself) were based on measurement of 24-hr mean plasma levels of estrone and estradiol. This approach was adopted because of the widely reported episodic variations in the plasma concentrations of many hormones, including estrogens; 24-hr mean concentrations are much less variable and therefore afford an opportunity for greater reproducibility, precision, and discriminating power. The subjects of our studies were 18 obese women 20 to 44 years old and ranging from 53 to 218% above ideal weight and 16 nonobese women 22 to 51 years old; all subjects were cycling regularly, were rigorously screened to rule out any significant past or present illness, and were taking no medications. They were admitted to the Clinical Research Center at Montefiore Hospital, where an indwelling venous catheter was placed, and blood samples were withdrawn every 20 min for 24 hr. Aliquots from each sample were pooled, and the estrone and estradiol concentrations of the pool were measured by radioimmunoassay.

Neither estradiol nor estrone levels showed a significant difference between obese and nonobese women (Chart 1). The average estrone level of obese women was 72 compared with 64 pg/ml in controls and the average estradiol level of obese women was 65 compared with 57 pg/ml in controls. This is in marked contrast to the readily demonstrable elevations of both estrone and estradiol that we have observed in obese men (Chart 2), confirming the findings of Schneider *et al.* (39) and those of Kley *et al.* (27). When the plasma concentrations of estrone and estradiol were plotted against the percentage of deviation from ideal weight in the combined obese plus nonobese female group, a statistically significant ($p < 0.05$) positive correlation of low slope ($y = 63 + 0.12$) was seen for estrone but not for estradiol. This finding suggests that the formation of estrone (presumably by aromatization of Δ^4-androstenedione) may indeed be slightly increased in obese premenopausal women. However, the magnitude of the effect seems to be too small in comparison with the ovarian production of estrogens to produce a statistically significant elevation of plasma estrone levels. Thus, unless increased estrone formation is also occurring within the breast, in direct contact with the target epithelial tissues (a possibility for or against which we have no evidence), these tissues would have no way of "seeing" the slightly increased overall estrone formation that seems to be mathematically demonstrable.

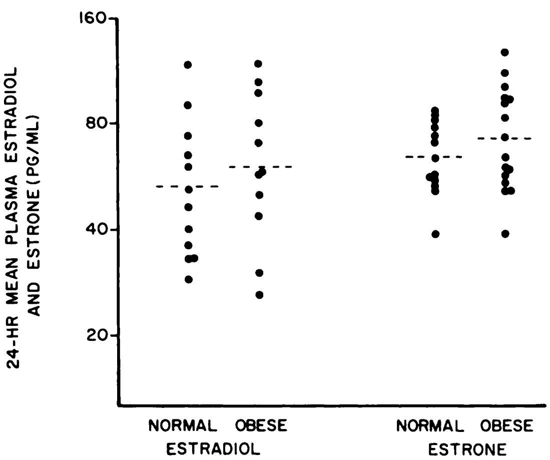

Chart 1. Twenty-four-hr mean plasma estradiol and estrone in normal and obese women in the follicular stage of the menstrual cycle.

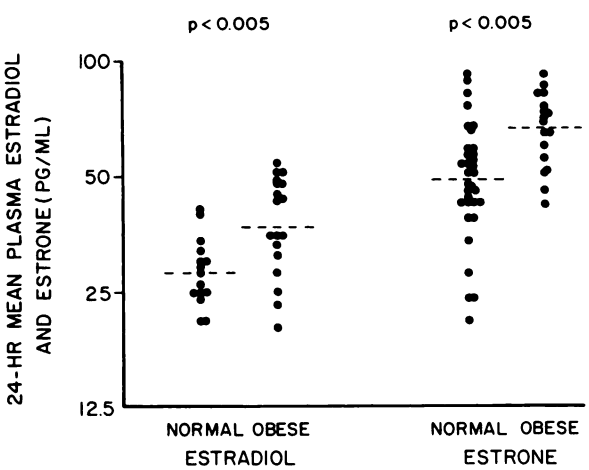

Chart 2. Twenty-four-hr mean plasma estradiol and estrone in normal and obese men.

Summarizing the available data, there appears to be a consensus that obese women have increased formation of estrone by aromatization of Δ^4-androstenedione, the extent of the increase being proportional to the degree of obesity. However, the weight of evidence in both postmenopausal and premenopausal women is that the increase in estrone formation is too small in magnitude to produce a detectable increase in plasma estrone or estradiol levels. This being the case, increased estrone formation cannot be "seen" by breast epithelial tissues and may therefore be biologically irrelevant unless it is also occurring within the breast in direct proximity to the epithelial tissues, a possibility that cannot be supported or ruled out at present.

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Discussion

Dr. Judd: Dr. Zumoff, you have quoted me somewhat incorrectly. The paper that you quoted indicated that we did not find any difference between estrogen levels of fat and thin people. Indeed we did in our first paper in 1976, in which we studied 16 patients with endometrial cancer and 10 postmenopausal women without it. We expanded that study to include 35 patients with and 35 patients without endometrial cancer and published the results in 1979 in the *American Journal of Obstetrics and Gynecology*. We again found a striking correlation with body size not only for estrone but also for estradiol levels. We expanded our study further to 155 postmenopausal women and again in a 1980 publication reported finding a striking correlation between body size and both estrone and estradiol. And we expanded that even further in light of the observations of Dr. Siiteri that the delivery of estradiol may be somewhat different in obese and thin people because of SHBG[1] levels. In the paper that we published with Dr. Siiteri, we looked at total estradiol levels, SHBG levels, percentage non-SHBG-bound estrogen levels, and free estradiol levels, comparing fat and thin individuals. The difference in body size between our thin patients and fat patients was only about 50 pounds. In spite of this relatively small difference in body size, we observed quite large differences in circulating estradiol. The circulating estradiol level in our thin patients was approximately half of that of our heavy patients. When you add the issue of SHBG, if the free hormone has something to do with what is biologically available, there is clearly a 4-fold difference. As we look at the literature, not only our own work but also the work of others, we come up with an entirely different conclusion from yours. As observed originally by Siiteri and McDonald, there is a major difference in percentage of conversion of androstenedione to estrone with obese people, and this difference is absolutely seen in the circulation if you measure concentrations of these hormones.

Dr. Zumoff: Because of the demands of time, I did not go into a very elaborate discussion, and I apologize if Dr. Judd feels that he was somewhat taken out of context. My understanding on reading the earlier papers was that a positive correlation between blood levels and the degree of obesity exists, which indeed we too find. Everybody finds that. However, I was struck by the fact that even at the upper end of the correlation curve the values were not very high; they were within the generally accepted range of normal levels for both estrone and estradiol. I don't know whether that's still true in some of your recent papers, but the ones that I have seen both in the 1976 and 1979 publications and in your presentation at the Endocrine Society indicated to me that you were still talking about variations within the normal range. Of course, we did not look at all at the exceedingly intriguing problem of free *versus* total estradiol in the areas that Dr. Siiteri has talked about very recently with regard to breast cancer and endometrial cancer. He showed a very markedly increased fraction of free estradiol, which may change the whole complexion of the subject. I did not find mention of the gross elevation of plasma estrogens outside the normal range in obese women in the papers that you and your group published.

Dr. R. H. Purdy (Southwest Foundation for Research and Education, San Antonio, Texas): I would like to show a couple of slides of

[1] The abbreviation used is: SHBG, sex hormone-binding globulin.