

Serum oestradiol and breast cancer risk

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Abstract

Breast cancer risk is increased by early menarche and late menopause, suggesting that the long duration of exposure of the breasts to the high levels of ovarian steroids in premenopausal women increases risk. Recent prospective studies have shown that postmenopausal women who develop breast cancer have significantly greater prediagnostic serum concentrations of oestradiol than postmenopausal women who remain healthy. Estimation of long-term oestradiol concentrations in premenopausal women is difficult, and few data are available from prospective studies, but these are compatible with the hypothesis that relatively high oestradiol concentrations in premenopausal women are also associated with an increase in breast cancer risk. Women in populations with low breast cancer rates have low serum oestradiol concentrations both before and after the menopause. The serum concentration of oestradiol is probably a major determinant of breast cancer risk, but more data are needed to confirm this and to investigate the possible roles of other sex hormones.

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Introduction

Breast cancer risk is increased by early menarche and by late menopause (Kelsey 1979). This suggests that the high serum concentrations of oestradiol, progesterone, or both, in premenopausal women cause a greater increase in breast cancer risk per year than the much lower concentrations of oestradiol and progesterone in postmenopausal women. Neither oestradiol nor progesterone is genotoxic, and it is likely that the high serum concentrations of these hormones in premenopausal women increase breast cancer risk by increasing the mitotic rate of the breast epithelial cells (Cohen & Ellwein 1990, Preston-Martin *et al.* 1990, Pike *et al.* 1993).

Oestradiol alone has been shown to stimulate breast cell mitosis in model systems (McManus & Welsch 1984), but the observation that the mitotic rate of human breast epithelial cells is greatest during the luteal phase of the menstrual cycle led to the hypothesis that progesterone might augment the mitotic action of oestradiol (Anderson *et al.* 1982, Key & Pike 1988, Pike *et al.* 1993). A recent study of the effects of hormones on normal breast tissue implanted into athymic mice showed that progesterone did not cause a further increase in the mitotic rate of breast cells exposed to a maximally stimulatory dose of oestradiol (Laidlaw *et al.* 1995), but it is possible that the doses used in this study were not representative of human physiology and that progesterone may augment mitosis in normal premenopausal women (Pike *et al.* 1996).

The simplest hypothesis in relation to hormones and breast cancer is that oestradiol is the major determinant of the mitotic rate of human breast epithelial cells and that breast cancer risk is increased by relatively high serum concentrations of oestradiol in both premenopausal and postmenopausal women. The results of epidemiological studies that have tested this hypothesis are described in this paper. The relationship of circulating oestradiol with breast cancer risk is described first for postmenopausal women, because hormonal exposure in premenopausal women is more complex and more difficult to estimate in epidemiological studies.

Oestradiol and breast cancer risk in postmenopausal women

Early studies examined oestradiol concentrations and breast cancer risk by measuring serum concentrations or urinary excretion of oestrogens in women diagnosed with breast cancer and in women without breast cancer. Most of these case-control studies showed that postmenopausal women with breast cancer had higher oestrogen concentrations than control women (Key & Pike 1988, Thomas *et al.* 1997d), but these findings must be interpreted very cautiously because the oestrogen levels in the women with cancer could be affected by the presence of the cancer or by the treatment for cancer. To eliminate this problem, it is necessary to conduct prospective studies in which oestrogen concentrations are measured in serum samples

Key: Serum oestradiol and breast cancer risk

collected from women before the diagnosis of breast cancer and compared with oestrogen concentrations in serum from women of the same age who did not develop breast cancer during the same period.

Results from several studies of this type have now been published. The earlier studies did not indicate that women who developed breast cancer subsequent to blood collection had higher oestradiol concentrations than the control women (Wysowski *et al.* 1987, Garland *et al.* 1992, Helzlsouer *et al.* 1994), but the numbers of cases in these studies were relatively small (39, 15 and 29 respectively). The more recent, generally larger studies have reported that relatively high oestradiol concentrations are related to an increased risk for breast cancer (Toniolo *et al.* 1995, Berrino *et al.* 1996, Dorgan *et al.* 1996, Thomas *et al.* 1997a). The results of a systematic review of the six prospective studies for which comparable data were available are shown in Fig. 1, in which the data from each study are summarized as the mean concentration in cases divided by the mean concentration in controls (Thomas *et al.* 1997d). Overall, women who were diagnosed with breast cancer subsequent to blood collection had a 15% higher mean serum concentration of oestradiol than the control women; this difference was statistically highly significant and there was no significant heterogeneity between the results of the six studies.

Thus the data available from prospective studies strongly support the hypothesis that relatively high serum oestradiol concentrations in postmenopausal women are associated with an increase in breast cancer risk. However,

the six prospective studies in the review included only 329 women with breast cancer, therefore firm conclusions should not be drawn until more data are available.

The possible roles of other sex hormones and of sex hormone binding globulin

The prospective studies that have reported data on oestradiol and breast cancer risk in postmenopausal women have also reported data for several other sex hormones and for sex hormone binding globulin (SHBG), although the hormones measured have varied between studies. For testosterone, five studies reported that cases had higher mean concentrations than controls (Wysowski *et al.* 1987, Berrino *et al.* 1996, Dorgan *et al.* 1996, Thomas *et al.* 1997a, Zeleniuch-Jacquotte *et al.* 1997), and only the small study by Garland *et al.* (1992; 15 cases) did not observe this difference. Four studies reported that the mean concentration of dehydroepiandrosterone sulphate was greater in cases than in controls (Gordon *et al.* 1990, Berrino *et al.* 1996, Dorgan *et al.* 1996, 1997, Zeleniuch-Jacquotte *et al.* 1997), and only the small study by Barrett-Connor *et al.* (1990; 15 cases) did not observe this difference. Three studies that measured androstenedione reported higher mean concentrations in cases than in controls (Wysowski *et al.* 1987, Helzlsouer *et al.* 1994, Dorgan *et al.* 1996), and only the small study by Garland *et al.* (1992; 15 cases) did not observe this difference. Three studies reported that cases had lower mean concentrations of SHBG than controls (Berrino *et al.* 1996,

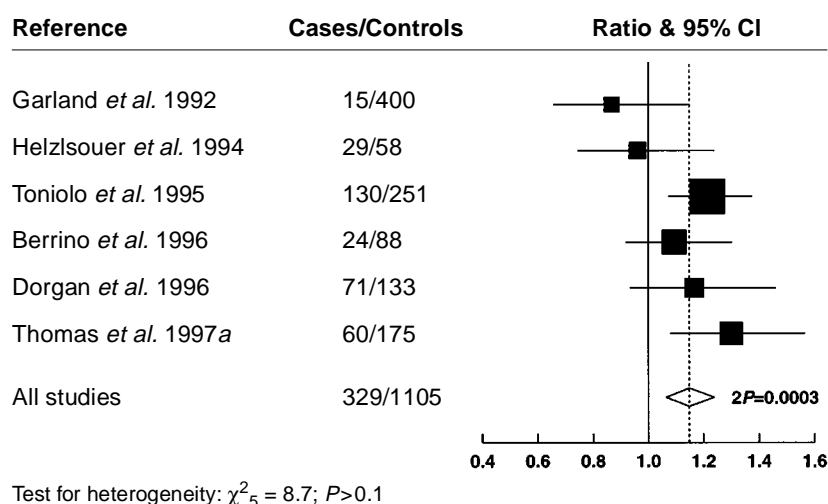


Figure 1 Ratios of serum oestradiol concentrations in cases and controls: data from prospective studies (adapted from Thomas *et al.* 1997d).

Dorgan *et al.* 1996, Thomas *et al.* 1997a), and only the small studies by Garland *et al.* (1992; 15 cases) and Helzlsouer *et al.* (1994; 29 cases) reported marginally higher SHBG in cases than in controls.

These data suggest that, in addition to having relatively high serum concentrations of oestradiol, postmenopausal women who develop breast cancer also have relatively high serum concentrations of testosterone, dehydroepiandrosterone sulphate and androstenedione, and relatively low serum concentrations of SHBG. The coexistence of relatively high levels of these four sex hormones might be expected, because serum concentrations of these hormones are correlated; for example, among the 133 control women in the study by Dorgan *et al.* (1996), the Pearson correlation coefficients of log oestradiol concentration with the log concentrations of testosterone, dehydroepiandrosterone sulphate and androstenedione were 0.39, 0.34 and 0.44 respectively. Three studies have presented the odds ratios for breast cancer associated with oestradiol and testosterone adjusted for each other. In the relatively small study by Berrino *et al.* (1996), these analyses suggested that (free) testosterone was more closely associated with risk than was oestradiol, but in the larger studies of Thomas *et al.* (1997a) and Zeleniuch-Jacquotte *et al.* (1997), the association of testosterone with risk was explained by its association with oestradiol, implying that oestradiol is the hormone more directly involved in the aetiology of breast cancer. More data are needed to confirm this tentative conclusion and to understand the possible roles of other sex hormones in breast cancer risk.

The serum concentration of SHBG is a determinant of the proportion of oestradiol that is available to enter the breast epithelial cells. However, the major determinant of the amount of available oestradiol is the total concentration of oestradiol; for example, among the 133 control women studied by Dorgan *et al.* (1996), non-SHBG-bound oestradiol had a correlation of 0.97 with total oestradiol, but of only -0.23 with SHBG. The majority of

studies have reported that cases have lower serum concentrations of SHBG than controls (described above), and two studies have reported that breast cancer risk is more strongly associated with bioavailable oestradiol than with total oestradiol (Toniolo *et al.* 1995, Dorgan *et al.* 1996).

Oestradiol and breast cancer risk in premenopausal women

Four prospective studies have reported on oestrogens and breast cancer in premenopausal women (Table 1). The two earlier, relatively small studies from the Washington County Cohort (Wysowski *et al.* 1987, Helzlsouer *et al.* 1994) reported no significant differences in oestradiol concentrations between cases and controls. The more recent, slightly larger studies (Rosenberg *et al.* 1994, Thomas *et al.* 1997b) suggested that mean oestradiol concentrations may be greater in cases than in controls, but this difference was not statistically significant in either study.

Together, these four prospective studies included only 179 women who developed breast cancer subsequent to blood collection. Few conclusions can be drawn from these scant data – they suggest that oestradiol concentrations are not grossly increased in women who subsequently develop breast cancer, but they are fully compatible with the hypothesis that breast cancer risk is increased by the existence of moderately increased oestradiol concentrations in premenopausal women.

Body mass index and breast cancer risk

Breast cancer risk is increased by greater body mass index in postmenopausal women (Hunter & Willett 1993). The principal source of oestradiol in postmenopausal women is via the extraglandular aromatization of androstenedione (Siiteri & MacDonald 1973), and oestradiol increases with increasing body mass index in postmenopausal women

Table 1 Prospective studies of oestradiol and breast cancer in premenopausal women

Reference	Cases (n)	Controls (n)	Cycle phase	Oestradiol ratio (cases/controls) ^a
Wysowski <i>et al.</i> 1987	17	67	Any, matched	0.83
Helzlsouer <i>et al.</i> 1994	12	24	Follicular	1.17
	10	20	Luteal	0.72
Rosenberg <i>et al.</i> 1994	79	306	Any, matched	+0.20 ^b
Thomas <i>et al.</i> 1997b	61	179	Any, matched ^c	1.12

^aRatio of mean or median concentration in cases to mean or median concentration in controls. ^bMean difference between cases and controls in units of standard deviations, after adjustment for cycle phase by three-piece spline model. ^cControls were matched to case by day of cycle, and mean results were further adjusted for day of cycle.

(Vermeulen & Verdonck 1978, Cauley *et al.* 1989, Thomas *et al.* 1997c). It is likely that the relationship between body mass index and breast cancer risk can largely be explained by the relationship of body mass index with serum oestradiol concentrations.

Oestradiol in populations at different risk for breast cancer

Breast cancer rates vary about sixfold between different countries. Some of the low risk in countries with low breast cancer rates can be explained by differences in well established risk factors: late menarche, younger age at first birth, and higher parity. However, these factors cannot explain all of the difference between high-risk and low-risk countries, and Pike *et al.* (1983, 1993) have therefore suggested that the remainder of the difference may be explained by lower oestradiol concentrations in women in the low-risk populations.

There is now good evidence that serum oestradiol concentrations are indeed substantially lower in women in low-risk countries than in women in high-risk countries (Goldin *et al.* 1986, Bernstein *et al.* 1990, Key *et al.* 1990). These differences have been observed among both premenopausal and postmenopausal women and, together with the differences in age at menarche and parity, are large enough to explain all the difference in breast cancer rates (Pike *et al.* 1993). Much of the difference between countries in terms of oestradiol concentrations in postmenopausal women can probably be explained by differences in body mass index. The differences in premenopausal women are probably not directly due to differences in body weight (Bernstein *et al.* 1990); they might be explained by differences in diet (Goldin *et al.* 1986), but the relationship of diet with oestradiol

concentrations in premenopausal women is not well understood.

Limitations of epidemiological studies of serum oestradiol and breast cancer risk

The studies reviewed here have relied on one blood sample to characterize a woman's long term exposure to endogenous oestradiol. This is a serious limitation, because oestradiol concentrations change so greatly at menopause and because, even within the premenopausal or postmenopausal period of a woman's life, one blood sample may be very poorly correlated with her average oestradiol concentration.

Several recent studies have examined the intraclass (within-person) correlations between measurements of serum oestradiol concentration in two samples collected at least 1 year apart from each woman (Table 2). Among postmenopausal women, intraclass correlation coefficients were moderately high for oestradiol and somewhat higher for testosterone and SHBG. This shows that a single blood sample can give substantial information about a postmenopausal woman's usual, long-term oestradiol concentration. However, in the one study with data for premenopausal women, the intraclass correlation coefficient for oestradiol was very low, although the correlation for testosterone was moderately high (Muti *et al.* 1996). The important implication of this study is that a single blood sample is a very poor measure of an individual premenopausal woman's usual, long-term oestradiol concentration. Ideally, future prospective studies of oestradiol and breast cancer risk in premenopausal women should collect several samples from each woman.

Table 2 Reliability of serum sex hormone concentrations in women: intraclass correlation coefficients between two samples collected at least 1 year apart

Study	n	Mean interval (years)	Oestradiol	Testosterone	SHBG
Premenopausal					
Muti <i>et al.</i> 1996	60	1	0.06 ^a	0.60	—
Postmenopausal					
Cauley <i>et al.</i> 1991	174	2	0.36	—	—
Hankinson <i>et al.</i> 1995	79	2-3	0.68	0.88	0.92
Muti <i>et al.</i> 1996	47	1	—	0.88	—
Thomas <i>et al.</i> 1997a	64	8	0.56	0.57	0.63

^aSamples collected on the same day of the luteal phase of the menstrual cycle.
n, number studied.

Conclusions

Among postmenopausal women, breast cancer risk is strongly related to the serum concentration of oestradiol. High risk is also associated with relatively high concentrations of other sex hormones. Mechanistic arguments suggest that oestradiol is likely to be the most important hormone in determining risk, but the epidemiological data are currently insufficient to establish this. There are relatively few data for premenopausal women; the data available are inconclusive, but are compatible with the hypothesis that breast cancer risk is increased by relatively high oestradiol concentrations in premenopausal women.

Note added to proof

Two recent papers have strongly confirmed the hypothesis that relatively high serum oestradiol concentrations in postmenopausal women are associated with an increase in breast cancer risk. Hankinson *et al.* (1998) reported that, median oestradiol was 14% higher in 154 women who subsequently developed breast cancer than in 306 controls, and Cauley *et al.* (1999) reported that median oestradiol was 34% higher in 97 women who subsequently developed breast cancer than in 244 controls.

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Key: Serum oestradiol and breast cancer risk

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