Chapter 10

Endogenous Hormone Levels and Risk of Breast, Endometrial and Ovarian Cancers:
Prospective Studies

A. Heather Eliassen* and Susan E. Hankinson

Abstract

Multiple lines of evidence support a central role of hormones in the etiology of breast, endometrial and ovarian cancers. Evidence of an association between circulating hormones and these cancers varies by both hormone and cancer site, with the most consistent associations observed for sex steroid hormones and breast cancer risk among postmenopausal women. Recently, evidence has begun to accumulate suggesting an important role for endogenous hormones in premenopausal breast cancer, endometrial cancer and possibly ovarian cancer. In this chapter, prospective epidemiologic studies, where endogenous hormones are measured in study subjects prior to disease diagnosis, are summarized. Overall, a strong positive association between breast cancer risk and circulating levels of both estrogens and testosterone has now been well confirmed among postmenopausal women; women with hormone levels in the top 20% of the distribution (versus bottom 20%) have a two-to-three-fold higher risk of breast cancer. Evidence among premenopausal women is more limited, though increased risk associated with higher levels of testosterone is consistent. Evidence to date of hormonal associations for endometrial cancer is limited, though a strong association with sex steroid hormones is suggested. Studies of ovarian cancer have been few and small with no consistent associations observed with endogenous hormones. Clearly more evaluation is needed to confirm the role of endogenous hormones in premenopausal breast cancer, endometrial cancer and ovarian cancer.

Introduction

A hormonal etiology has long been suspected for breast, endometrial and ovarian cancers as several risk factors for each cancer are hormonally related. Early age at menarche, nulliparity and late age at menopause, increase the risk of breast cancer.[1] In addition, after menopause, adipose tissue is the major source of estrogen and obese postmenopausal women have both higher levels of endogenous estrogen and a higher risk of breast and endometrial cancer.[2,3] In addition to body mass index, early menarche, late age at menopause, nulliparity and postmenopausal hormone use increase the risk and oral contraceptive use decreases the risk of endometrial cancer.[3] Finally, ovarian cancer risk is reduced with increasing parity, oral contraceptive use and risk is increased by postmenopausal hormone use.[4,5] More recently, evidence has begun to accumulate of a direct

*Corresponding Author: Heather Eliassen—Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA. Email: heather.eliassen@channing.harvard.edu

Innovative Endocrinology of Cancer, edited by Lev M. Berstein and Richard J. Santen.
©2008 Landes Bioscience and Springer Science+Business Media.

involvement of hormone concentrations in each of these cancers. Although there are limited data for ovarian and endometrial cancers, as well as for premenopausal breast cancer, direct evidence of a hormonal etiology of breast cancer is quite strong among postmenopausal women. This chapter reviews the current literature on endogenous hormones and breast, endometrial and ovarian cancer. The hormones included are estrogens, androgens, insulin-like growth factor I and its binding proteins, prolactin (breast cancer) and gonadotropins (ovarian cancer). Because of the potential for these tumors to affect circulating levels of hormones, only data from prospective studies (i.e., "nested" case-control studies), in which hormone levels are measured prior to cancer diagnosis, will be reviewed.

Mechanistically, estrogens contribute to tumor growth by promoting the proliferation of cells with existing mutations or perhaps by increasing the opportunity for mutations.[6] Androgens have been hypothesized to increase cancer risk either directly, by increasing cellular growth and proliferation, or indirectly, by their conversion to estrogen.[7-9] Insulin-like growth factor I (IGF-I) may increase cell proliferation and decrease apoptosis while the IGF binding proteins (IGFBPs) limit the bioavailability of IGF-I.[10-12] Prolactin also may increase breast cell proliferation and inhibit apoptosis.[13] Progesterone has been hypothesized to both decrease and increase breast cancer risk and evidence from animal and in vitro studies supports each hypothesis.[14,15] While postmenopausal estrogen use alone increases breast cancer risk, the association is stronger with the combination of estrogen and progestin.[1] Progesterone is hypothesized to decrease endometrial and ovarian cancer risk,[16,17] although to our knowledge no prospective studies have evaluated progesterone levels with respect to these cancers. Gonadotropins have been hypothesized to increase ovarian cancer risk directly or indirectly by stimulating the production of steroid hormones.[18]

Methodologic Considerations

Evaluating the association of circulating hormones with cancer risk is complicated in epidemiologic studies. Because of logistic and financial restraints, most studies only have a single blood sample for each study subject. However, a single blood sample has been found to reflect long-term hormone levels fairly well. For example, over a two-to-three year period, the correlations for IGF-I, the IGFBPs and postmenopausal gonadotropin and steroid hormones, ranged from 0.5 to 0.9.[19-25] In premenopausal women androgens are similarly well correlated over time[19,24,25] but estrogens (evaluated separately in the follicular and luteal phase) and progesterone (evaluated in the luteal phase) are more modestly correlated.[19,26] Thus, the use of a single blood measure likely causes some attenuation of relative risk (RR) estimates. However, this reproducibility is similar to that of blood pressure or serum cholesterol, parameters that are reasonably measured and consistent predictors of disease in epidemiologic studies.[27]

Although circulating hormone levels are most often measured in epidemiologic studies, relatively little is known about how these levels correlate with exposure in breast, endometrial or ovarian tissue. Levels of 17β-estradiol within the breast tissue are higher than circulating levels,[28] due to its conversion from steroid precursors.[29] The correlation between local nonmalignant tissue levels and circulating levels is not known because most studies evaluated the correlation between circulating levels and tumor tissue hormone levels or did not present correlations between circulating levels and nonmalignant tissue.[30-32] However, the consistent positive associations between circulating hormone levels and risk in postmenopausal women (described below) indicate these levels may be an important marker of tissue exposure. Although few studies have assessed the association between circulating and endometrial tissue hormone levels, evidence suggests the correlation is high and circulating levels of some hormones have been associated with endometrial hyperplasia.[3,33] Given the avascular nature of ovarian epithelium, it is possible that paracrine and autocrine hormonal activity is more important than endocrine activity within the ovaries.[34] In addition, evidence of an association between circulating hormones and ovarian cancer (described below) is more limited.

Breast Cancer

Postmenopausal Women

Estrogens

Substantial prospective data have accrued over the last several years on estrogen concentrations and breast cancer risk in postmenopausal women. In 2002, a pooled analysis was published consisting of all nine prospective studies available at that time.[35] None of the women were using exogenous hormones at blood collection and the analysis included 663 breast cancer cases and 1765 controls. Median time between blood collection and cancer diagnosis ranged from 2 to 12 years. Circulating estrogen levels were positively associated with breast cancer risk. The RRs (95% confidence interval (CI)) for increasing quintiles of estradiol level, relative to the lowest quintile, were 1.4, 1.2, 1.8 and 2.0 (1.5-2.7) (Table 1). Estrone, estrone sulfate and free estradiol were similarly related to risk. The variation in RRs between studies was not statistically significant for any of the hormones and the associations did not vary significantly according to the type of laboratory assay used. Subsequent to the pooled analysis, a Swedish prospective study with 173 cases reported similar positive associations between circulating estrogens and postmenopausal breast cancer.[36] In addition, urinary estrogen levels also were positively associated with breast cancer risk in two prospective studies.[37,38]

More recently, findings from the large multi-country European Prospective Investigation into Cancer and Nutrition (EPIC) study were reported.[39] In EPIC, 677 incident breast cancer cases and 1309 age and recruitment center matched controls were accrued among postmenopausal women over six years of follow-up; findings confirmed those of the pooled analysis of nine studies. For example, for circulating estradiol, the RRs (95% CI) for increasing quintile of levels were 1.0, 1.1, 1.4, 1.7, 2.3 (1.6-3.2) (Table 1). Other estrogens again were similarly related to risk.

Updated analyses from two cohorts included in the pooled analysis have expanded upon the observed associations in important ways. With 13 years of follow-up after blood collection in the New York University Women's Health Study (NYUWHS), the associations with circulating hormones remained unchanged with the exclusion of the first five years of follow-up.[40] In addition, the authors assessed if the change in levels over time varied between cases and controls with two blood samples collected from a large number of women (for cases, one within five years of diagnosis and a second at least five years post diagnosis). Changes in estrogens and testosterone were comparable between the two groups. Thus, this study provides strong evidence that circulating hormones are truly a marker of increased risk in postmenopausal women and not simply a result of tumor-related hormone production.

Only a single detailed assessment of the association between plasma hormones and breast cancer risk by estrogen and progesterone receptor (ER/PR) status of the tumor has been published.[41] While strong positive associations were observed for ER+/PR+ tumors, weak or no associations were noted for ER+/PR– and ER–/PR– tumor types (too few ER–/PR+ tumors were available to evaluate separately). For example, for estradiol, the top versus bottom quartile RR (95% CI) was 3.3 (2.0-5.4) for ER+/PR+ tumors (p-trend<0.001), 1.0 (0.4-2.6; p-trend = 0.82) for ER+/PR- tumors and 1.0 (0.4-2.4; p-trend = 0.46) for ER–/PR– tumors (p for heterogeneity<0.001).

In two recent studies, whether the association between plasma estrogens and postmenopausal breast cancer is similar in women at varying levels of breast cancer risk has been evaluated. No association between plasma estradiol and breast cancer risk was observed among 89 cases and 141 non-cases in the high risk population of the National Surgical Adjuvant Breast and Bowel Project Cancer Prevention Trial (P-1) (top versus bottom quartile RR = 0.96, 95% CI (0.5-2.0)).[42] Within the Nurses' Health Study (NHS) cohort, with 418 cases and 817 controls,[43] the associations of plasma estradiol and estrone sulfate with breast cancer were robust across risk categories regardless of which metric was used to define risk (e.g., 5-year modified Gail score or by family history of breast cancer). For example, estradiol appeared as or more strongly associated with breast cancer in women with higher predicted risk by the Gail risk score (modified Gail score >2.25%: RR = 4.5, 95% CI (2.1-9.5)), compared to lower risk (modified Gail score <1.66%: RR = 2.1, 95% CI

Table 1. ***Circulating hormone levels and breast cancer risk in postmenopausal women***

	Study	Cases/Controls	Category Unit	RR (95% CI)
Estradiol				
	EHBCCG*, 2002	663/1765	Quintiles	2.0 (1.5-2.7)
	Zeleniuch-Jacquotte, 2004**	297/563	Quintiles	2.5 (1.5-4.2)
	Kaaks, 2005	677/1309	Quintiles	2.3 (1.6-3.2)
	Missmer, 2004***	322/643	Quartiles	2.1 (1.5-3.2)
	Manjer, 2003	173/438	Top 20% vs. bottom 80%	1.7 (0.7-1.7)
Testosterone				
	EHBCCG, 2002	585/1574	Quintiles	2.2 (1.6-3.1)
	Zeleniuch-Jacquotte, 2004**	297/562	Quintiles	2.4 (1.4-4.0)
	Kaaks, 2005	668/1280	Quintiles	1.9 (1.3-2.6)
	Missmer, 2004***	312/628	Quartiles	1.6 (1.0-2.4)
	Manjer, 2003	154/417	Quartiles	1.9 (1.1-3.3)
Progesterone				
	Missmer, 2004***	270/530	Quartiles	0.9 (0.6-1.5)
IGF-I				
	Hankinson, 1998	305/483	Quartiles	0.9 (0.5-1.4)
	Toniolo, 2000	115/220	Quartiles	1.0 (0.5-1.9)
	Kaaks, 2002	274/519	Quartiles	1.3 (0.8-2.1)
	Krajcik, 2002	60/60	Quartiles	0.8 (0.2-2.6)
	Muti, 2002	64/238	Quartiles	0.6 (0.2-1.4)
	Keinan-Boker, 2003	149/333	Quartiles	1.1 (0.6-2.1)
	Gronbaek, 2004	411/397	25 unit increase	1.0 (1.0-1.1)
	Schernhammer, 2005	514/754	Quintiles	1.0 (0.7-1.4)
	Allen, 2005	47/141	Tertiles	0.8 (0.3-1.7)
	Rollison, 2006	152/152#	Tertiles	1.4 (0.8-2.4)
		91/91##	Tertiles	1.7 (0.8-3.6)
	Rinaldi, 2006	808/1560###	Quintiles	1.4 (1.0-1.9)
	Baglietto, 2007	220/8885	Quartiles	1.6 (1.0-2.4)
Prolactin				
	Wang, 1992	40/1180	Quintiles	1.6 (0.6-4.7)
	Hankinson, 1999	306/448	Quartiles	2.0 (1.3-3.3)
	Kabuto, 2000	26/56	Log_{10} unit increase	6.5 (0.0-43.9)
	Manjer, 2000	173/438	Quartiles	1.3 (0.8-2.2)
	Tworoger, 2004	851/1275	Quartiles	1.3 (1.0-1.8)
	Tworoger, 2007	916/1410	Quartiles	1.3 (1.1-1.7)

*Endogenous Hormone and Breast Cancer Collaborative Group. **Extension of study included in EHBCCG analysis; 168 new cases and 316 new controls included here. ***Extension of study included in EHBCCG analysis; 167 new cases and 333 new controls included here. #Premenopausal at blood collection, postmenopausal at diagnosis. ##Postmenopausal at blood collection and diagnosis. ###Age at diagnosis >50 years.

(1.2-3.6)), but these differences in relative risk were not statistically significant. The association between plasma estrone sulfate and breast cancer also was similar in the two groups. Thus evidence from this larger cohort suggests that circulating estrogens are predictive of risk in women across both low and high predicted risk of breast cancer, however confirmation in other studies is needed.

Only one prospective study has addressed whether estradiol levels are associated with breast cancer risk in women using postmenopausal hormones.[44] Modest positive associations were observed (top versus bottom quartile RR (95% CI) for estradiol = 1.3 (0.9-2.0) p-trend = 0.20) which were stronger and statistically significant among women who were older, leaner and who had the longest duration of non-use of hormones since menopause. Thus, even in postmenopausal hormone users, plasma estradiol levels appear to be at least modestly associated with risk.

Androgens

Although androstenedione, DHEA and DHEAS have been investigated with respect to breast cancer risk in postmenopausal women, this chapter will focus on associations with testosterone specifically given the amount of data available and limited space. The pooled analysis of nine prospective studies described above[35] and the recently published report from the EPIC study[39] provide a comprehensive summary of evidence on circulating testosterone levels and breast cancer risk in postmenopausal women (Table 1). In the pooled analysis, breast cancer risk increased with increasing testosterone levels: the RRs (95% CI) for increasing quintile (relative to the lowest quintile) were 1.3, 1.6, 1.6 and 2.2 (1.6-3.1). Results were similar in analyses excluding cases diagnosed within two years of blood collection. Extensions of these findings, with up to 13 years of follow-up after the initial blood collection, have been published for 2 of the studies included in the pooled analysis and the observed associations were very similar.[40,43] In the EPIC cohort, similar associations were observed.[39] In addition, the association of plasma testosterone levels and subsequent breast cancer risk was generally similar in women using postmenopausal hormones.[44]

In each of these analyses, adjustment for estradiol in the statistical models only modestly attenuated relative risks for testosterone, suggesting some independent association of testosterone levels with breast cancer.[35,39] However, possible differences between estradiol and testosterone in assay precision, stability of levels 'within woman' over time and intracellular conversion of androgens to estrogens complicate the interpretation of these epidemiologic analyses.

In the NHS, the association between testosterone and breast cancer was stronger for ER+/PR+ tumors (p for heterogeneity = 0.03).[41] Specifically, the top versus bottom quartile RR (95% CI) was 2.0 (1.2-3.4; p-trend<0.001) for ER+/PR+ tumors, 1.9 (0.7-5.0; p-trend = 0.12) for ER+/PR– tumors and 0.7 (0.3-1.6; p-trend = 0.35) for ER–/PR– tumors.

In the two studies previously described, the association between circulating testosterone and breast cancer risk across categories of predicted risk has been addressed. No association was observed between testosterone levels and breast cancer risk in the P-1 trial with 89 cases and 141 non-cases (RR (95% CI) for top versus bottom quartile: 0.5 (0.2-1.1)),[42] although the association was noted to be quite robust in the larger NHS cohort.[43]

Progesterone

Only one large prospective study, with 270 cases, has evaluated the association of postmenopausal circulating progesterone and breast cancer risk. No association was observed either overall (top versus bottom quartile of levels: RR = 0.9; 95% CI = 0.6-1.5; p-trend = 0.90) (Table 1), when evaluated by tumor hormone receptor status or stratified by circulating estradiol levels.[41]

Insulin-Like Growth Factor I and IGF Binding Proteins

The association between IGF-I and IGFBP-3 levels and breast cancer risk has been investigated in 11 prospective studies to date, with a weak positive or no association observed (Table 1).[45-55] In the two largest studies to date, no association was observed in the NHS with 514 cases (top versus bottom quintile RR = 1.0, 95% CI (0.7-1.4)) and a weak positive association was observed in EPIC with 808 cases (top versus bottom quintile RR = 1.4, 95% CI (1.0-1.9)).[51,54] The association between IGFBP-3 and breast cancer risk is more ambiguous, with studies suggesting positive, inverse and null associations.[20,46-48,51]

Prolactin

Prolactin levels and risk of breast cancer among postmenopausal women has been evaluated in several studies to date.[36,56-60] Most, though not all,[36] studies have observed a significant posi-

tive association, with case numbers ranging from 26[56] to 915[60] (Table 1). In the largest to date, an updated analysis within the NHS and NHSII cohorts with 915 postmenopausal women, a marginally significant trend was observed across quartiles of prolactin level, (top versus bottom quartile RR = 1.4, 95% CI (1.0-1.9), p-trend = 0.05).[60] In this two-cohort analysis, the association of prolactin with breast cancer did not differ by menopausal status (p = 0.95). Among premenopausal and postmenopausal women combined (1539 cases), the association was stronger for invasive cases (top versus bottom quartile RR = 1.4, 95% CI (1.1-1.7), p-trend = 0.001) than in situ cases (comparable RR = 1.2, 95% CI (0.8-1.6), p-trend = 0.43). In addition, the association was significantly different by ER/PR status of the tumor (p-heterogeneity = 0.03) with RRs (95% CI) for top versus bottom quartiles of 1.6, (1.3-2.0), p-trend<0.001 for ER+/PR+, 1.7, (1.0-2.7), p-trend = 0.06 for ER+/PR– and 0.9, (0.6-1.3), p-trend = 0.70 for ER–/PR–. There were too few ER–/PR+ cases to evaluate separately.

Conclusion

The positive association between circulating estrogens and testosterone in postmenopausal women and subsequent risk of breast cancer is now well established. For both estradiol and testosterone, women in the top, versus bottom, 20% of estrogen levels have a two- to three-fold higher breast cancer risk. Although confirmation is needed, the association appears strongest for ER+ breast tumors and seems robust across groups of women at varying risk of breast cancer. Whether the association observed with testosterone is direct or indirect (through its conversion to estradiol) is unclear; both may be true. Although recent results are mixed for an association between IGFBP-3 and breast cancer, accumulated evidence suggests no strong association between IGF-I and breast cancer risk among postmenopausal women. Prolactin levels appear to be a modest risk factor for both premenopausal and postmenopausal breast cancer with a stronger association among invasive and ER+ breast tumors.

Studies are now needed to determine if circulating hormone measurements add substantially to existing breast cancer risk prediction models. Several statistical models have been developed for use as an entry criterion into breast cancer chemoprevention trials (e.g., NSABP P-1 trial), in counseling women on the potential use of chemopreventives (e.g., tamoxifen or aromatase inhibitors) and to provide general insight into a woman's individual breast cancer risk[61-64] but none of them include circulating hormone levels. Similarly, whether circulating sex steroid levels can be used to identify women who would most benefit from anti-estrogens is as yet unknown; baseline estradiol levels predicted the subsequent reduction in breast cancer risk associated with raloxifene use in the MORE trial[65] but not with tamoxifen use in the P-1 trial.[42]

Premenopausal Women

In contrast to the rapidly accumulating data on postmenopausal women, relatively few studies on circulating hormone levels and breast cancer have been conducted in premenopausal women. This is largely due to the variation in sex steroid hormone levels, particularly estrogen levels, over the menstrual cycle thus making epidemiologic studies with a single blood sample from each study subject particularly complex.

Estrogens

Seven prospective studies in premenopausal women have been published to date, although five of the seven had fewer than 80 cases (range 14-79 cases).[56,66-69] In none of the five smaller studies were significant associations between estrogen levels and breast cancer risk noted, although as expected given their size, precision of the estimates was uniformly low. Two much larger studies have recently been published. In the largest study to date, conducted in the EPIC cohort, with 285 invasive breast cancer cases and 555 controls, a single blood sample was collected per woman and the day of collection within the menstrual cycle was recorded.[70] Controls were matched to cases on age, study center and time of day of collection and phase of the menstrual cycle at blood collection (in five categories). Comparisons between case and control hormone levels were based on residuals from spline regression models; the residuals indicated how much an individual's

hormone level deviated from the predicted hormone levels on that day. Overall, no association was observed for either estradiol or estrone (e.g., top to bottom quartile comparison RR = 1.0, 95% CI (0.7-1.5) for estradiol) (Table 2). Of note, because blood samples were collected across the menstrual cycle, the investigators had relatively limited ability to evaluate associations within specific parts of the cycle.

In the second large prospective study, conducted within the NHSII, both early follicular (day three to five) and mid-luteal (seven to nine days prior to next cycle) samples were collected from each woman.[71] Timing of the luteal sample collection was by backward dating from the onset of the next menstrual cycle. The analysis included 197 cases (in situ and invasive combined) with 394 controls matched on age, luteal day, date and time of blood draw and fasting status. Follicular, but not luteal, total and free estradiol were significantly associated with breast cancer risk (top to bottom quartile comparison RR = 2.1, 95% CI (1.1-4.1) for follicular total estradiol) (Table 2). Associations were stronger among the 89 ER+/PR+ cases (comparable RR = 2.7, 95% CI (1.2-6.0) for follicular total estradiol). No association was observed with either estrone or estrone sulfate (in either phase of the cycle).

Testosterone

As with estrogens, few prospective studies have evaluated the association between circulating testosterone and breast cancer. Of the five prospective studies published to date, three had 65 or fewer cases; in these studies significant positive[72] or null[66,69] associations with testosterone were reported. Again, confidence intervals were wide.

In the large EPIC cohort, with 370 invasive breast cancer cases and 726 controls, significant positive associations were observed between circulating levels of testosterone and risk of breast cancer.[70] The RRs (95% CI) with increasing testosterone level (in quartile categories) were 1.0, 1.4, 1.4 and 1.7 (1.2-2.6) (p-trend = 0.01) (Table 2).

In the NHSII, with 197 cases (including both in situ and invasive disease) and 394 controls, modest, but not statistically significant, positive associations were observed for testosterone (in both the follicular and luteal phase); the associations, particularly for follicular testosterone, did not appear entirely linear.[71] The associations were stronger and statistically significant when restricting to invasive (comparable case group to the EPIC study) or ER+/PR+ tumors. For example, in the luteal phase, women in the top (versus bottom) 25% of testosterone levels had a twofold increased risk of invasive cancer (RR = 2.0, 95% CI (1.1-3.6), p-trend = 0.05) and a threefold higher risk of an ER+/PR+ tumor (RR = 2.9, 95% CI (1.4-6.0), p-trend = 0.02). Findings for free testosterone generally mirrored those for total testosterone.

Progesterone

To date, only six prospective studies have examined progesterone levels and breast cancer risk in premenopausal women, with four of the six studies including 65 or fewer cases.[66,67,72,73] Nonsignificant inverse associations were observed in three of the smaller studies,[66,69,72] and a nonsignificant positive association was observed in the fourth.[67]

In the large EPIC cohort study, with 285 cases and 555 controls, a significant inverse association was observed between progesterone levels (residuals from spline regression model) and breast cancer risk (top to bottom quartile comparison RR = 0.6, 95% CI (0.4-1.0)) (Table 2).[70] This association was driven by women with samples drawn in the luteal phase and was only apparent among cases and controls matched by forward dating, not among those matched by the more accurate backward dating approach. In the second large study, utilizing backward dating with 197 cases and 394 controls, no association was observed between luteal progesterone levels and risk.[71]

Insulin-Like Growth Factor I and IGF Binding Proteins

Eleven analyses within nine cohort studies have examined IGF-I levels and breast cancer risk in premenopausal women.[20,45-48,51,52,54,55,74,75] Among earlier studies, with a range of 66[48] to 121[47] cases, most but not all[47] studies observed an increased risk of breast cancer with higher levels of IGF-I (Table 2). For instance, in both the NHS and NYUWHS studies, women in the top 20-25%

Table 2. ***Circulating hormone levels and breast cancer risk in premenopausal women***

	Study	Cases/Controls	Category Unit	RR (95% CI)
Estradiol				
	Kaaks, 2005	285/555	Quartiles	1.0 (0.7-1.5)
	Eliassen, 2006	185/368	Quartiles	2.1 (1.1-4.1)
	Follicular			
	Luteal	175/349	Quartiles	1.0 (0.5-1.9)
Testosterone				
	Micheli, 2004	40/108	Tertiles	2.2 (0.6-7.6)
	Kaaks, 2005	370/726	Quartiles	1.7 (1.2-2.6)
	Eliassen, 2006	190/374	Quartiles	1.3 (0.8-2.4)
	Follicular			
	Luteal	192/390	Quartiles	1.6 (0.9-2.8)
Progesterone				
	Micheli, 2004	40/108	Tertiles	0.1 (0.0-0.5)
	Kaaks, 2005	277/524	Quartiles	0.6 (0.4-1.0)
	Eliassen, 2006	195/391	Quartiles	0.9 (0.5-1.7)
	Luteal			
IGF-I				
	Hankinson, 1998	76/105	Quintiles	2.3 (1.1-5.2)
	Toniolo, 2000	172/486	Quartiles	2.3 (1.1-4.9)
	Kaaks, 2002	116/330*	Quartiles	0.6 (0.3-1.4)
	Krajcik, 2002	66/66	Quartiles	3.5 (0.7-18.7)
	Muti, 2002	69/265	Quartiles	3.1 (1.1-8.6)
	Allen, 2005	70/209	Tertiles	1.2 (0.6-2.5)
	Rinaldi, 2005	138/259	Quartiles	1.9 (1.0-3.7)
	Schernhammer, 2005	218/281	Tertiles	1.6 (1.0-2.5)
	Schernhammer, 2006	239/478	Quartiles	1.0 (0.7-1.5)
	Rinaldi, 2006	270/528**	Quintiles	1.0 (0.6-1.8)
	Baglietto, 2007	151/6352	Quartiles	0.8 (0.5-1.4)
Prolactin				
	Wang, 1992	71/2596	Quintile	1.1 (0.5-2.2)
	Helzlsouer, 1994	21/42	Tertile	1.1 (0.3-4.1)
	Kabuto, 2000	46/94	Log_{10} unit increase	1.0 (0.0-47.4)
	Tworoger, 2006	239/478	Quartile	1.5 (1.0-2.5)
	Tworoger, 2007	492/1001	Quartile	1.4 (1.0-1.9)

*Age <50 years at blood collection. **Age at diagnosis ≤50.

of IGF-I levels had a significant 2.3-fold higher risk of breast cancer compared to women in the lowest category.[45,46] However, in an analysis of two Swedish cohorts combined, no increased risk was observed (top vs. bottom quartile RR = 0.6, 95% CI (0.3-1.4)).[47] In more recent studies, estimates have been more modest[51,74] or null[54,55,75] (Table 2). In an extended analysis within the NHS, with 218 cases, a modest increased risk was observed (top versus bottom tertile RR = 1.6, 95% CI (1.0-2.5)).[51] In the largest analysis of premenopausal women to date, in EPIC with 270 cases, no overall association was observed between IGF-I levels and breast cancer risk (top versus bottom quintile RR = 1.0, 95% CI (0.6-1.8)).[54]

Analyses of IGFBP-3 levels and breast cancer risk in premenopausal women have been, as with postmenopausal women, quite inconsistent, with suggested positive,[20,46,48,74] null[47,51,75] and suggested

inverse[52] associations observed. To date, four studies have examined IGFBP-1 levels and breast cancer risk in premenopausal women, with no association observed in any of the four.[47,48,51,75]

Prolactin

To date there have been only five prospective studies of prolactin levels and breast cancer risk among premenopausal women (Table 2). In three small studies, with 21-71 cases each,[56,57,67] no association was observed, but a significant positive association was observed among 239 cases in the NHSII.[76] As noted above, in the combined analysis of NHS and NHSII no significant difference was observed by menopausal status and prolactin levels were modestly associated with breast cancer risk in premenopausal women.[60] With 492 premenopausal cases, the top versus bottom quartile RR was 1.4, 95% CI (1.0-1.9), p-trend = 0.05.

Conclusion

Although there are few prospective studies of premenopausal testosterone and breast cancer risk, a positive association has been observed consistently with approximate twofold increases in invasive breast cancer risk among women with high levels. The associations between estrogen and progesterone levels in premenopausal women and breast cancer risk have not been consistent and further assessments are needed. In the only study to detect a significant association with estrogen, follicular, but not luteal, estradiol levels were associated with risk. It is possible that follicular levels better reflect breast tissue estrogen exposure[77-79] or that estradiol has a greater impact in the low-progesterone environment of the follicular phase.[80-84] This finding was not consistent across estrogens, as no associations were observed with estrone or estrone sulfate. The stronger associations observed with ER+/PR+ tumors is consistent with findings among postmenopausal women, although again this needs to be replicated in future studies. The two largest studies also had conflicting findings for progesterone. The importance of timing within the menstrual cycle needs to be resolved since the association was only apparent in the EPIC study when the less accurate form of menstrual cycle timing was utilized. Thus, while evidence is beginning to accumulate supporting an association between premenopausal sex steroid hormones and breast cancer risk, the nature and magnitude of the associations require further study.

Earlier evidence suggested a positive association between IGF-I and breast cancer risk among premenopausal women, but more recent evidence from larger studies has been null. Whether the differences in results are attributable to differences in study populations or assay methods needs to be examined to determine the source of these substantial inconsistencies. Assessments of IGFs and breast cancer survival are also needed. While there are still few studies of prolactin levels and breast cancer risk in premenopausal women, accumulated evidence suggests that prolactin is a modest, independent risk factor for breast cancer in premenopausal women.

Endometrial Cancer

Estrogens

To date, the association between estrogen levels and endometrial cancer risk has been investigated in only two prospective studies, both among postmenopausal women not using postmenopausal hormones. Cases (n = 57) from the first study from NYUWHS,[85] were then included in a combined analysis of the NYUWHS, Umea Sweden and Hormones and Diet in the Etiology of Breast Cancer Risk (ORDET) cohorts[86] among postmenopausal women (124 cases). Estradiol and estrone were both strongly and significantly associated with endometrial cancer risk (top versus bottom quartile RR = 5.4, 95% CI (2.5-11.6), p-trend = 0.0001 for estradiol and RR = 4.6, 95% CI (2.3-9.1), p-trend = 0.0001 for estrone). Adjustment for BMI, SHBG levels, or androgen levels slightly attenuated these associations but they remained strong and statistically significant (Table 3).

SHBG was inversely associated with endometrial cancer risk in the combined analysis (top versus bottom quartile RR = 0.4, 95% CI (0.2-0.7), p-trend = 0.0006), as expected given the strong inverse association between BMI and SHBG.[86]

Androgens

The association between circulating androgens and endometrial cancer risk has only been investigated in the combined analysis of postmenopausal women (124 cases),[86] with significant direct associations observed for androstenedione (top versus bottom quartile RR = 2.1, 95% CI (1.1-4.0), p-trend = 0.03), testosterone (comparable RR = 2.1, 95% CI (1.1-4.0), p-trend = 0.02) and DHEAS (comparable RR = 3.1, 95% CI (1.5-6.0), p-trend = 0.0001). After adjustment for BMI, the associations were attenuated but remained strong and all but the testosterone association remained statistically significant (Table 3). Adjusting for estradiol and estrone significantly attenuated the associations and the effects of androstenedione and testosterone were no longer significant, but DHEAS, though attenuated, remained significant after adjustment for estrone and was marginally significant after adjustment for estradiol.

Insulin-Like Growth Factor I and IGF Binding Proteins

Only one study, combining the NYUWHS, Umea and ORDET cohorts with 166 cases in total, has investigated circulating IGF-I and endometrial cancer risk and no association was observed.[87] Similarly, no association was observed with IGFBP-3. IGFBP-1 and -2 have been investigated in the combined analysis[87] as well as within EPIC,[88] with conflicting findings. In the combined analysis, IGFBP-2 was unrelated to endometrial cancer risk but IGFBP-1 was inversely associated with risk (top versus bottom quintile RR = 0.3, 95% CI (0.2-0.6), p-trend = 0.002); the association with IGFBP-1 was substantially weakened after adjusting for BMI (p-trend = 0.06).[87] In contrast, in the EPIC investigation, no association was observed with IGFBP-1 levels, but a significant inverse association was observed with IGFBP-2 levels (top versus bottom quartile RR = 0.6, 95% CI (0.4-0.9), p-trend = 0.03).[88]

Conclusion

Although few studies have been conducted to date, evidence suggests strong positive associations between circulating androgens, estrogens and endometrial cancer. These findings should be confirmed and better quantified in future, larger prospective studies. Evidence for an association with IGF-I and its binding proteins is limited and more mixed, with null and inverse associations observed. While the question remains of whether there is a correlation between circulating and tissue levels of hormones, the strong positive associations with estrogens and androgens suggest that circulating levels are an indirect marker of tissue exposure.

Ovarian Cancer

Gonadotropins

Although gonadotropins have been hypothesized to contribute to a hormonal etiology of ovarian cancer,[18] the few studies that have investigated FSH and LH levels have found either null or inverse associations (Table 4). In the NYUWHS study with 58 cases (22 premenopausal and 36 postmenopausal), the point estimate for the highest tertile of LH levels, compared with the lowest, was below one but was not statistically significant (RR = 0.4, 95% CI (0.1-2.1)).[89] Similarly, in a small study by Helzlsouer et al, with 31 cases, a nonsignificant inverse association was observed among premenopausal and postmenopausal women combined (RR = 0.4, 95% CI (0.1-2.0)).[90] FSH levels were statistically significantly inversely associated with ovarian cancer in this study (top versus bottom tertile RR = 0.1, 95% CI (0.0-1.0), p-trend = 0.02), with the association most apparent among postmenopausal women (p = 0.05). However, in a combined analysis of the NYUWHS, Umea and ORDET cohorts, with 88 postmenopausal cases, no association was observed (top versus bottom tertile RR = 0.9, 95% CI (0.4-2.0)).[91] Thus, the limited data available to date do not support a positive relation between gonadotropins and ovarian cancer as originally hypothesized.

Table 3. Circulating hormone levels and endometrial cancer risk

	Study	Menopausal Status	Hormone	Cases/Controls	Category Unit	RR (95% CI)
Estrogens						
	Lukanova, 2004(a)	Postmenopausal	Estradiol	122/230	Quartiles	4.1 (1.8-9.7)
			Estrone	122/230	Quartiles	3.7 (1.7-7.9)
Androgens						
	Lukanova, 2004(a)	Postmenopausal	Androstenedione	124/236	Quartiles	2.2 (1.1-4.4)
			Testosterone	124/236	Quartiles	1.7 (0.9-3.5)
			DHEAS	124/236	Quartiles	2.9 (1.4-5.9)
IGF-I						
	Lukanova, 2004(b)	Pre and Postmenopausal	IGF-I	166/314	Quintiles	0.9 (0.4-1.8)

Estrogens

Estrone levels have been examined in two studies (119 cases in total), with no significant associations observed in premenopausal and postmenopausal women combined,[90] or in postmenopausal women alone (Table 4).[92] In a small study of both premenopausal and postmenopausal women estradiol levels were not significantly different between cases and controls.[90]

Androgens

Several studies have investigated the associations between both ovarian and adrenal androgens, including androstenedione, testosterone, DHEA and DHEAS, and the risk of ovarian cancer. In an early small (31 cases) study androstenedione levels were significantly positively associated with ovarian cancer risk (Table 4).[90] However, in two subsequent, larger studies (132 and 192 cases) results generally were null,[92,93] although in one study a positive association among premenopausal women was suggested (44 cases) (RR = 2.4, 95% CI (0.8-6.8)).[92] Testosterone levels have been investigated in two studies, with no associations observed; however a significant inverse association was observed between free testosterone and ovarian cancer risk among postmenopausal, but not premenopausal, cases (n = 136) (Table 4).[93] DHEA levels were significantly higher in cases compared with controls in one small study;[90] to our knowledge plasma DHEA levels have not been examined in any other study. DHEAS levels were suggestively positively associated with ovarian cancer risk in a small study,[90] but no association was observed among premenopausal or postmenopausal women in two subsequent, larger studies (Table 4).[92,93]

Insulin-like Growth Factor I and IGF Binding Proteins

Only four analyses have examined the association between IGF-I, its binding proteins and ovarian cancer risk. In a combined analysis of three cohorts (NYUWHS, Umea Sweden and ORDET), with 132 cases, no overall association was observed with IGF-I (Table 4), but an increased risk was observed among 41 cases who were diagnosed at ages <55 years (top versus bottom tertile RR = 5.0, 95% CI (1.2-20.2)).[94] A similar pattern was observed in the EPIC cohort, with 214 cases, with no overall association (Table 4) but a suggested increased risk among those diagnosed at ages <55 years (66 cases) (top versus bottom tertile RR = 2.4, 95% CI (0.9-6.4)).[95] In a combined analysis within the NHS, NHSII and Women's Health Study (WHS) cohorts, with 179 cases, a modest inverse association was observed (top versus bottom quartile RR = 0.6, 95% CI (0.3-1.0)), but the trend was not significant (p-trend = 0.14).[96] In contrast to the two previous studies, no significant association was observed among the 59 cases diagnosed at ages <55 years. In all three studies, the association with IGFBP-3 was null among all cases and among those diagnosed at ages <55 years. In the only study to date to investigate IGFBP-1 no association was observed for levels of the binding protein overall or among cases diagnosed at ages <55 years.[97] Two studies have investigated IGFBP-2, with no associations observed overall or among younger women.[96,97]

Conclusions

While ovarian cancer has a hormonal etiology, at least in part, studies to date of circulating hormone levels and risk have not consistently shown the hypothesized associations. Data on estrogens and ovarian cancer are limited and one of the prior studies combined premenopausal and postmenopausal women, which is likely not appropriate for estrogen levels that differ so substantially by menopausal status. To date, circulating androgen levels do not appear important in predicting risk. IGF-I levels may be directly related to ovarian cancer in younger women, although the data again are limited and not entirely consistent; associations with IGF binding proteins have thus far been null. Future larger prospective studies are needed and separate examination by menopausal status would be important for estrogens and gonadotropins. A potential explanation for the lack of associations observed could be that circulating levels of hormones do not reflect hormone exposure at the ovarian epithelial cell. In addition, most epidemiologic studies include a combination of subtypes of epithelial ovarian cancer. While it is possible that these subtypes have different etiologies, the limited case numbers in prospective analyses of ovarian cancer currently preclude any subtype specific assessments.

Table 4. ***Circulating hormone levels and ovarian cancer risk***

	Study	Menopausal Status	Hormone	Cases/Controls	Category Unit	RR (95% CI)
Estrogens	Helzlsouer, 1995	Pre and Postmenopausal	Estradiol	31/62	Tertiles	3.0 (0.6-14.9)
			Estrone	31/62	Tertiles	1.7 (0.4-7.6)
	Lukanova, 2003	Postmenopausal	Estrone	88/171	Quartiles	1.2 (0.5-2.8)
Androgens	Helzlsouer, 1995	Pre and Postmenopausal	Androstenedione	31/62	Tertiles	7.6 (1.2-48.7)
			DHEA	31/62	Tertiles	2.3 (0.7-7.6)
			DHEAS	31/62	Tertiles	2.7 (0.7-10.0)
	Lukanova, 2003	Premenopausal	Androstenedione	44/84	Tertiles	2.4 (0.8-6.8)
			Testosterone	44/83	Tertiles	1.4 (0.5-4.1)
			DHEAS	44/84	Tertiles	1.5 (0.5-4.3)
		Postmenopausal	Androstenedione	86/173	Quartiles	0.6 (0.3-1.3)
			Testosterone	88/169	Quartiles	1.3 (0.6-3.1)
			DHEAS	87/172	Quartiles	1.0 (0.4-2.3)
	Rinaldi, 2007	Premenopausal	Androstenedione	54/104	Above vs. below median	1.1 (0.6-2.3)
			Testosterone	52/97	Above vs. below median	1.2 (0.5-2.7)
			DHEAS	56/109	Above vs. below median	1.2 (0.6-2.5)
			Free testosterone	50/92	Above vs. below median	1.3 (0.6-2.9)
		Postmenopausal	Androstenedione	128/222	Tertiles	0.7 (0.4-1.2)
			Testosterone	125/203	Tertiles	0.7 (0.4-1.3)
			DHEAS	134/232	Tertiles	0.8 (0.5-1.4)
			Free testosterone	118/186	Tertiles	0.5 (0.2-0.9)
IGF-I	Lukanova, 2002	Pre and Postmenopausal	IGF-I	132/263	Quartiles	1.4 (0.7-2.8)
	Peeters, 2007	Pre and Postmenopausal	IGF-I	214/388	Tertiles	1.1 (0.7-1.7)
	Tworoger, 2007	Pre and Postmenopausal	IGF-I	179/599	Quartiles	0.6 (0.3-1.0)
Gonadotropins	Akhmedkhanov, 2001	Pre and Postmenopausal	LH	58/116	Tertiles	0.4 (0.1-2.1)
	Helzlsouer, 1995	Pre and Postmenopausal	LH	31/62	Tertiles	0.4 (0.1-2.0)
			FSH	31/62	Tertiles	0.1 (0.0-1.0)
	Arslan, 2003	Postmenopausal	FSH	88/168	Tertiles	0.9 (0.4-2.0)

Summary

As cumulative indirect evidence has suggested, sex steroid hormones are important in the etiology of breast cancer. Among postmenopausal women, the associations between estrogens, testosterone and breast cancer risk are consistent and well established. IGF-I and its binding proteins have not been consistently associated with an increased risk, but prolactin levels appear to be a modest relatively well confirmed risk factor for breast cancer. Recent work has helped identify subgroups of women in whom hormone levels appear particularly important (e.g., those with ER+/PR+ tumors) and hormone levels may improve current models used to predict a woman's risk of breast cancer. Premenopausal sex steroid hormones also appear to play an important role in breast cancer although evidence is not as plentiful nor as consistent hence further research is necessary to elucidate these relationships. IGF-I results have been puzzlingly inconsistent, with more recent studies not confirming the positive association observed among premenopausal women in earlier studies. Accumulating evidence suggests that prolactin levels in premenopausal women are predictive of breast cancer risk, with a similar magnitude observed for both premenopausal and postmenopausal women.

In contrast to breast cancer, fewer studies have investigated circulating hormone levels and risk of endometrial and ovarian cancer. Sex steroid hormones appear to be an important and strong predictor of endometrial cancer risk, but results from studies of ovarian cancer do not suggest a strong association. From the current literature, it is unclear whether IGF-I is an important risk factor for either endometrial or ovarian cancer. Several studies have investigated the role of circulating gonadotropins and ovarian cancer risk, but thus far none has supported the gonadotropin hypothesis of the etiology of ovarian cancer.

Further study is required to continue to elucidate the hormonal etiology of these three cancers. With strong evidence to date of a role of sex steroid hormones in the etiology of postmenopausal breast cancer, the next step is to consider the roles of these hormones in existing prediction models to help determine a woman's risk of breast cancer. Among premenopausal women, further prospective studies with careful attention paid to menstrual cycle timing are necessary to confirm the magnitude and direction of estimates. Although all of the studies summarized are prospective, it is possible that blood collected shortly before diagnosis may be affected by a subclinical tumor. However, evidence to date suggests that hormone concentrations are associated with breast cancer risk in postmenopausal women at least 10 years after blood collection; with more follow-up the importance of timing can be confirmed in both premenopausal and postmenopausal women. Larger prospective studies are required to confirm the sex steroid hormone association with endometrial cancer and further investigation into growth factors and the associations with obesity are necessary. The continuing investigation of the role of circulating hormones in the etiology of ovarian cancer in larger prospective studies is necessary, with separate analysis of premenopausal and postmenopausal women and attention to menstrual cycle timing among premenopausal women. In addition, larger studies may allow a separation of subtypes, which may have different etiologies.

Acknowlegement

This work was supported by Research Grant CA49449 and CA67262 from the National Cancer Institute. Dr. Eliassen was supported by Cancer Education and Career Development Grant R25 CA098566-02 from the National Cancer Institute.

References

1. Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle and hormones. Breast Cancer Res 2004; 6:213-218.
2. van den Brandt PA, Spiegelman D, Yaun SS et al. Pooled analysis of prospective cohort studies on height, weight and breast cancer risk. Am J Epidemiol 2000; 152:514-527.
3. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002; 11:1531-1543.
4. Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. Cancer Epidemiol Biomarkers Prev 2005; 14:98-107.

5. Danforth KN, Tworoger SS, Hecht JL et al. A prospective study of postmenopausal hormone use and ovarian cancer risk. Br J Cancer 2007; 96:151-156.
6. Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000; 21:427-433.
7. Liao DJ, Dickson RB. Roles of androgens in the development, growth and carcinogenesis of the mammary gland. J Steroid Biochem Mol Biol 2002; 80:175-189.
8. Syed V, Ulinski G, Mok SC et al. Expression of gonadotropin receptor and growth responses to key reproductive hormones in normal and malignant human ovarian surface epithelial cells. Cancer Res 2001; 61:6768-6776.
9. Legro RS, Kunselman AR, Miller SA et al. Role of androgens in the growth of endometrial carcinoma: an in vivo animal model. Am J Obstet Gynecol 2001; 184:303-308.
10. Khandwala HM, McCutcheon IE, Flyvbjerg A et al. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000; 21:215-244.
11. Rajaram S, Baylink DJ, Mohan S. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocr Rev 1997; 18:801-831.
12. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000; 92:1472-1489.
13. Clevenger CV, Furth PA, Hankinson SE et al. The role of prolactin in mammary carcinoma. Endocr Rev 2003; 24:1-27.
14. Lanari C, Molinolo AA. Progesterone receptors—animal models and cell signalling in breast cancer. Diverse activation pathways for the progesterone receptor: possible implications for breast biology and cancer. Breast Cancer Res 2002; 4:240-243.
15. Campagnoli C, Clavel-Chapelon F, Kaaks R et al. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol 2005;96:95-108.
16. Siiteri PK. Steroid hormones and endometrial cancer. Cancer Res 1978; 38:4360-4366.
17. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998; 90:1774-1786.
18. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J Natl Cancer Inst 1983; 71:717-721.
19. Missmer SA, Spiegelman D, Bertone-Johnson ER et al. Reproducibility of plasma steroid hormones, prolactin and insulin-like growth factor levels among premenopausal women over a 2-3 year period. Cancer Epidemiol Biomarkers Prev 2006; 15:972-978.
20. Muti P, Quattrin T, Grant BJ et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002; 11:1361-1368.
21. Arslan AA, Zeleniuch-Jacquotte A, Lukanova A et al. Reliability of follicle-stimulating hormone measurements in serum. Reprod Biol Endocrinol 2003; 1:49.
22. Toniolo P, Koenig KL, Pasternack BS et al. Reliability of measurements of total, protein-bound and unbound estradiol in serum. Cancer Epidemiol Biomarkers Prev 1994; 3:47-50.
23. Hankinson SE, Manson JE, Spiegelman D et al. Reproducibility of plasma hormone levels in postmenopausal women over a 2-3-year period. Cancer Epidemiol Biomarkers Prev 1995; 4:649-654.
24. Micheli A, Muti P, Pisani P et al. Repeated serum and urinary androgen measurements in premenopausal and postmenopausal women. J Clin Epidemiol 1991; 44:1055-1061.
25. Muti P, Trevisan M, Micheli A et al. Reliability of serum hormones in premenopausal and postmenopausal women over a one-year period. Cancer Epidemiol Biomarkers Prev 1996; 5:917-922.
26. Michaud DS, Manson JE, Spiegelman D et al. Reproducibility of plasma and urinary sex hormone levels in premenopausal women over a one-year period. Cancer Epidemiol Biomarkers Prev 1999; 8:1059-1064.
27. Willett WC. Nutritional Epidemiology. 2nd ed. New York: Oxford University Press 1998.
28. van Landeghem AA, Poortman J, Nabuurs M et al. Endogenous concentration and subcellular distribution of estrogens in normal and malignant human breast tissue. Cancer Res 1985; 45:2900-2906.
29. Thijssen JH, Blankenstein MA, Miller WR et al. Estrogens in tissues: uptake from the peripheral circulation or local production. Steroids 1987; 50:297-306.
30. Vermeulen A, Deslypere JP, Paridaens R et al. Aromatase, 17 beta-hydroxysteroid dehydrogenase and intratissular sex hormone concentrations in cancerous and normal glandular breast tissue in postmenopausal women. Eur J Cancer Clin Oncol 1986; 22:515-525.
31. Recchione C, Venturelli E, Manzari A et al. Testosterone, dihydrotestosterone and oestradiol levels in postmenopausal breast cancer tissues. J Steroid Biochem Mol Biol 1995; 52:541-546.
32. Mady EA, Ramadan EE, Ossman AA. Sex steroid hormones in serum and tissue of benign and malignant breast tumor patients. Disease Markers 2000; 16:151-157.
33. Porias H, Sojo I, Carranco A et al. A simultaneous assay to quantitate plasma and endometrial hormone concentrations. Fertil Steril 1978; 30:66-69.

34. Godwin AK, Perez RP, Johnson SW et al. Growth regulation of ovarian cancer. Hematol Oncol Clin North Am 1992; 6:829-841.
35. Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002; 94:606-616.
36. Manjer J, Johansson R, Berglund G et al. Postmenopausal breast cancer risk in relation to sex steroid hormones, prolactin and SHBG (Sweden). Cancer Causes Control 2003; 14:599-607.
37. Key TJ, Wang DY, Brown JB et al. A prospective study of urinary oestrogen excretion and breast cancer risk. Br J Cancer 1996; 73:1615-1619.
38. Onland-Moret NC, Kaaks R, van Noord PA et al. Urinary endogenous sex hormone levels and the risk of postmenopausal breast cancer. Br J Cancer 2003; 88:1394-1399.
39. Kaaks R, Rinaldi S, Key TJ et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer 2005; 12:1071-1082.
40. Zeleniuch-Jacquotte A, Shore RE, Koenig KL et al. Postmenopausal levels of oestrogen androgen and SHBG and breast cancer: long-term results of a prospective study. Br J Cancer 2004; 90:153-159.
41. Missmer SA, Eliassen AH, Barbieri RL et al. Endogenous estrogen androgen and progesterone concentrations and breast cancer risk among postmenopausal women. J Natl Cancer Inst 2004; 96:1856-1865.
42. Beattie MS, Costantino JP, Cummings SR et al. Endogenous sex hormones, breast cancer risk and tamoxifen response: an ancillary study in the NSABP Breast Cancer Prevention Trial (P1). J Natl Cancer Inst 2006; 98:110-115.
43. Eliassen AH, Missmer SA, Tworoger SS et al. Endogenous steroid hormone concentrations and risk of breast cancer: does the association vary by a woman's predicted breast cancer risk? J Clin Oncol 2006; 24:1823-1830.
44. Tworoger SS, Missmer SA, Barbieri RL et al. Plasma sex hormone concentrations and subsequent risk of breast cancer among women using postmenopausal hormones. J Natl Cancer Inst 2005; 97:595-602.
45. Hankinson SE, Willett WC, Colditz GA et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998; 351:1393-1396.
46. Toniolo P, Bruning PF, Akhmedkhanov A et al. Serum insulin-like growth factor-I and breast cancer. Int J Cancer 2000; 88:828-832.
47. Kaaks R, Lundin E, Rinaldi S et al. Prospective study of IGF-I, IGF-binding proteins and breast cancer risk, in northern and southern Sweden. Cancer Causes Control 2002; 13:307-316.
48. Krajcik RA, Borofsky ND, Massardo S et al. Insulin-like growth factor I (IGF-I), IGF-binding proteins and breast cancer. Cancer Epidemiol Biomarkers Prev 2002; 11:1566-1573.
49. Keinan-Boker L, Bueno De Mesquita HB, Kaaks R et al. Circulating levels of insulin-like growth factor I, its binding proteins -1,-2, -3, C-peptide and risk of postmenopausal breast cancer. Int J Cancer 2003; 106:90-95.
50. Gronbaek H, Flyvbjerg A, Mellemkjaer L et al. Serum insulin-like growth factors, insulin-like growth factor binding proteins and breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2004; 13:1759-1764.
51. Schernhammer ES, Holly JM, Pollak MN et al. Circulating levels of insulin-like growth factors, their binding proteins and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005; 14:699-704.
52. Allen NE, Roddam AW, Allen DS et al. A prospective study of serum insulin-like growth factor-I (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. Br J Cancer 2005; 92:1283-1287.
53. Rollison DE, Newschaffer CJ, Tao Y et al. Premenopausal levels of circulating insulin-like growth factor I and the risk of postmenopausal breast cancer. Int J Cancer 2006; 118:1279-1284.
54. Rinaldi S, Peeters PH, Berrino F et al. IGF-I, IGFBP-3 and breast cancer risk in women: The European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2006; 13:593-605.
55. Baglietto L, English DR, Hopper JL et al. Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2007; 16:763-768.
56. Kabuto M, Akiba S, Stevens RG et al. A prospective study of estradiol and breast cancer in Japanese women. Cancer Epidemiol Biomarkers Prev 2000; 9:575-579.
57. Wang DY, De Stavola BL, Bulbrook RD et al. Relationship of blood prolactin levels and the risk of subsequent breast cancer. Int J Epidemiol 1992; 21:214-221.
58. Hankinson SE, Willett WC, Michaud DS et al. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1999; 91:629-634.
59. Tworoger SS, Eliassen AH, Rosner B et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004; 64:6814-6819.
60. Tworoger SS, Eliassen AH, Sluss P et al. A prospective study of plasma prolactin concentrations and risk of premenopausal and postmenopausal breast cancer. J Clin Oncol 2007; 25:1482-1488.

61. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90:1371-1388.
62. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000; 152:950-964.
63. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004; 23:1111-1130.
64. Freedman AN, Seminara D, Gail MH et al. Cancer risk prediction models: a workshop on development, evaluation and application. J Natl Cancer Inst 2005; 97:715-723.
65. Cummings SR, Duong T, Kenyon E et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA 2002; 287:216-220.
66. Wysowski DK, Comstock GW, Helsing KJ et al. Sex hormone levels in serum in relation to the development of breast cancer. Am J Epidemiol 1987; 125:791-799.
67. Helzlsouer KJ, Alberg AJ, Bush TL et al. A prospective study of endogenous hormones and breast cancer. Cancer Detect Prev 1994; 18:79-85.
68. Rosenberg CR, Pasternack BS, Shore RE et al. Premenopausal estradiol levels and the risk of breast cancer: a new method of controlling for day of the menstrual cycle. Am J Epidemiol 1994; 140:518-525.
69. Thomas HV, Key TJ, Allen DS et al. A prospective study of endogenous serum hormone concentrations and breast cancer risk in premenopausal women on the island of Guernsey. Br J Cancer 1997; 75:1075-1079.
70. Kaaks R, Berrino F, Key T et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2005; 97:755-765.
71. Eliassen AH, Missmer SA, Tworoger SS et al. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. J Natl Cancer Inst 2006; 98:1406-1415.
72. Micheli A, Muti P, Secreto G et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. Int J Cancer 2004; 112:312-318.
73. Thomas HV, Key TJ, Allen DS et al. A prospective study of endogenous serum hormone concentrations and breast cancer risk in postmenopausal women on the island of Guernsey. Br J Cancer 1997; 76:401-405.
74. Rinaldi S, Kaaks R, Zeleniuch-Jacquotte A et al. Insulin-like growth factor-I, IGF binding protein-3 and breast cancer in young women: a comparison of risk estimates using different peptide assays. Cancer Epidemiol Biomarkers Prev 2005; 14:48-52.
75. Schernhammer ES, Holly JM, Hunter DJ et al. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3) and growth hormone and breast cancer risk in The Nurses Health Study II. Endocr Relat Cancer 2006; 13:583-592.
76. Tworoger SS, Sluss P, Hankinson SE. Association between plasma prolactin concentrations and risk of breast cancer among predominately premenopausal women. Cancer Res 2006; 66:2476-2482.
77. Siiteri PK, Schwarz BE, Moriyama I et al. Estrogen binding in the rat and human. Adv Exp Med Biol 1973; 36:97-112.
78. Siiteri PK. Extraglandular oestrogen formation and serum binding of oestradiol: relationship to cancer. J Endocrinol 1981;89 Suppl:119P-129P.
79. Bulun SE, Price TM, Aitken J et al. A link between breast cancer and local estrogen biosynthesis suggested by quantification of breast adipose tissue aromatase cytochrome P450 transcripts using competitive polymerase chain reaction after reverse transcription. J Clin Endocrinol Metab 1993; 77:1622-1628.
80. Ricketts D, Turnbull L, Ryall G et al. Estrogen and progesterone receptors in the normal female breast. Cancer Res 1991; 51:1817-1822.
81. Markopoulos C, Berger U, Wilson P et al. Oestrogen receptor content of normal breast cells and breast carcinomas throughout the menstrual cycle. Br Med J (Clin Res Ed) 1988; 296:1349-1351.
82. Yue W, Santner SJ, Masamura S et al. Determinants of tissue estradiol levels and biologic responsiveness in breast tumors. Breast Cancer Res Treat. 1998;49 Suppl. 1:S1-7; discussion S33-37.
83. Gompel A, Somai S, Chaouat M et al. Hormonal regulation of apoptosis in breast cells and tissues. Steroids 2000; 65:593-598.
84. Sabourin JC, Martin A, Baruch J et al. bcl-2 expression in normal breast tissue during the menstrual cycle. Int J Cancer 1994; 59:1-6.
85. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer 2001; 84:975-981.
86. Lukanova A, Lundin E, Micheli A et al. Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. Int J Cancer 2004; 108:425-432.

87. Lukanova A, Zeleniuch-Jacquotte A, Lundin E et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP-1, -2 and -3 and risk of endometrial cancer. Int J Cancer 2004; 108:262-268.
88. Cust AE, Allen NE, Rinaldi S et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European prospective investigation into cancer and nutrition. Int J Cancer 2007; 120:2656-2664.
89. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A et al. Luteinizing hormone, its beta-subunit variant and epithelial ovarian cancer: the gonadotropin hypothesis revisited. Am J Epidemiol 2001; 154:43-49.
90. Helzlsouer KJ, Alberg AJ, Gordon GB et al. Serum gonadotropins and steroid hormones and the development of ovarian cancer. JAMA 1995; 274:1926-1930.
91. Arslan AA, Zeleniuch-Jacquotte A, Lundin E et al. Serum follicle-stimulating hormone and risk of epithelial ovarian cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003; 12:1531-1535.
92. Lukanova A, Lundin E, Akhmedkhanov A et al. Circulating levels of sex steroid hormones and risk of ovarian cancer. Int J Cancer 2003; 104:636-642.
93. Rinaldi S, Dossus L, Lukanova A et al. Endogenous androgens and risk of epithelial ovarian cancer: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Epidemiol Biomarkers Prev 2007; 16:23-29.
94. Lukanova A, Lundin E, Toniolo P et al. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. Int J Cancer 2002; 101:549-554.
95. Peeters PH, Lukanova A, Allen N et al. Serum IGF-I, its major binding protein (IGFBP-3) and epithelial ovarian cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2007; 14:81-90.
96. Tworoger SS, Lee IM, Buring JE et al. Insulin-like growth factors and ovarian cancer risk: a nested case-control study in three cohorts. Cancer Epidemiol Biomarkers Prev 2007 (In press).
97. Lukanova A, Lundin E, Micheli A et al. Risk of ovarian cancer in relation to prediagnostic levels of C-peptide, insulin-like growth factor binding proteins-1 and -2 (USA, Sweden, Italy). Cancer Causes Control 2003; 14:285-292.