Annals of Oncology 22: 1102–1108, 2011
doi:10.1093/annonc/mdq565
Published online 13 October 2010

Maternal and cord blood hormone levels in the United States and China and the intrauterine origin of breast cancer

P. Lagiou[1,2], E. Samoli[2], W. Okulicz[3], B. Xu[4], A. Lagiou[5], L. Lipworth[6], C. Georgila[2], L. Vatten[7], H. O. Adami[1,8], D. Trichopoulos[1]* & C. C. Hsieh[1,9]

[1]*Department of Epidemiology, Harvard School of Public Health, Boston, USA;* [2]*Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, University of Athens, Athens, Greece;* [3]*Department of Physiology, ILAT Steroid RIA Laboratory, University of Massachusetts Medical School, Worcester, USA;* [4]*Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China;* [5]*Faculty of Health Professions, Athens Technological Educational Institute, Athens, Greece;* [6]*International Epidemiology Institute, Rockville, USA;* [7]*Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway;* [8]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden;* [9]*Division of Biostatistics and Epidemiology, UMass Cancer Center, University of Massachusetts Medical School, Worcester, USA*

Received 22 June 2010; accepted 16 August 2010

Background: Breast cancer is less common in China than in the United States and perinatal characteristics predict breast cancer risk in the offspring. We determined levels of pregnancy hormones in Boston and Shanghai to identify those possibly involved in the intrauterine origin of breast cancer.
Participants and methods: We compared maternal and cord blood levels of estradiol, estriol, testosterone, progesterone, prolactin, insulin-like growth factors (IGF) 1 and 2, insulin-like growth factor-binding protein 3, adiponectin and sex hormone-binding globulin (SHBG) in 241 Caucasian and 295 Chinese women.
Results: In both centers, hormone levels at the 16th were predictive of those at the 27th gestational week, but there was little correlation between maternal and cord blood levels. In cord blood, we found significantly ($P < 0.01$) higher levels of estradiol (44.2%), testosterone (54.5%), IGF-2 (22.7%) and strikingly SHBG (104.6%) in Shanghai women, whereas the opposite was true for IGF-1 (−36.8%).
Conclusions: Taking into account the current understanding of the plausible biological role of the examined endocrine factors, those likely to be involved in the intrauterine origin of breast cancer are SHBG and IGF-2, with higher cord blood levels among Chinese, and IGF-1, with higher cord blood levels among Caucasian women.
Key words: breast cancer, cord blood, hormones, IGF, pregnancy, SHBG

introduction

The hypothesis that perinatal factors affect breast cancer risk was formally articulated in the early 1990s [1]. Since then, the accumulated evidence has linked two important perinatal factors with this risk, namely birth size [2–5] and pregnancy toxemia [3]. The underlying biological mechanisms are not known, but the endocrine environment during the perinatal period is thought to influence the risk of breast cancer in adulthood [6–10]. Our goal was to harvest information on early life endocrine factors which could account for the sharply higher incidence of breast cancer among Caucasian women in United States compared with Chinese women in China. To that end, we have determined levels of hormones with mammotropic potential in the maternal serum as well as the cord blood, in pregnancies of Caucasian women in Boston, USA and Chinese women in Shanghai, China. Although some results from this project have been previously reported [6, 11, 12], this paper presents new data on several additional hormones as well as an integrated picture of maternal and cord blood hormone levels in the two populations with contrasting breast cancer incidence.

*Correspondence to: Prof. D. Trichopoulos, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.
Tel: +1-617-432-4560; Fax: +1-617-566-7805; E-mail: dtrichop@hsph.harvard.edu

materials and methods

subjects

From March 1994 to October 1995, all pregnant women coming for their first routine prenatal visit to the collaborating maternity clinics of the Beth Israel hospital in Boston, USA, and the Shanghai Medical University in China were met by authorized health professionals, who ascertained the woman's eligibility to participate, explained to her the objectives of the study and obtained informed consent [6]. A total of 402 Caucasian women in Boston, USA, and 424 Asian women in Shanghai, China, were identified. The study was approved by the Institutional Review Boards of the Beth Israel Hospital, Shanghai Medical University and Harvard School of Public Health. Eligibility criteria included age <40 years old, a maximum parity of two, absence of a prior diagnosis of diabetes mellitus or thyroid disease, no hormonal medication during the index pregnancy and no known fetal abnormality. The maximum parity of two criterion was imposed by the one-child policy implemented in China and the need for comparability of the two cohorts.

Of the 402 eligible women in Boston, 77 refused to participate in one or more aspects of the study, 9 were subsequently excluded because of a spontaneous or induced abortion in the index pregnancy, 2 were excluded because of twin birth, whereas 10 were lost to follow-up after the initial meeting. Of the remaining 304 women, we excluded 35 women with gestational age below 37 or above 42 weeks, 16 additional women with pregnancy toxemia and another 12 women with missing information. Eventually, 241 Caucasian women were considered in the present analysis. Additional exclusions were necessary due to limited availability of biological samples for some pregnancies.

Of the 424 eligible women in Shanghai, 15 refused to participate in one or more aspects of the study, 2 women were excluded owing to induced abortion in the index pregnancy and another two because of twin birth, whereas 7 women were lost to follow-up leaving a total of 398 women. For 59 of those, no blood collection was accomplished. Of the remaining 339 women, we excluded 44 women who had gestation duration outside the range of 37–42 weeks inclusive. There were no Asian women with preeclampsia. Eventually, 295 Asian women were considered in the present analysis. Additional exclusions were necessary due to limited availability of biological samples for some pregnancies. It is noteworthy that, although exclusions were numerous, they were done for technical or administrative reasons, so their consequence is reduction of statistical power but not introduction of bias. Exclusions that could theoretically affect validity were those generated by losses to follow-up and these were minimal (2.5% for women in Boston and 1.7% for women in Shanghai).

baseline data and laboratory measurements

Baseline sociodemographic and lifestyle information was recorded in interviews at the 16th and the 27th gestational week visit of the women to the clinic. Information about medical conditions was abstracted from the women's medical records. At delivery, additional information concerning the newborn, including duration of gestation and birth size parameters, was recorded. Detailed information concerning the study protocol and implementation has been published [6].

During the visits to the maternity clinics at the 16th and the 27th gestational week, 10 ml of venous blood was drawn from every woman at each visit. At delivery, cord blood was also collected. All blood samples were collected into sterile tubes without preservatives and stored at −4°C for up to 24 h until centrifugation. Samples were then centrifuged, and the serum was aliquoted and stored for hormonal assays at −80°C. In Shanghai, blood samples were transported in a cooler to a laboratory near Shanghai Medical University. Serum aliquots were stored at −20°C for 5–7 days in the laboratory before being transported to Shanghai Medical University and stored at −80°C. All samples were shipped by air on dry ice to Boston where they were stored at −80°C together with the samples from Boston.

Levels of estradiol (E2), estriol (E3), progesterone, sex hormone-binding globulin (SHBG), testosterone, adiponectin, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP3) were measured in both the maternal sera and the cord blood. Prolactin was measured only in maternal sera and insulin-like growth factor 2 (IGF-2) only in cord blood.

Measurements were conducted in two time periods. Maternal levels of E2, E3, SHBG, progesterone and prolactin were measured in the late 1990s at the Department of Clinical Chemistry of the Uppsala University Hospital in Sweden [6], whereas maternal levels of testosterone, adiponectin, IGF-1 and IGFBP3 as well as all hormone levels in cord blood were measured in 2006 at the ILAT Steroid RIA Laboratory of the University of Massachusetts Medical School. Measurements per each hormone were conducted simultaneously for samples from Boston and Shanghai.

Maternal estradiol-17b was measured with a time-resolved competitive solid-phase fluoroimmunoassay (AutoDELFIA Estradiol Kit; Wallac Oy, Turku, Finland), with laboratory imprecision 4.6% ± 0.8%. Maternal unconjugated E3 was measured with a similar time-resolved competitive solid-phase fluoroimmunoassay method (AutoDELFIA Unconjugated Oestriol Kit; Wallac Oy), with laboratory imprecision 8.0% ± 1.8%. Maternal SHBG was measured with a time-resolved noncompetitive solid-phase sandwich fluoroimmunoassay (AutoDELFIA SHBG Kit; Wallac Oy), with laboratory imprecision 4.8% ± 1.3%. Maternal progesterone was measured with a time-resolved competitive solid-phase fluoroimmunoassay (AutoDELFIA Progesterone Kit; Wallac Oy), with laboratory imprecision 1.7% ± 0.9%. Maternal prolactin was measured with a time-resolved noncompetitive solid-phase sandwich fluoroimmunoassay (AutoDELFIA Prolactin Kit; Wallac Oy), with laboratory imprecision 3.0% ± 0.3%. Maternal and cord blood testosterone was measured by radioimmunoassay kits from Diagnostic Products Corporation (DPC, Los Angeles, CA), with inter- and intra-assay coefficients of variation (CVs) of 8.9% and 5.6%, respectively. Maternal and cord blood adiponectin was measured by radioimmunoassay (Linco Research, St. Charles, MO) with inter- and intra-assay CV of 7.2% and 4.7%, respectively. Maternal and cord blood IGF-1 and IGFBP3 as well as cord blood IGF-2 were measured by coated-tube immunoradiometric assay kits (Diagnostic System Laboratories, Inc., Webster, TX). The laboratory-estimated inter- and intra-assay CVs were, respectively, 9.0% and 3.3% for IGF-1; 8.0% and 4.8% for IGFBP3 and 5.9% and 3.4% for IGF-2. There was no detectable cross-reactivity of the IGF-1 assay with IGF-2 according to the manufacturer's specificity assessment. Cord blood E2 was measured by radioimmunoassay using kits from DPC (Los Angeles, CA). The inter-assay CV was 6.8% and the intra-assay CV was 3.4%. Cord blood unconjugated E3, progesterone and SHBG were measured using chemiluminescent immunoassay methodologies from DPC (Los Angeles, CA). The inter-assay CVs were 9.2%, 7.9% and 4.8% and the intra-assay CVs were 6.6%, 6.3% and 2.0%, respectively.

statistical analyses

The statistical analyses were conducted using the SPSS statistical package (Statistical Package for Social Sciences v. 16.0, Chicago, IL). At first, we distributed Caucasian and Chinese women by maternal–offspring characteristics and we estimated the mean values, standard deviations, as well as percentiles of the studied endocrine compounds measured in maternal sera at the 16th and 27th gestational weeks and in the cord blood. We also calculated three Spearman correlation coefficients for each endocrine compound, between the 16th week maternal sera measurement, the 27th week maternal sera measurement and the cord blood measurement. Finally, we used multiple regression to compare log-transformed cord blood and maternal serum hormone levels measured at the 16th and 27th gestational week between Boston (referent) and Shanghai, controlling for maternal age, maternal height, body mass index (BMI) before pregnancy and weight gain, as well as parity, duration of gestation, exact gestational week for maternal sampling and gender of offspring.

results

The characteristics of women and their singleton offspring in Boston, MA, USA, and Shanghai, China are shown in Table 1. In comparison to women in Boston, women in Shanghai were younger, of shorter stature, with lower prepregnancy BMI and generally primiparous (on account of the one-child policy in China), whereas their offspring were more frequently boys and of lower birth weight. These factors were accounted for in comparisons of hormones between centers.

Tables 2 and 3 present central values and measures of dispersion for maternal hormones at around the 16th and the 27th gestational week, respectively, in Boston, USA, and Shanghai, China. In both centers, values of estradiol, estriol, prolactin, progesterone and IGF-1 tend to considerably increase with the progression of the pregnancy, whereas the rate of increase is lower for SHBG and IGFBP3 and even lower for testosterone. Adiponectin does not appear to increase between the 16th and the 27th gestational week and may in fact be declining.

Table 4 shows central values and measures of dispersion for hormones in the umbilical cord blood in Boston, USA, and Shanghai, China. Comparisons of maternal hormone levels with hormone levels at the umbilical cord are meaningful only with respect to hormones measured at the same laboratory with the same method in maternal and cord blood (i.e. testosterone, adiponectin, IGF-1 and IGFBP3). In both Boston and Shanghai, in comparison to maternal blood levels, cord blood levels of testosterone and adiponectin were considerably higher, whereas those of IGF-1 and IGFBP3 were considerably lower. Notwithstanding the different methods used in maternal and cord blood, levels of SHBG in both centers appeared to be substantially lower in the umbilical cord compared with maternal blood.

Spearman correlation coefficients between the levels of the hormones measured in maternal blood at the 16th and 27th gestational week and the levels of these hormones in the cord blood in the two settings are shown in Table 5. Since correlation coefficients are dimensionless, it is acceptable to calculate these coefficients, even when the measurements are done at different laboratories with different methods, provided the rankings within laboratories are not very different. It is evident that the measured hormones track during pregnancy, so that levels at the 16th gestational week are predictive of levels at the 27th gestational week and vice versa. The correlations

Table 1. Characteristics of women[a] and their singleton offspring in Boston, MA, USA, and Shanghai, China

	Boston (n = 241)	Shanghai (n = 295)
Age (years)	31.0 (3.1)	25.3 (3.7)
Parity		
1	143 (59.3)	290 (98.3)
2	98 (40.7)	5 (1.7)
Duration of gestation (weeks)	40.0 (1.2)	40.0 (1.1)
Gestational week at first measurement	16.7 (1.1)	17.0 (2.0)
Gestational week at second measurement	27.1 (1.7)	26.9 (1.5)
Maternal weight gain until the second measurement (kg)	11.5 (4.7)	8.6 (4.4)
Maternal height (cm)	164.3 (6.6)	160.1 (4.8)
Prepregnancy BMI (kg/m^2)	22.0 (3.0)	20.0 (2.2)
Gender of offspring		
Male	128 (53.1)	175 (59.3)
Female	113 (46.9)	120 (40.7)
Birth weight (g)	3568.8 (478.7)	3421.6 (433.0)

For continuous variables, mean (SD); for categorical variables, n (%).
[a]Women with pregnancy duration between 37 and 42 weeks and no pregnancy toxemia.
BMI, body mass index; SD, standard deviation.

Table 2. Maternal serum levels of the indicated hormones at around the 16th gestational week in Boston, USA (n = 232[a]), and Shanghai, China (n = 279[a])

	Mean	SD	Percentiles				
			5%	25%	50%	75%	95%
Boston							
Estradiol (ng/ml)	3.8	1.8	1.9	2.6	3.5	4.6	7.1
Estriol (ng/ml)	1.1	0.5	0.5	0.8	1.0	1.3	2.1
SHBG (nmol/l)	362.9	89.6	219.0	298.1	360.6	423.0	524.9
Prolactin (μg/l)	43.9	25.1	15.7	27.4	38.4	54.3	86.8
Progesterone (ng/ml)	41.7	9.9	27.3	34.2	41.1	47.7	59.5
Testosterone (ng/ml)	0.6	0.4	0.2	0.4	0.5	0.8	1.2
Adiponectin (μg/ml)	17.6	8.1	8.0	12.3	15.7	21.4	34.4
IGF-1 (ng/ml)	192.7	83.2	70.8	126.0	194.0	247.0	331.4
IGFBP3 (ng/ml)	6481.1	2508.5	3633.2	4157.0	6208.0	8691.0	10415.2
Shanghai							
Estradiol (ng/ml)	5.5	2.5	2.4	3.7	4.9	6.8	11.0
Estriol (ng/ml)	1.8	1.0	0.6	1.1	1.5	2.1	3.7
SHBG (nmol/l)	427.0	91.7	272.6	371.3	422.6	487.2	586.9
Prolactin (μg/l)	62.5	33.1	22.1	40.3	57.9	78.4	125.6
Progesterone (ng/ml)	44.6	10.8	27.6	37.1	43.7	51.2	64.7
Testosterone (ng/ml)	0.6	0.3	0.2	0.4	0.6	0.7	1.3
Adiponectin (μg/ml)	15.9	7.1	7.4	11.0	14.7	18.7	29.5
IGF-1 (ng/ml)	139.3	72.0	23.0	95.0	131.0	177.0	259.0
IGFBP3 (ng/ml)	6833.3	2094.4	3783.0	4885.0	6974.0	8343.0	10233.0

[a]For certain hormones, slightly fewer number of samples (<10%) were available for analysis.
IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor-binding protein 3; SD, standard deviation; SHBG, sex hormone-binding globulin.

are strong with respect to SHBG, estradiol and testosterone; modest with respect to progesterone and adiponectin and weaker with respect to estriol, IGF-1 and IGFBP3. In contrast, there was little or no correlation between hormone levels in maternal blood and levels of these hormones in cord blood.

In Table 6, the levels of hormones measured in maternal blood at the 16th and 27th gestational week and in the cord blood are compared between Boston (reference) and Shanghai. Differences are evident between centers for most of the hormones in maternal blood or in the cord blood. In maternal

Table 3. Maternal serum levels of the indicated hormones at around the 27th gestational week in Boston, USA ($n = 225^{a}$), and Shanghai, China ($n = 281^{a}$)

	Mean	SD	Percentiles				
			5%	25%	50%	75%	95%
Boston							
Estradiol (ng/ml)	10.8	4.8	5.2	7.6	10.0	12.9	18.9
Estriol (ng/ml)	4.1	1.3	2.2	3.1	3.9	4.7	6.7
SHBG (nmol/l)	428.	111.8	258.2	348.9	420.2	500.1	646.4
Prolactin (µg/l)	92.4	36.7	42.1	65.8	89.9	111.7	147.5
Progesterone (ng/ml)	82.0	20.7	52.4	66.4	78.8	96.2	117.1
Testosterone (ng/ml)	0.7	0.3	0.3	0.4	0.6	0.8	1.2
Adiponectin (µg/ml)	15.8	7.3	7.4	10.8	14.0	19.8	28.3
IGF-1 (ng/ml)	238.4	110.1	87.3	160.0	231.5	302.8	442.2
IGFBP3 (ng/ml)	6818.2	2647.9	3678.7	4301.5	6878.0	8800.0	11275.8
Shanghai							
Estradiol (ng/ml)	13.1	5.0	7.6	9.9	12.2	15.3	22.3
Estriol (ng/ml)	6.4	2.8	3.4	4.7	5.9	7.3	10.3
SHBG (nmol/l)	475.4	123.7	297.5	389.4	454.3	543.8	714.7
Prolactin (µg/l)	115.9	38.0	61.7	90.0	112.1	138.0	185.8
Progesterone (ng/ml)	78.3	25.9	49.5	62.3	74.1	86.0	129.7
Testosterone (ng/ml)	0.8	0.4	0.4	0.5	0.7	0.9	1.4
Adiponectin (µg/ml)	12.0	5.1	5.9	8.5	10.9	14.2	22.1
IGF-1 (ng/ml)	206.1	85.9	87.2	140.0	194.0	260.0	371.6
IGFBP3 (ng/ml)	6385.9	2465.1	3425.6	4075.0	6182.0	8570.0	10229.3

[a]For certain hormones, slightly fewer number of samples (<12%) were available for analysis.

IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor-binding protein 3; SD, standard deviation; SHBG, sex hormone-binding globulin.

Table 4. Cord serum levels of the indicated hormones in Boston, USA (n = 92), and Shanghai, China (n = 110)

	Mean	SD	Percentiles				
			5%	25%	50%	75%	95%
Boston							
Estradiol (ng/ml)	35.4	18.7	10.9	22.4	30.0	44.3	82.1
Estriol (ng/ml)	382.9	160.2	173.6	273.5	360.5	462.0	738.1
SHBG (nmol/l)	42.0	42.1	19.3	26.0	31.6	38.6	126.1
Progesterone (ng/ml)	1078.5	771.7	384.6	574.8	878.0	1325.0	2565.1
Testosterone (ng/ml)	2.9	1.5	1.2	2.0	2.6	3.3	6.5
Adiponectin (µg/ml)	52.9	23.0	14.4	36.5	52.5	65.6	95.2
IGF-1 (ng/ml)	98.4	35.7	51.0	70.3	94.5	121.8	172.8
IGF-2 (ng/ml)	492.5	100.3	293.5	427.5	499.0	550.8	640.9
IGFBP3 (ng/ml)	2419.1	1696.8	437.7	1248.0	1992.0	3217.3	5948.8
Shanghai							
Estradiol (E2) (ng/ml)	79.7	75.5	21.7	44.2	61.3	87.0	251.3
Estriol (ng/ml)	406.9	135.7	168.0	318.0	395.0	490.0	628.0
SHBG (nmol/l)	116.1	117.1	24.7	33.1	51.7	175.3	374.9
Progesterone (ng/ml)	1058.3	685.4	176.4	652.7	875.5	1365.0	2818.0
Testosterone (ng/ml)	6.2	7.2	2.0	3.2	4.5	6.7	13.9
Adiponectin (µg/ml)	37.5	20.7	9.3	18.6	34.9	54.5	71.9
IGF-1 (ng/ml)	79.0	48.9	9.1	50.3	73.0	102.0	182.3
IGF-2 (ng/ml)	587.8	140.1	364.8	518.8	587.0	659.5	841.8
IGFBP3 (ng/ml)	3265.3	2186.4	1026.5	1809.8	2532.0	4112.8	7541.8

SHBG, sex hormone-binding globulin; IGF, insulin-like growth factor; IGFBP3, insulin-like growth factor-binding protein 3.

Table 5. Spearman correlation coefficients between maternal serum levels of the indicated hormones at the 16th and 27th gestational week and levels of these hormones in the cord blood in Boston, USA, and Shanghai, China

	Boston	Shanghai
Maternal serum measurement at weeks 16 and 27		
Estradiol	0.72**	0.61**
Estriol	0.37**	0.20*
SHBG	0.85**	0.67**
Progesterone	0.45**	0.39**
Testosterone	0.83**	0.62**
Adiponectin	0.46**	0.44**
IGF-1	0.25**	0.32**
IGFBP3	0.16*	0.32**
Maternal serum measurement at weeks 16 with cord blood measurement		
Estradiol	0.09	0.15
Estriol	−0.04	−0.06
SHBG	0.09	−0.09
Progesterone	−0.001	0.03
Testosterone	−0.001	0.05
Adiponectin	0.18	−0.12
IGF-1	0.02	−0.02
IGFBP3	0.19	0.01
Maternal serum measurement at weeks 27 with cord blood measurement		
Estradiol	0.17	0.12
Estriol	0.22*	0.00
SHBG	0.03	−0.12
Progesterone	0.09	0.06
Testosterone	0.16	0.17
Adiponectin	0.06	−0.20*
IGF-1	0.18	0.29*
IGFBP3	−0.02	−0.04

*$P < 0.05$; **$P < 0.001$.

SHBG, sex hormone-binding globulin; IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor-binding protein 3.

sera, levels of estriol and prolactin (during both the 16th and 27th gestational week) as well as estradiol and IGFBP3 (only during the 16th gestational week), and testosterone (only during the 27th gestational week) were significantly higher in Shanghai than in Boston, whereas the opposite was true for levels of IGF-1 and adiponectin (during both the 16th and 27th gestational week) as well as progesterone (only during the 27th gestational week); no significant differences were evident between the two centers with respect to SHBG at either gestational week. In the cord blood, levels of estradiol, testosterone, IGF-2, IGFBP3 and most strikingly SHBG were significantly higher in Shanghai, whereas the opposite was true for levels of adiponectin and IGF-1.

discussion

We have studied singleton pregnancies and offspring of Caucasian women in Boston, USA, and Chinese women in Shanghai, China, and we determined a range of maternal blood hormones at the 16th and 27th gestational week, as well as in umbilical cord blood. We have established levels and the range of variation of the measured hormones in Caucasian and Chinese women and we have examined the possible concordance of the relative levels of these hormones with the sharp ecological contrast in the two populations with respect to breast cancer incidence. Results concerning maternal levels of estrogens, SHBG, prolactin and progesterone have been previously published [6], as have results concerning umbilical cord blood levels of IGF-1, IGF-2 and IGFBP3 [12]. In contrast, hormone determinations conducted in the ILAT Steroid RIA Laboratory of the University of Massachusetts Medical School for maternal testosterone, adiponectin, IGF-1 and IGFBP3 as well as cord blood estradiol, estriol, SHBG, progesterone, testosterone and adiponectin have not been previously reported. Certain cord blood hormones were also measured in a different laboratory in smaller subsamples of the

Table 6. Comparison (%)[a] of the indicated hormones in maternal blood at the 16th and 27th gestational week and in the cord blood between Boston, USA (reference), and Shanghai, China

	16th gestational week[b]		27th gestational week[b]		Cord blood[c]	
	Shanghai versus Boston	P	Shanghai versus Boston	P	Shanghai versus Boston	P
Estradiol (ng/ml)	23.0 (10.9, 36.5)	<0.001	7.2 (−2.1, 17.3)	0.127	44.2 (12.5, 84.8)	0.004
Estriol (ng/ml)	34.9 (22.2, 49.0)	<0.001	42.9 (31.7, 55.0)	<0.001	2.6 (−13.2, 21.2)	0.775
SHBG (nmol/l)	4.2 (−1.7, 10.5)	0.170	−0.5 (−6.6, 6.0)	0.888	104.6 (47.2, 184.5)	<0.001
Prolactin (μg/l)	30.3 (14.9, 47.9)	<0.001	18.3 (8.1, 29.5)	<0.001	–	
Progesterone (ng/ml)	−3.2 (−8.7, 2.7)	0.274	−10.7 (−16.1, −4.8)	0.001	−20.4 (−40.1, 5.8)	0.120
Testosterone (ng/ml)	0.9 (−10.7, 14.0)	0.895	13.8 (1.3, 27.4)	0.023	54.5 (22.2, 95.4)	<0.001
Adiponectin (μg/ml)	−11.5 (−20.2, −1.8)	0.022	−23.8 (−31.3, −15.5)	<0.001	−26.9 (−43.0, −6.3)	0.015
IGF-1 (ng/ml)	−36.9 (−45.4, −27.10)	<0.001	−14.9 (−24.7, −3.9)	0.011	−36.8 (−52.2, −16.3)	0.002
IGF-2 (ng/ml)	–		–		22.7 (9.2, 38.0)	0.001
IGFBP3 (ng/ml)	12.2 (2.52, 22.80)	0.013	0.5 (−9.0, 11.0)	0.937	33.7 (0.1, 78.4)	0.049

[a]Hormone levels were log transformed; the coefficient expresses % difference between centers.

[b]Controlling for maternal age, BMI, height and weight gain, parity, duration of gestation, exact gestational week and gender of offspring.

[c]Controlling as in footnote b except for exact gestational week.

BMI, body mass index; IGF, insulin-like growth factor; IGFBP3, insulin-like growth factor-binding protein 3; NA, not applicable; SD, standard deviation; SHBG, sex hormone-binding globulin.

studied pregnancies [11]; no significant differences were noted with respect to cord blood levels of estradiol, estriol and IGF-1, whereas, in line with the findings of the present study, cord blood levels of testosterone and IGFBP3 were significantly higher among Chinese compared with Caucasian.

In addition to providing reliable data about the normal variations of the examined endocrine compounds in the two populations, this study allows examination of the correlations between the indicated hormones in the maternal blood at the 16th and 27th gestational week and in the cord blood in the two settings (Table 5). Levels of the hormones at the 16th gestational week were predictive of levels at the 27th gestational week and vice versa, whereas there was little or no correlation between hormone levels in maternal blood and levels of these hormones in cord blood.

We have attempted to interpret our findings in light of the considerably higher incidence of breast cancer in Caucasian compared with Chinese women, taking into account what is currently known about the role of these hormones in breast cancer etiology [13]. We have considered differences in cord blood levels as more relevant to the fetal endocrine environment and the possible long-term breast cancer risk of the offspring.

In adult life, estrogens and testosterone have been consistently positively associated with breast cancer risk [13]. Both maternal and cord blood levels of estradiol, estriol and testosterone, however, were higher in Shanghai than in Boston by anywhere between 0.9% and 54.5% (Table 6). Thus, levels of these pregnancy hormones by themselves are unlikely to be critical actors in the intrauterine origin of breast cancer since, if anything, they are higher in the population with substantially lower breast cancer incidence. In contrast, levels of SHBG were sharply higher in the cord blood of women in Shanghai (by 104.64%), raising the possibility that these high levels in Chinese women may reduce the bioavailability of active endogenous estrogens and testosterone in the fetus. In adult life, SHBG in relation to breast cancer has been studied mainly as a modulator of the effects of estradiol and testosterone [14], but there is also evidence that high levels of this compound may be more directly associated with a reduction in breast cancer risk [15].

With respect to progesterone in adult life, results on its association with breast cancer risk have been inconsistent [13], with some studies suggesting an inverse association [16] and others indicating no association [17]. For prolactin, the evidence points to a positive association of adult life levels with breast cancer risk [18], whereas for adult life adiponectin, the reported results indicate an inverse association with this risk [19, 20]. In our study, maternal and cord blood progesterone and adiponectin levels were, if anything, lower, whereas maternal prolactin levels were higher, among Chinese compared with Caucasian women, sharply reducing the likelihood that any of these three hormones plays a major role in the intrauterine origin of breast cancer.

Adult life IGF-1 has been positively associated with breast cancer risk [21] and there is limited evidence that adult life IGF-2 may be inversely associated with this risk [22]. Because IGF-1 is substantially and significantly higher in maternal sera, and particularly in cord blood, among Caucasian women in the United States, whereas the opposite is true with respect to cord blood levels of IGF-2, it appears that these two components of the IGF system have distinct roles and that the balance of IGF-1 and IGF-2 in cord blood may be a key early life determinant of adult life breast cancer risk.

Strengths of our study are its longitudinal design, considerable sample size, measurement of a wide range of hormones and the implementation of an identical protocol in two population groups with sharply different breast cancer incidence rates, allowing meaningful ecological contrasts. A weakness of the study is that hormone determinations were done in two laboratories, but all comparisons between centers were for measurements undertaken at the same laboratory.

In conclusion, our study provides central values and measures of variation of a range of hormones during pregnancy in maternal and cord blood in Caucasian women in Boston and Chinese women in Shanghai. Taking into account the lower incidence of breast cancer among Chinese compared with Caucasian women and our current understanding of the role of the examined hormones in breast cancer risk, the endocrine factors likely to be involved in the intrauterine origin of breast cancer in the offspring are SHBG and IGF-2, with higher cord blood levels among Chinese, and IGF-1, with higher cord blood levels among Caucasian women.

funding

W81XWH-05-1-0314 Innovator Award, US; Department of Defense Breast Cancer Research Program, Office of the Congressionally Directed Medical Research Programs.

disclosure

The authors declare no conflict of interest.

references

1. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990; 335: 939–940.
2. Michels KB, Xue F. Role of birthweight in the etiology of breast cancer. Int J Cancer 2006; 119: 2007–2025.
3. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. Lancet Oncol 2007; 8: 1088–1100.
4. dos Santos Silva I, De Stavola B, McCormack V; Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS Med 2008; 5: e193.
5. Park SK, Kang D, McGlynn KA et al. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. Breast Cancer Res 2008; 10(1): R8.
6. Lipworth L, Hsieh C-C, Wide L et al. Maternal pregnancy hormone levels in an area with a high incidence (Boston, USA) and in an area with a low incidence (Shanghai, China) of breast cancer. Br J Cancer 1999; 79: 7–12.
7. Wuu J, Hellerstein S, Lipworth L et al. Correlates of pregnancy oestrogen, progesterone and sex hormone-binding globulin in the USA and China. Eur J Cancer Prev 2002; 11: 283–293.

8. Schernhammer ES. In-utero exposures and breast cancer risk: joint effect of estrogens and insulin-like growth factor? Cancer Causes Control 2002; 13: 505–508.
9. Troisi R, Potischman N, Johnson CN et al. Estrogen and androgen concentrations are not lower in the umbilical cord serum of pre-eclamptic pregnancies. Cancer Epidemiol Biomarkers Prev 2003; 12: 1268–1270.
10. Xu B, Lipworth L, Wide L et al. Maternal and gestational correlates of pregnancy prolactin and growth hormone in USA and China. Eur J Cancer Prev 2003; 12: 35–42.
11. Troisi R, Lagiou P, Trichopoulos D et al. Cord serum estrogens, androgens, insulin-like growth factor-I, and insulin-like growth factor binding protein-3 in Chinese and U.S. Caucasian neonates. Cancer Epidemiol Biomarkers Prev 2008; 17: 224–231.
12. Lagiou P, Hsieh CC, Lipworth L et al. Insulin-like growth factor levels in cord blood, birth weight and breast cancer risk. Br J Cancer 2009; 100: 1794–1798.
13. Hankinson S, Tamimi R, Hunter D. Breast cancer. In Adami HO, Hunter D, Trichopoulos D (eds), Textbook of Cancer Epidemiology, 2nd edition. New York: Oxford University Press 2008; 403–445.
14. Fortunati N, Catalano MG, Boccuzzi G, Frairia R. Sex Hormone-Binding Globulin (SHBG), estradiol and breast cancer. Mol Cell Endocrinol 2010; 316: 86–92.
15. Lipworth L, Adami HO, Trichopoulos D et al. Serum steroid hormone levels, sex hormone-binding globulin, and body mass index in the etiology of postmenopausal breast cancer. Epidemiology 1996; 7: 96–100.
16. 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.
17. 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.
18. Tworoger SS, Eliassen AH, Rosner B et al. Plasma prolactin concentrations and risk of postmenopausal breast cancer. Cancer Res 2004; 64: 6814–6819.
19. Miyoshi Y, Funahashi T, Kihara S et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003; 9: 5699–5704.
20. Mantzoros C, Petridou E, Dessypris N et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab 2004; 89: 1102–1107.
21. The Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010; 11(6): 530–542.
22. Walker K, Fletcher O, Johnson N et al. Premenopausal mammographic density in relation to cyclic variations in endogenous sex hormone levels, prolactin, and insulin-like growth factors. Cancer Res 2009; 69: 6490–6499.