

SPECIAL THEME: CANCER

Birthweight differences between USA and China and their relevance to breast cancer aetiology

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Background There has been renewed interest about determinants of birth size following the propagation of hypotheses that birth size parameters may have long-term consequences on the occurrence of common diseases in adulthood, including breast cancer.**Methods** In the context of a cohort study, 296 Caucasian pregnant women in Boston, USA and 329 Chinese pregnant women in Shanghai, China were followed to term. Birth size characteristics of the baby and maternal anthropometry were measured using standardized protocols. Analyses were conducted through multiple regression procedures.**Results** No significant difference was found between US and Chinese newborns with respect to gestational age. Among US women, pregravid oral contraceptive use was strongly associated with higher birthweight. In both US and Chinese women, birthweight was positively associated with height, pre-pregnancy body mass index, and weight gain during pregnancy. More importantly, the difference in these three maternal variables between the two samples fully explains the birthweight difference between the two populations.**Conclusions** We postulate that babies in China may have lower birthweight because their mothers' anthropometry imposes constraints on the growth of the fetus. When Chinese women migrate to the US, they tend to grow taller and heavier so that their babies can reach, on the average, a higher birthweight. The recurrence of this process in successive generations could explain why eventually Chinese Americans tend to have comparable birth and adult anthropometric characteristics, as well as comparable breast cancer rates, to those of Caucasian Americans.**Keywords** Birthweight, China, US, breast cancer

There is a vast literature concerning determinants of gestational duration and intrauterine growth.^{1–5} Most of the literature

focuses on determinants and means of prevention of preterm birth and/or intrauterine growth retardation, which can affect survival as well as development in childhood.⁶ During the last 20 years, however, there has also been interest in the possibility that perinatal events and conditions, intimately linked to birth size parameters, may have long-term consequences on the occurrence of common diseases in adulthood, including cardiovascular diseases and some forms of cancer, particularly breast cancer.^{7–9}

We have compared determinants of birthweight using an identical protocol in two populations, one Caucasian in Boston, USA and the other Chinese in Shanghai, China. Our objective was to gain insight into the causes of birthweight difference between these populations and the way this difference may be related to the contrasting incidence of breast cancer in the two populations.

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Materials and Methods

Between March 1994 and October 1995, a total of 402 Caucasian and 424 Asian eligible women were identified respectively at the Beth Israel hospital in Boston, USA and the Shanghai Medical University in Shanghai, China. Authorized health professionals met all pregnant women coming for their first routine prenatal visit to the collaborating maternity clinic, ascertained whether the woman was eligible to participate, explained to her the objectives of the study and obtained informed consent. The study was approved by the Institutional Review boards of the Beth Israel Hospital, Shanghai Medical University, and Harvard School of Public Health. All women had to be less than 40 years old and have a parity of no more than two. Women were not eligible if they had taken any hormonal medication during the index pregnancy, if they had a prior diagnosis of diabetes mellitus or thyroid disease, or if the fetus had a known major anomaly. Of the 402 eligible women in Boston, 85 refused to participate in one or more aspects of the study or had crucial missing values, 9 were subsequently excluded because of a spontaneous or induced abortion in the index pregnancy, 2 were excluded because of twin birth, whereas only 10 were lost to follow-up after the initial meeting. Of the 424 eligible women in Shanghai, 78 refused to participate in one or more aspects of the study or had crucial missing values, 2 were subsequently excluded due to induced abortion in the index pregnancy, 2 were excluded because of twin birth, 6 were excluded because data on gestational duration were unreliable, whereas only 7 were lost to follow-up. Thus, 296 Caucasian and 329 Chinese pregnant women who delivered live single births were eventually included in the analysis. With respect to age and parity, women who refused to participate were not different from those who participated.

Baseline demographic information was abstracted from the medical records of consenting participants at the 16th week visit. In both Boston and Shanghai gestational age was defined as the time since the first day of the last menstrual period. At the 27th week visit, an authorized health professional conducted a confidential interview with the study participant and abstracted relevant routine data from her records. Maternal characteristics included the woman's age (years), weight before pregnancy (kg), height (cm), body mass index (BMI) (kg/m^2), education (up to high school or more than high school), and previous live birth (yes, no). Characteristics related to the pregnancy were also recorded. These included the weight gained by the time of the two visits (kg), history of smoking, coffee, tea and alcohol consumption, and administration of antibiotics during pregnancy. At delivery, the placenta was weighed (g) before discarding; additional information concerning the delivery and the newborn was ascertained from medical records and paediatric charts. This included total gestation duration (weeks), birthweight (g), birth length (cm), head circumference (cm), and gender. Information concerning questionnaire administration and medical record reviewing has also been given in an earlier publication.¹⁰ Smoking during pregnancy was coded as current smoker during pregnancy versus not current smoker during pregnancy. Caffeine intake was computed summing caffeine contents from daily intake of cups of coffee and tea together. Pre-eclampsia was based on physician's diagnosis of this condition during pregnancy and urogenital infection was determined from the existence of a cervical or bladder infection.

The statistical analysis initially relied on simple cross-tabulations. Subsequently, birthweight was evaluated as a continuous variable through multiple linear regression. Analyses were undertaken first within study centre, that is, separately for Caucasian and Asian women. Direct comparison between the two study sites was performed with adjustment for different covariates. The analyses were conducted using SAS Software version 8.0.

Results

Table 1 shows mean, median, and standard deviation values of weight, height, head circumference, and gestational age at delivery of newborns in Boston, USA and Shanghai, China. Newborn babies are clearly heavier and slightly longer in the US than in China. In contrast, there is no difference between Caucasian US newborns and Chinese newborns with respect to head circumference or gestational duration. It is of interest that the variability of birthweight is higher among US newborns than among Chinese newborns (F ratio = 1.39, $P \sim 0.002$).

Compared with the US pregnant women, Chinese pregnant women are younger and shorter, with lower BMI and less weight gain during pregnancy (Table 2). Almost all Chinese women are primiparous, few of them have used oral contraceptives, they rarely smoke, and their caffeine intake during pregnancy (including caffeine from tea) is minimal. Both pre-eclampsia and urogenital infections are uncommon among Chinese women, although under-diagnosis cannot be excluded. The male to female ratio is higher among mature Chinese newborn than mature US newborn.

Table 3 differs from Table 2 in that it concerns only babies born between 37 and 42 completed weeks of gestation and examines mean birthweight in the specified categories of the maternal characteristics among US women and, separately, Chinese women. The data in Table 3 are univariate and, thus, inherently confounded. Nevertheless, they provide valuable descriptive information that can be used for comparative purposes, because data are frequently presented in this straightforward way in the literature.

The information presented in Table 4 is aetiologically interpretable because results have been mutually adjusted through multiple regression. Because the distribution of

Table 1 Mean, median and standard deviation values of weight, height, head circumference, and gestational age of 296 newborns in Boston, USA and 329 newborns in Shanghai, China

	Mean (SD)	Median
Birthweight (g)		
US newborns	3489 (543)	3511
Chinese newborns	3384 (465)	3400
Birth length (cm)		
US newborns	50.2 (2.7)	50.9
Chinese newborns	49.8 (2.7)	50.0
Head circumference (cm)^a		
US newborns	34.3 (1.9)	34.5
Chinese newborns	34.5 (2.0)	34.0
Gestational age (wk)		
US newborns	39.8 (1.9)	39.9
Chinese newborns	39.8 (1.8)	39.9

^a There were 8 missing values among US newborns and 14 missing values among Chinese newborns.

Table 2 Maternal characteristics of US and Chinese study participants^a

Maternal characteristics	US women	Chinese women
	(N = 296) N (%)	(N = 329) N (%)
Age (years)		
18–24	6 (2)	167 (51)
25–29	86 (30)	118 (36)
30–34	174 (60)	34 (10)
≥35	24 (8)	10 (3)
Maternal education^b		
Level 1	52 (18)	116 (49)
Level 2	118 (41)	93 (39)
Level 3	120 (41)	27 (11)
Parity		
1	187 (63)	323 (98)
2	109 (37)	6 (2)
Height (cm)		
–159	63 (22)	142 (43)
160–164	70 (24)	126 (38)
165–169	85 (29)	52 (16)
170+	72 (25)	9 (3)
Pre-pregnancy BMI^c (kg/m²)		
–18	34 (12)	119 (36)
19–21	134 (46)	157 (48)
22–24	75 (26)	42 (13)
25+	45 (16)	9 (3)
Weight gain (kg)		
–7	56 (21)	142 (47)
8–11	88 (33)	81 (27)
12–14	68 (26)	47 (16)
15+	54 (20)	29 (10)
Previous oral contraceptive use		
Yes	229 (77)	3 (1)
No	67 (23)	320 (99)
Smoking in pregnancy		
Yes	16 (6)	0 (0)
No	274 (94)	326 (100)
Caffeine intake in pregnancy (mg/day)		
0	11 (4)	315 (96)
1–149	253 (95)	14 (4)
150+	2 (1)	0 (0)
Pre-eclampsia		
Yes	22 (7)	0 (0)
No	274 (93)	329 (100)
Urogenital infection in pregnancy		
Yes	11 (4)	1 (0)
No	278 (96)	327 (100)
Gender of offspring		
Male	153 (52)	188 (57)
Female	143 (48)	141 (43)

^a The numbers do not always add up because of missing values.

^b Among US women, level 1 = high school education, level 2 = college education, level 3 = graduate education; among Chinese women, level 1 = 9 years of schooling or less, level 2 = 10–12 years of schooling, level 3 = ≥13 years of schooling.

^c Body mass index.

Table 3 Birthweight (g) of babies born between 37 and 42 weeks of gestation according to maternal characteristics of 267 Caucasian women from Boston, US and 303 Chinese women from Shanghai, China^a

Maternal characteristics	US women		Chinese women	
	N	Mean (SE)	N	Mean (SE)
Maternal age (years)				
18–24	6	3761 (231)	152	3422 (36)
25–29	70	3460 (58)	111	3412 (43)
30–34	163	3605 (36)	31	3332 (77)
35+	23	3488 (97)	9	3542 (96)
Maternal education^b				
Level 1	45	3609 (73)	107	3402 (40)
Level 2	106	3591 (47)	87	3413 (52)
Level 3	111	3509 (44)	23	3473 (88)
Parity				
1	164	3538 (36)	298	3408 (26)
2	103	3583 (48)	5	3666 (165)
Height (cm)				
–159	56	3443 (65)	130	3328 (35)
160–164	63	3531 (64)	117	3457 (42)
165–169	78	3583 (51)	47	3443 (60)
170+	65	3657 (56)	9	3899 (192)
Pre-pregnancy BMI^c (kg/m²)				
–18	30	3445 (78)	111	3336 (40)
19–21	120	3536 (43)	142	3407 (36)
22–24	67	3656 (54)	39	3562 (75)
25+	43	3535 (85)	9	3753 (135)
Weight gain (kg)				
–7	48	3443 (63)	129	3322 (39)
8–11	81	3478 (48)	75	3496 (54)
12–14	63	3563 (52)	42	3431 (53)
15+	49	3817 (81)	28	3572 (84)
Previous oral contraceptive use				
Yes	205	3597 (33)	3	3365 (32)
No	62	3416 (59)	294	3412 (26)
Smoking in pregnancy				
Yes	12	3652 (201)	0	– (–)
No	250	3555 (29)	300	3415 (25)
Caffeine intake in pregnancy (mg/day)				
0	10	3556 (102)	289	3415 (25)
1–149	227	3552 (32)	14	3373 (161)
150+	1	3480 (–)	0	– (–)
Pre-eclampsia				
Yes	16	3370 (101)	0	– (–)
No	251	3567 (30)	303	3413 (25)
Urogenital infection in pregnancy				
Yes	10	3725 (116)	1	3394 (–)
No	251	3551 (30)	302	3413 (25)
Gender of offspring				
Male	137	3602 (37)	178	3436 (34)
Female	130	3506 (45)	125	3379 (37)

^a The numbers do not always add up because of missing values.

^b See relevant footnote in Table 2.

^c Body mass index.

maternal age is very different between US and Chinese women, all ages below 30 had to be combined among US women and all ages above 30 had to be combined among Chinese women. The remarkable findings in Table 4 are the strong, statistically significant and apparently unconfounded association of pregravid oral contraceptive use with higher birthweight, evaluated only

among US women, and the independent effects that height, pre-pregnancy BMI and weight gain during pregnancy have on birthweight, both in the US and China. There is also evidence for interaction between ethnic group and height ($P = 0.10$) and ethnic group and pre-pregnancy BMI ($P < 0.05$) with respect to birthweight. These interactions may indicate that the effects

Table 4 Multivariate regression-derived^a coefficients showing changes in birth weight per indicated contrasts or changes in predictor variable. Newborns after a gestation lasting from 37 to 42 weeks, inclusive in Boston, USA and Shanghai, China

	US women			Chinese women							
	Birthweight change (SE)		P-value	Birthweight change (SE)		P-value					
Maternal age (years)											
18–24	}	Ref.		Ref.		0.07					
25–29				+116.7			64.6				
30–34				+65.3			63.3	}	-110.0	107.5	0.31
35+				-22.6			104.0				
Maternal education											
Per level increase ^b	-39.7	40.4	0.33	-6.5	46.6	0.89					
Parity											
1	Ref.			Not evaluated (only 6 with parity of 2)							
2	+117.9	57.1	0.04								
Height											
Per 5 cm increase	+39.2	20.8	0.06	+102.9	32.4	0.002					
Pre-pregnancy BMI^c											
Per 2 kg/m ² increase	+15.4	17.9	0.39	+129.2	28.4	<0.0001					
Weight gain											
Per 2 kg increase	+34.2	11.9	0.004	+16.0	13.0	0.22					
Previous oral contraceptive use											
No	Ref.			Not evaluated (only 3 OC users)							
Yes	+189.3	65.4	0.004								
Smoking in pregnancy											
No	Ref.			Not evaluated (zero smokers)							
Yes	-14.7	129.4	0.91								
Pre-eclampsia											
No	Ref.			Not evaluated (zero with preeclampsia)							
Yes	-72.7	123.0	0.55								
Gender of offspring											
Male	Ref.			Ref.							
Female	-135.9	53.3	0.01	-31.9	57.7	0.58					
Gestational age											
Per week increase	+160.6	21.2	<0.0001	+71.2	24.6	0.004					

^a Mutually adjusting for all other variables in the Table.

^b See footnote b in Table 2.

^c Body mass index.

of height and pre-pregnancy BMI on birthweight may be approaching their upper limits within the group of the taller and heavier Caucasian US women.

We examined whether difference in birthweight between US and China newborns could be explained by maternal anthropometric characteristics by adjusting successively for different covariates. When only one of the maternal anthropometric variables (height, BMI, or weight gain) was included in the model, the crude difference in birthweight was reduced, but not eliminated. Table 5, however, shows that the difference observed between US and Chinese newborns could be fully accounted for by the combined effects of differences in maternal height, pre-pregnancy BMI, and weight gain during pregnancy. Because the US study population has a small proportion of subjects who never used oral contraceptives (OC), analyses excluding OC users were not informative. We have also limited the analysis to primiparous women and the results were similar in that the observed crude difference in birthweight was eliminated after adjusting for the maternal anthropometric variables.

Discussion

In this paper, we present data on birth size aspects and birthweight determinants derived from samples of pregnant women in Boston, USA and Shanghai, China. Although the samples studied were not representative of the respective populations, even at the city level, they provide a meaningful contrast. We have documented that height and pre-pregnancy BMI are important birthweight determinants, particularly among Chinese women, whereas weight gain during pregnancy is an important birthweight determinant, particularly among US women. More important, and uniquely demonstrable on a study design with parallel sampling in contrasting populations, the difference in height, pre-pregnancy BMI, and weight gain during pregnancy between the two samples fully explains the mean birthweight difference between the two populations. We have also found that pregravid oral contraceptive use is associated with higher birthweight, an unexpected finding that we intend to fully explore in another paper.

Table 5 Birthweight difference comparing US and Chinese newborns, with adjustment for different covariates

	Crude			Adjusted for gender and gestational age			Further adjusted for maternal height, pre-pregnancy BMI^a, and weight gain		
	Birthweight difference (SE)		<i>P</i> -value	Birthweight difference (SE)		<i>P</i> -value	Birthweight difference (SE)		<i>P</i> -value
China	Ref.			Ref.			Ref.		
US	+104.7	40.4	0.01	+104.5	36.4	0.004	-36.8	42.1	0.38

^a Body mass index.

The present study is of moderate size, but the statistical power was sufficient to allow documentation of the important findings concerning maternal anthropometry in relation to birthweight. The data were collected in a standardized way and with an identical protocol in the two settings. There is also no evidence for the operation of important biases, since the findings were generally compatible with those reported by other investigators and those expected from the socio-cultural environment in the two populations.¹⁻⁵

The results of our study complement those of an earlier paper by Wen and colleagues.¹¹ These authors have compared birthweight distributions between Chinese and Caucasian infants and found that the lower mean birthweight in Chinese infants is due to slower fetal growth towards the end of the third trimester. We postulate that Chinese babies in China have lower birthweight because the lower height and pre-pregnancy BMI of their mothers imposes constraints on the growth of the fetus towards the end of the pregnancy. The literature concerning changes in somatometry and particularly birthweight among Chinese and Chinese migrating to the US is limited.¹²⁻¹⁴ The existing evidence, however, suggests that when Chinese women migrate to the US, they tend to grow taller and heavier and their babies tend to have higher birthweight.¹¹⁻¹⁴ This is likely to recur in successive generations, so that eventually Chinese Americans have comparable anthropometric characteristics to Caucasian Americans and, indeed, comparable breast cancer rates.¹⁵⁻¹⁷

Established adult life risk factors for breast cancer explain little of the more than fourfold difference in the incidence of this disease between the US and China.¹⁸ This has led to the hypothesis that early life events and conditions may influence subsequent

risk for breast cancer.^{19,20} Birthweight has been associated with breast cancer risk in a number of studies,²¹⁻²³ but the breast cancer risk gradient in relation to birthweight is again too limited to explain the difference in breast cancer incidence between the US and China or Japan. It has been hypothesized, however, that a critical determinant of breast cancer risk may be mammary gland mass, which is indeed considerably larger among Caucasians than among Chinese.^{20,24} Indeed, mammary gland mass is likely to be a predictor of the number of immature mammary cells that are susceptible to carcinogenic initiation.²⁴ In ethnic contrasts, but not necessarily in individual intra-ethnic comparisons, birthweight may be related to mammary gland mass in a non-linear way, so that small differences in birthweight (and pre-adolescence growth patterns) generate large differences in mammary gland mass in adult life. In this context and in an admittedly speculative way, our study provides support to the ideas that perinatal influences and mammary gland mass are important determinants of adult life breast cancer risk. Indeed, our findings could allow an explanation of the pattern of increase of breast cancer incidence among the Asian Americans over successive generations.^{16,17} The cycle whereby bigger women give birth to bigger babies who, in turn, may have a larger pool of stem cells for mammary gland development in adolescence is compatible with the increasing trends in breast cancer incidence that have been noted in most populations during periods of economic growth and prosperity.²⁵

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KEY MESSAGES

- Newborns in China have lower birthweight in comparison to Caucasian newborns in the US.
- The difference in birthweight between Chinese newborns in China and Caucasian newborns in the US is accounted for by maternal anthropometry.
- Migration from China to the US is associated, in successive generations, with increasing birthweight and anthropometry, and this may underlie the increasing incidence of breast cancer in successive generations of Chinese migrants.

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Commentary: Inter-ethnic studies of breast cancer risk

Mona Okasha

In this issue of the *International Journal of Epidemiology*, Lagiou and colleagues present data comparing maternal anthropometric determinants of birthweight in USA and China.¹ They performed two parallel cohort studies of pregnant women, and described the determinants of the offspring's birthweight within each population. They then looked for determinants of the difference between the birthweights, in an inter-population comparison.

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Higher birthweight has been repeatedly shown to be associated with a higher breast cancer risk in data from case-control studies^{2,3} and cohort studies.^{4,5} Although not all studies have replicated this finding,^{6,7} the weight of evidence suggests that there is a modest, positive association between birthweight and breast cancer. The strength of the relationship varies between studies, but is in the range of 50% to 100% increased risk when comparing the top to the bottom quartile of the birthweight distribution. It is of interest to note that most of the above

studies were performed in Caucasian populations, and the only study carried out in a low-risk population (Shanghai) did not find any evidence of an association between birthweight and breast cancer.⁷

Lagiou's study found a number of interesting associations in the crude intra-population comparisons. These included higher birthweight among the offspring of women who were taller, heavier, and gained weight during pregnancy. What the authors do not comment on is the differences in magnitude of the associations found between US and Chinese women. For example, the birthweight increase associated with each 2 kg/m² higher pre-pregnancy body mass index (BMI) was 15 g (SE: 18 g) in the US and 129 g (SE: 28 g) in China. In the intra-population comparisons, the authors found that the difference in mean birthweight between American and Chinese infants (105 g) was entirely explained when adjusted for maternal anthropometric factors (height, pre-pregnancy BMI, and weight gain in pregnancy).

Chinese women experience a considerably lower risk of breast cancer than Caucasian American women.⁸ Lagiou and colleagues speculate that their observations could allow an explanation of the pattern of higher breast cancer incidence among Chinese Americans over successive generations due to changes in maternal anthropometry. However, the epidemiological evidence regarding the change in disease rates in Chinese migrants remains equivocal. A review of Chinese migrants to North America found standardized mortality ratios (SMR) of 0.5 to 0.8 among first-generation migrants.⁹ Breast cancer mortality was similar in second compared with first generation immigrants. However, other studies have shown increases in breast cancer rates over generations,¹⁰ and these eventually approach the rates experienced by Caucasian Americans. A clearer understanding of determinants of inter-ethnic differences in breast cancer is required before accepting the suggestion that maternal anthropometry may be the key to understanding these differences.

The authors acknowledge that the magnitude of the association between birthweight and breast cancer is too small for this to be the only explanation of the difference in the incidence of breast cancer between the US and China. They postulate that birthweight may be magnified by features of childhood growth to affect breast cancer risk through mammary gland mass.

It has been suggested that breast size is related to breast cancer, since larger breasts may contain more cells susceptible to malignant change.¹¹ Breasts are composed not only of glandular tissue, in which cancers arise, but also of fibrous and fatty tissue. Given the differences in levels of obesity between America and China, observed differences in breast size between the countries may be due to fat deposits rather than differences in the amount of glandular tissue in the breasts of women. This is supported by the observation that the difference in mammographically dense breast area between Caucasian and Chinese women in Hawaii is substantially attenuated having adjusted for BMI and other factors.¹² New techniques in the manipulation of digital images can determine the relative volumes of glandular and fatty tissue in the breast. This will allow a better understanding in the future of the importance of breast components in relation to cancer risk.

The authors suggest that small differences in birthweight and pre-adolescent growth may interact to produce large differences in mammary gland mass, leading to an increased risk of breast cancer. This suggestion is consistent with observed modification of the association between birthweight and breast cancer by

childhood growth which has been demonstrated by De Stavola and colleagues.⁴ Using data from the 1946 UK birth cohort, they described fourfold risks of breast cancer among women who were born heavy (≥ 3.5 kg) and grew to a taller height in childhood (≥ 1.22 m at age 7), compared with those born light (< 3.5 kg). Whether this observation could be related to the development of larger breasts among girls who grow taller in childhood is not suggested by De Stavola and colleagues. They do postulate that higher levels of insulin-like growth factors (IGF) may underlie observed associations between growth and cancer risk. Associations between height and cancers of the colo-rectum and prostate may also be explained by the actions of IGF.^{13,14}

In conclusion, the results presented in Lagiou's paper are of relevance to breast cancer aetiology. They provide further evidence of an association between peri-natal events and breast cancer in two populations that experience different risks of disease. To investigate the authors' hypothesis further, an ideal study would involve considerations of inter-generational effects of maternal and offspring anthropometric measures at birth and in childhood, as well as breast size and cancer incidence data among Chinese, Asian American, and Caucasian American women. In the absence of ideal research, we must continue to make inferences regarding breast cancer aetiology from studies such as Lagiou's.

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