Body shape throughout life and correlations with IGFs and GH

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Abstract

Both insulin-like growth factors (IGF) and body size have been linked to premenopausal breast cancer risk. However, observational studies of IGF have not been consistent, and they suggest that perhaps earlier levels of IGF might be more strongly related to breast cancer than those measured at mid-age. We therefore sought to explore associations between several measures of body size throughout life and IGF levels in premenopausal women. We examined cross-sectional associations of birth weight, body shape (or somatotype) at ages 5 and 10, body mass index (BMI) at age 18 and adulthood, bra cup size at age 20, adult waist circumference and waist-to-hip ratio (WHR), and attained height with plasma levels of IGF-I, IGF binding protein 3 (IGFBP-3), IGFBP-1, and GH. Participants were 592 healthy premenopausal women aged 34–52 from the Nurses' Health Study II. Using multiple linear regression, we computed least-square mean hormone levels across the categories of early life anthropometric factors. We observed consistent and strong inverse associations between body shape at various stages in life and IGF levels. Somatotype at ages 5 and 10 was inversely associated with IGF-I (*P* for difference, <0.01) and positively with IGFBP-3 measured later in adulthood. Further, comparing women with a BMI ≥ 25 kg/m^2 at age 18 vs <19 kg/m^2, similar associations were observed for IGF-I (*P* for trend, 0.005) and IGFBP-3 (*P* for trend, 0.01), which were even stronger for BMI at blood collection (BMI <20 versus BMI ≥ 30, mean IGF-I 254 ng/ml, 95% CI, 239–271 vs 208 ng/ml, 95% CI, 195–222). Both waist circumference and WHR were strongly and inversely related to IGFBP-1 levels (top versus bottom quartile of waist circumference: 14.5 vs 40.0 ng/ml, *P* for trend 0.0005; WHR: 18.3 vs 39.4 ng/ml, *P* for trend 0.002), with similar results for bra cup size at age 20 although they did not reach statistical significance. There was no association between height and IGF or GH levels. Birth weight, on the other hand, was weakly positively associated with both IGF-I and IGFBP-1 levels, and inversely with GH. Our results suggest that childhood and adult body size may affect premenopausal breast cancer risk differently than birth weight, through associations with IGF and GH levels.

Introduction

The insulin-like growth factor (IGF) system is a complex system of ligands, receptors, and binding proteins. IGF-I and its prime regulator, growth hormone (GH), are essential for normal growth. In fully developed organisms, together with the binding proteins of IGF-I, they play an important role in homeostasis and have been implicated in disease causation (most notably, carcinogenesis) as well as disease progression both early in life (Le Roith & Butler 2005) as well as in adulthood (Pollak *et al.* 2004). Since the pulsatility of GH secretion would require frequent blood sampling, IGF-I, which has only minor circadian fluctuations (Minuto *et al.* 1981), is

widely used in clinical and observational studies. The primary IGF-binding protein (IGFBP) is IGFBP-3.

IGF-I may increase premenopausal breast cancer risk, although associations between IGF-I and breast cancer risk have not been entirely consistent (Renehan *et al.* 2006). Earlier findings of strong positive associations between IGF-I and premenopausal breast cancer risk (Hankinson *et al.* 1998, Toniolo *et al.* 2000, Kaaks *et al.* 2002, Krajcik *et al.* 2002, Muti *et al.* 2002, Allen *et al.* 2005, Rinaldi *et al.* 2005, Schernhammer *et al.* 2005) have not been replicated in recent studies (Rinaldi *et al.* 2006, Schernhammer *et al.* 2006). Body size through out life, from birth weight (Ahlgren *et al.* 2003, McCormack *et al.* 2005, Vatten *et al.* 2005, Barba *et al.* 2006, Park *et al.* 2006) to adult body mass index (BMI; Carmichael & Bates 2004), has been related to premenopausal breast cancer risk, although the direction of the associations changes (positive with birth weight and inverse with adult premenopausal BMI), even after accounting for later BMI. Hence, we decided to evaluate associations between IGF and body size throughout life to assess if IGFs may play a role in the observed body size/breast cancer relationships. To test this hypothesis, we examined the cross-sectional associations of birth weight, body shape at ages 5 and 10, BMI at age 18 and adulthood, bra cup size at age 20, adult waist circumference and waist-to-hip ratio (WHR), as well as attained height in relation to IGF-I, IGFBP-3, IGFBP-1, and GH levels in 592 healthy premenopausal women enrolled in the Nurses' Health Study II (NHS II).

Materials and methods

Study population

The NHS II is a prospective cohort study that started in 1989, when 116 609 registered female U.S. nurses aged 25–42 from 14 US states were enrolled. The NHS II was designed akin to the NHS, an earlier, independent cohort study of similar size which was initiated in 1976 (Colditz & Hankinson 2005). The baseline questionnaire sought hormone use, reproductive history, current medication, history of disease, and a number of life-style factors. Since then, women have been followed biennially by mailed questionnaires, ascertaining any diagnosis of breast cancer, including date of diagnosis and updating exposures. Further details of the cohort have been published (Rockhill *et al.* 1998).

Women who had not previously reported a diagnosis of cancer were eligible for sample collections; in total, 29 611 women in the NHS II cohort participated in our blood collection study from 1996 to 1999. We provided blood collection kits and advised each participant to have blood samples drawn by a local laboratory or colleague. Premenopausal women not pregnant, breast feeding, or on hormone therapy were asked to provide two samples timed within their menstrual cycle. First samples were drawn in the follicular phase of the menstrual cycle; second samples were collected in the luteal phase. Samples were returned to our laboratory via overnight courier, with a frozen water sample to keep them cool. Of the 29 611 participants, 18 521 provided two timed blood samples, and 11 090 women provided a single, untimed blood sample. A brief questionnaire was included with the blood kit, asking the specific date and time when blood samples were drawn, the first day of the nurse's current menstrual cycle, the number of hours since she had last eaten, her current weight, medication used, and any changes in her menstrual cycle characteristics. For women who gave both follicular and luteal samples, we used luteal samples in this study, because cyclic variations of IGF are only modest (Juul *et al.* 1997, Helle *et al.* 1998).

Women in this analysis were premenopausal controls who were matched to breast cancer cases diagnosed after blood collection and before June 2003 ($n=479$; Tworoger *et al.* 2006), and a subset of women who provided three sets of timed follicular and luteal samples over 2–3 years ($n=113$). (We considered only the baseline samples for these women; Missmer *et al.* 2006). The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital and the Harvard School of Public Health.

We defined menopausal status at the time of blood collection. Women who provided a timed sample were considered to be premenopausal. Women providing a single untimed sample were considered premenopausal if they a) reported that periods had not ceased or b) had a hysterectomy but had at least one ovary remaining and were ≤ 45 (for nonsmokers) or ≤ 47 (for smokers) years old–at these ages, fewer than $<10\%$ of the cohort had had a natural menopause.

Covariate information

Information on exposure measures and potential covariates were asked on a questionnaire completed at blood collection and the biennial study questionnaires. In 1989, NHS II participants recalled their body fatness at ages 5 and 10, using a nine-level figure drawing (Baer *et al.* 2005) originally developed by Stunkard *et al.* (1983). The recall of body shape in childhood, among elderly women, was validated

against weight and height measurements taken in childhood (Must *et al.* 1993). Oral contraceptive use, age at menarche, cycle regularity between ages 18 and 22, weight at age 18, and height were reported at baseline in 1989; oral contraceptive use was updated on subsequent biennial questionnaires. Birth weight was reported in 1991 and the participants were asked to choose one of the following categories: unknown, <5.5, 5.5–6.9, 7.0–8.4, 8.5–9.9, or 10+ pounds. Current weight and details about the blood collection date, time, and fasting status were reported on the blood questionnaire. BMI at age 18 and current BMI were calculated using adult height as weight in kg divided by height in meters squared. In 1993, women were asked to measure their waist and hip circumferences, to the nearest ¼ inch, if they had a tape measure easily available; 64% of women provided these measurements.

Laboratory assays

For IGFBP-1 analyses, only fasting blood samples were used. Total IGF-I, IGFBP-1, IGFBP-3, and GH levels were assayed by ELISA after acid extraction, using reagents from Diagnostic Systems Laboratory (Webster, TX, USA). Masked split specimens included within each batch were used to calculate the coefficient of variation within batches; for IGF-I, IGFBP-3, IGFBP-1, and GH, these were 6.8, 4.2, 1.6, and 11.3% respectively.

Statistical analysis

For each of the biomarkers, we excluded women with missing values related to assay difficulties or low volume. We also identified statistical outliers based on the generalized extreme studentized deviate many-outlier detection approach (Rosner 1993); one woman with an improbable IGFBP-1 concentration was identified as an outlier and excluded. In sum, a total of 592 healthy premenopausal controls (254 women in the IGFBP-1 analysis) formed the study population for the current analyses.

We used the natural logarithms of IGF-I, its binding proteins, and GH measurements in the analyses because the transformed values were more normally distributed. To test for differences in IGF levels by categories of covariates, we used mixed-effects regression models for clustered data to adjust for possible confounding due to other life style and reproductive factors (Zeger *et al.* 1988). Primary analyses calculated adjusted geometric means by category of exposure. Exposures consisted of birth weight (<5.5, 5.5–6.9, 7.0–8.4, 8.5+ lbs), somatotype at ages 5 and 10 (1, 2, 3, 4, 5+), BMI at age 18 (<19, 19–<21, 21–<23, 23–<25, 25+ kg/m^2), BMI at blood collection (<20, 20–<22.5, 22.5–<25, 25–<27.5, 27.5–<30, 30+), and quartiles of waist circumference (<60.5, 60.5–<65.5, 65.5–<72.6, 72.6+ cm), WHR (<0.73, 0.73–<0.77, 0.77–<0.82, 0.82+), bra cup size (A or less, B, C, D or more), and height (<139, 139–<143, 143–<147, 147+ cm). Tests for trend were conducted by modeling continuous, ln-transformed hormone levels (on continuous exposure measures) and calculating the Wald statistic (Hosmer & Lemeshow 1989). In the analyses of birth weight and somatotype at ages 5 and 10, we excluded women born pre-term or as part of a multiple birth. Stratified analyses by age and BMI at blood draw used a multiplicative interaction term.

Multivariate models adjusted for assay batch (1, 2), age at blood draw (<40, 40–<45, 45+ years), fasting status (yes, no), time of day of blood draw (0100–0800 h, 0900 h–noon, 1300 h–midnight), month of blood draw (continuous), difference between luteal blood draw date and date of the next menstrual period (3–7, 8–21 days, other/unknown/untimed), and duration of past oral contraceptive use (never, <4, 4+ years, missing). In addition, models with IGF-I or IGFBP-3 were mutually adjusted for each other. In analyses of waist circumference and WHR, we additionally adjusted for BMI (continuous). We also considered other potential confounders including simple hysterectomy, history of benign breast disease, family history of breast cancer, and parity; however, these did not change the results and therefore were not included in the final model.

Statistical analyses were performed with SAS software (SAS Institute, Cary, NC, USA). When the underlying variable was continuous, such as age or BMI, *P* values were reported for the linear trend across categories. For categorical variables (such as smoking history or family history of cancer), the *P* value reported represents the level of significance of the difference comparing extreme categories. All *P* values were based on two-sided tests and were considered statistically significant if ≤ 0.05.

Results

The 592 women who were available for analysis ranged in age from 34 to 52 years (median 43.5 years) at blood collection (Table 1). Eighty-six percent of women provided timed samples, and of those, 91.1% were ovulatory, setting progesterone values >10 nmol/l for the acceptance of ovulation. Among women born full-term, 3.3% weighed <5.5 pounds (equals <2.5 kg) at birth and 15.2% weighed >8.5 pounds (equals >3.9 kg).

Table 1 Baseline characteristics of 592 women

All women	Median	Range (10th–90th percentile)
Age (years)	43.5	37.8–48.5
BMI at blood draw	23.8	19.9–32.1
Age at menarche (years)	12.0	11.0–14.0
BMI at age 18	20.6	18.3–24.0
Waist circumference (inches, 1986)	65.5	57.2–82.0
Waist-to-hip ratio (1986)	0.77	0.70–0.87
Height (inches)	143.0	136.4–149.6
Number of pregnancies[a]	2	1–3
Plasma levels		
IGF-I (ng/ml)	245.4	146.5–347.9
IGFBP-3 (ng/ml)	4765	3297–5896
IGFBP-1 (ng/ml)	33.6	11.5–67.9
GH (ng/ml)	0.24	0.14–4.14

	Percent
Full-term pregnancies	90.9
Birth weight[b,c]	
<5.5 lbs	3.3
5.5–6.9 lbs	26.6
6.9–8.4 lbs	54.9
8.5+lbs	15.2
Bra cup size at age 20	
A or less	32.9
B	44.4
C	18.4
D	4.3
Somatotype at age 5[c]	
1	19.7
2	31.7
3	28.9
4	13.1
5+	6.6
Somatotype at age 10[c]	
1	17.7
2	30.0
3	25.6
4	16.8
5+	9.9

At natural menopause or bilateral oophorectomy.
[a]Among parous women only.
[b]Thirty women answered 'Don't know' to this question.
[c]Among women ($n=538$) who were born full-term.

Few women had a large body size at ages 5 (6.6%) and 10 (9.9%), and, on average, women had a considerably lower BMI at age 18 (median, 20.6 kg/m^2) than at blood collection (median, 23.8 kg/m^2). Birth weight among full-term babies was relatively weakly correlated with body shape at ages 5 and 10 (Spearman's $r=0.13$ and 0.14 respectively, both $P<0.01$), whereas body shape at ages 5 and 10 were strongly correlated with each other ($r=0.80, P<0.01$). Levels of IGF-I, IGFBP-3, IGFBP-1, and GH were in the expected range for premenopausal women (Hankinson & Schernhammer 2003, Renehan *et al.* 2004). The median values for IGF-I and IGFBP-3 were 245 and 4765 ng/ml respectively. Median values and their ranges for IGFBP-1 and GH along with information on other early life correlates are provided in Table 1.

In multivariate analyses, we observed a trend for higher IGF-I levels, lower IGFBP-3, and higher IGFBP-1 levels measured in adulthood in the babies that were born heavier (P for difference 0.20, 0.11, and 0.04 respectively) with a suggestion for higher GH levels in the leanest babies (Table 2). However, starting at age 5, this trend appeared to reverse, with consistently higher levels of adult IGF-I seen in the leanest girls and women, which persisted throughout adulthood. Specifically, at ages 5 and 10, girls with the heaviest stature had significantly lower adult IGF-I levels (age 5, 197 ng/ml; 95% CI, 176–219; age 10, 203 ng/ml; 95% CI, 186–221) than the leanest girls (age 5, 238 ng/ml; 95% CI, 226–250, P for difference 0.003; at age 10, 240 ng/ml; 95% CI, 228–253, P for difference <0.001). These girls had higher adult IGFBP-3 levels and lower adult IGFBP-1 levels. Similarly, BMI at age 18 was a strong predictor of IGF levels: women with the highest BMI had a mean IGF-I level of 210, whereas the mean IGF-I level of the leanest women at age 18 was 239 (P for trend, 0.005); IGFBP-1 levels were also significantly lower in these women (P for trend, 0.01). Finally, women with a BMI of ≥ 30 at blood collection had mean IGF-I levels of 208 ng/ml (95% CI, 195–222), compared with women with a BMI of less than 20 whose mean IGF-I level was 254 ng/ml (95% CI, 239–271, P for trend, <0.001), and their IGFBP-1 and GH levels were again significantly lower, whereas their IGFBP-3 levels were not significantly higher than those of the women with the lowest BMI.

Waist circumference and WHR were similarly related to IGF-I and IGFBP-3, but were particularly strong predictors of IGFBP-1 levels (top versus bottom quartile of waist circumference: 14.5 vs 40.0 ng/ml, P for trend 0.0005; WHR: 18.3 vs 39.4 ng/ml, P for trend 0.002).

Current BMI (as assessed at blood draw) was strongly correlated with BMI at age 18 (Spearman's $r=0.54$, $P<0.001$) and to a lesser degree also with early somatotypes (somatotype at age 5, $r=0.24$; age 10, $r=0.30$, $P<0.001$). We therefore adjusted for current BMI in secondary analyses and results remained largely unchanged. Specifically, there was still a strong inverse trend between early somatotypes and IGF-I levels as well as between WHR and waist circumference and IGFBP-1 levels, and a positive association between birth weight and IGFBP-1 levels

Table 2 Multivariate adjusted geometric mean plasma levels of insulin-like growth factor I (IGF-I), IGF binding protein 3 (IGFBP-3), IGFBP-1, and growth hormone (GH) by the categories of anthropometric correlates[a]

			Geometric means, 95% CI			
	Category definition	***N***	IGF-I[b]	IGFBP-3[b]	IGFBP-1[c]	GH[d]
Birth weight (pounds)[e]	<5.5	17	218 (190–249)	4821 (4493–5173)	23.2 (15.4–34.9)	0.78 (0.42–1.48)
	5.5–6.9	135	228 (217–241)	4632 (4496–4771)	31.8 (26.1–38.7)	0.43 (0.34–0.55)
	7.0–8.4	279	233 (226–241)	4538 (4450–4628)	28.7 (25.4–32.5)	0.50 (0.42–0.59)
	≥8.5	77	239 (227–251)	4516 (4348–4690)	35.9 (29.1–44.4)	0.50 (0.36–0.68)
	P for difference	508	0.21	0.11	0.04	0.21
Somatotype at age 5[e]	1	105	238 (226–250)	4524 (4371–4683)	31.2 (25.4–38.3)	0.47 (0.35–0.63)
	2	169	236 (227–246)	4499 (4379–4623)	28.4 (23.7–34.1)	0.57 (0.46–0.72)
	3	154	243 (233–253)	4506 (4392–4622)	32.4 (27.9–37.6)	0.43 (0.34–0.54)
	4	70	211 (197–225)	4821 (4642–5006)	28.6 (22.9–35.6)	0.50 (0.35–0.70)
	5+	35	197 (176–219)	4762 (4555–4978)	33.2 (24.6–44.7)	0.59 (0.36–0.95)
	P for difference	533	0.002	0.08	0.74	0.43
Somatotype at age 10[e]	1	95	240 (228–253)	4580 (4421–4744)	33.1 (27.4–40.0)	0.47 (0.35–0.64)
	2	161	241 (231–252)	4515 (4394–4640)	28.2 (23.5–33.9)	0.48 (0.38–0.59)
	3	137	239 (228–250)	4457 (4342–4576)	33.6 (29.0–38.8)	0.47 (0.37–0.60)
	4	90	219 (207–233)	4678 (4527–4835)	29.1 (22.8–37.2)	0.60 (0.43–0.84)
	5+	53	203 (186–221)	4804 (4598–5020)	23.5 (18.4–29.9)	0.52 (0.35–0.77)
	P for difference	536	<0.001	0.10	0.03	0.70
BMI at age 18 (kg/m^2)	<19	117	239 (227–250)	4581 (4464–4701)	33.8 (28.2–40.6)	0.45 (0.35–0.58)
	19–20.9	221	239 (231–248)	4516 (4421–4612)	32.7 (28.8–37.1)	0.46 (0.38–0.56)
	21–22.9	156	235 (225–245)	4541 (4415–4671)	29.4 (24.7–35.1)	0.54 (0.43–0.68)
	23–24.9	60	205 (187–225)	4676 (4484–4877)	22.3 (16.6–29.9)	0.64 (0.43–0.94)
	≥25	37	210 (192–229)	4780 (4506–5070)	24.0 (17.7–32.5)	0.39 (0.25–0.60)
	P for trend	591	0.005	0.81	0.01	0.79
Bra cup size at age 20	A or less	189	241 (233–249)	4562 (4467–4658)	31.5 (27.5–36.1)	0.49 (0.40–0.61)
	B	255	230 (222–239)	4598 (4504–4693)	31.6 (28.0–35.6)	0.52 (0.44–0.62)
	C	106	227 (214–240)	4520 (4367–4679)	27.1 (21.7–34.0)	0.48 (0.36–0.63)
	D or more	25	220 (192–252)	4549 (4237–4885)	21.5 (14.8–31.4)	0.41 (0.24–0.70)
	P for difference	575	0.21	0.94	0.06	0.53
BMI at blood draw (kg/m^2)	<20	62	254 (239–271)	4444 (4270–4625)	50.7 (41.6–61.7)	0.51 (0.34–0.77)
	20–22.4	156	235 (226–245)	4522 (4410–4636)	41.1 (36.3–46.5)	0.57 (0.46–0.72)
	22.5–24.9	142	236 (226–245)	4462 (4348–4580)	32.9 (28.0–38.7)	0.55 (0.43–0.72)
	25–27.4	88	244 (230–259)	4578 (4397–4767)	25.4 (21.6–29.9)	0.45 (0.34–0.59)
	27.5–29.9	50	216 (197–238)	4638 (4421–4868)	18.4 (14.2–23.9)	0.51 (0.35–0.73)
	≥30	90	208 (195–222)	4848 (4704–4996)	16.5 (13.4–20.3)	0.32 (0.26–0.40)
	P for trend	588	<0.001	0.23	<0.001	0.004

Table 2 *continued*

	Category definition	*N*	Geometric means, 95% CI			
			IGF-I[b]	IGFBP-3[b]	IGFBP-1[c]	GH[d]
Waist circumference[f]	Q1	95	238 (225–252)	4560 (4407–4717)	40.0 (34.8–48.3)	0.62 (0.45–0.85)
	Q2	99	241 (229–255)	4452 (4302–4608)	34.5 (29.3–40.5)	0.56 (0.42–0.75)
	Q3	84	239 (227–253)	4481 (4311–4657)	31.6 (27.0–37.1)	0.55 (0.39–0.76)
	Q4	103	222 (210–235)	4757 (4621–4898)	14.5 (12.1–17.4)	0.37 (0.29–0.48)
	P for trend	381	0.66	0.19	0.0005	0.13
Waist-to-hip ratio[f]	Q1	89	243 (230–256)	4538 (4381–4700)	39.4 (33.2–46.8)	0.67 (0.48–0.93)
	Q2	97	229 (217–242)	4565 (4413–4723)	30.5 (25.4–36.6)	0.53 (0.40–0.69)
	Q3	93	243 (229–258)	4490 (4335–4650)	30.7 (25.1–37.6)	0.46 (0.34–0.63)
	Q4	101	227 (215–240)	4658 (4507–4813)	18.3 (14.7–22.7)	0.44 (0.33–0.58)
	P for trend	380	0.57	0.77	0.002	0.16
Height (1976)	Q1	100	231 (219–244)	4616 (4466–4772)	31.6 (27.0–36.9)	0.54 (0.40–0.71)
	Q2	162	225 (215–237)	4626 (4501–4755)	27.8 (23.4–33.0)	0.48 (0.39–0.60)
	Q3	158	239 (230–249)	4557 (4451–4666)	31.6 (26.9–37.2)	0.46 (0.38–0.57)
	Q4	172	234 (224–244)	4495 (4391–4601)	30.7 (26.4–35.7)	0.50 (0.40–0.63)
	P for trend	592	0.96	0.41	0.35	0.86

[a]All factors are adjusted for analysis batch, age, fasting status, time of day blood drawn, drawn month, luteal difference, and duration of OC use. Ps refer to the linear trend test for ordinal variables (e.g., age, BMI, height) and a test of difference between extreme categories for non-ordinal variables (e.g., somatotype = 1 vs 5+).
[b]Models are mutually adjusted for IGF-I/IGFBP-3.
[c]There are fewer women with IGFBP-1 levels because we had fewer fasting samples and we did not have women from the subset of women who provided three sets of blood samples over 2–3 years.
[d]There are fewer women with GH because we did not have women from the subset of women who provided three sets of blood samples over 2–3 years.
[e]Among women ($n = 538$) who were born full-term.
[f]Waist-to-hip ratio and waist circumference were assessed in 1986.

(data not shown). Similarly in these models, the associations between plasma levels and current BMI were unchanged. In stratified analyses (age, BMI, and parity), we observed no noteworthy differences.

In secondary analyses with IGF-I and IGFBP-1, we additionally adjusted for current milk consumption and circulating insulin levels, respectively. In these analyses, the inverse associations between current BMI, waist circumference, and WHR and IGFBP-1 levels remained virtually unchanged (data not shown). Simultaneous adjustment for BMI and insulin also did not alter these estimates substantially.

Discussion

In one of the most comprehensive studies to date to explore associations between several indicators of body shape throughout a woman's life and premenopausal levels of IGF and GH, we found that weight at birth was weakly positively associated with adult IGF-I and IGFBP-1 levels, whereas indicators of heavier weight, as measured throughout childhood and at later age (though before menopause), were strongly inversely associated with adult IGF-I and IGFBP-1 levels. Our findings are in line with positive associations between birth weight and inverse associations between body fatness at young ages and adult BMI and premenopausal breast cancer risk, implying that the IGF axis might be one possible mechanism for these associations.

Birth weight, a surrogate for *in utero* hormone exposure, has been directly associated with an increased breast cancer risk (Okasha *et al.* 2002). When assessed simultaneously, circulating IGF-I levels are positively correlated with birth weight and other parameters of size at birth (Ong *et al.* 2000, Christou *et al.* 2001, Vatten *et al.* 2002, Boyne *et al.* 2003) and there are some suggestions that IGF-I and other members of the IGF family play important roles in intrauterine growth (Lo *et al.* 2002, Boyne *et al.* 2003). Polymorphisms in the *IGF-I* gene have previously been associated both with postnatal weight gain (Vaessen *et al.* 2002) and with low birth weight in a small for gestational age population (Johnston *et al.* 2003), suggesting that it affects fetal growth. Lower birth weight has been associated with higher circulating IGF-I levels in several studies of children (Fall *et al.* 1995, Ong *et al.* 2002). Generally, the most prominent explanation offered for an inverse association between birth weight and childhood IGF-I suggests that it is caused by decreased nutritional availability to the fetus, which, in turn, leads to reprogramming of the IGF axis resulting in increased levels of circulating IGF-I after birth among children experiencing a postnatal catch-up growth. Yet data on associations between birth weight and plasma markers of the GH–IGF axis in adulthood are sparse and have produced equivocal results. Inverse (37), positive (40) and null (42) associations between birth weight and IGF-I levels have been reported in young adult women (Jernstrom & Olsson 1998). In the few studies on middle-aged (similar to ours; Holt *et al.* 2004, Johnsen *et al.* 2004) and older (Kajantie *et al.* 2003) women, no association was found between birth weight and IGF-I levels, although several studies were smaller than ours (38, 41) and not all the studies were able to exclude preterm births in their analysis (39). Given that our results are not significantly positive and the two other studies are null–-although an association cannot be ruled out–-it seems unlikely that a strong relation exists between birth weight and mid-adult IGF-I.

Even fewer studies have explored associations between birth weight and GH and IGFBP-1 levels. Flanagan *et al.* (1999) reported that low birth weight was associated with reduced urinary GH production as assessed at age 20–21, whereas there was no such association in another, more carefully conducted albeit small study (Fall *et al.* 1998). One study associated birth weight positively with IGFBP-1 levels in older age (Kajantie *et al.* 2003), which is in line with our findings. Similarly, in the only other study (Kistner *et al.* 2004) among 50 young adult women, IGFBP-1 levels were lower in adult women born full-term but small for gestational age – yet, a correlation with birth weight was not reported.

Although height is strongly correlated with IGF-I levels in children (Juul *et al.* 1994*b*), the weight of evidence, including that from our study, suggests no important correlation between height and IGF levels in adulthood (Signorello *et al.* 2000, Suga *et al.* 2001, Vaessen *et al.* 2001, Helle *et al.* 2002, Teramukai *et al.* 2002).

Associations between body shape and circulating IGF are complex and remain poorly understood. For example, if assessed simultaneously, adiposity has not been related to plasma IGF-I levels in childhood or adolescence (Juul *et al.* 1994*a*) in the largest study, to date (877 children and adolescents), whereas a positive association between IGF-I and weight (independent of height) was noted among children aged 4 and 7 in another fairly large study ($n = 444$; Fall *et al.* 1995). Other reports also support the fact that levels of IGF-I measured in childhood are positively associated with childhood adiposity (Fall *et al.* 2000, Ong *et al.* 2002) and with childhood nutrition (Hoppe *et al.* 2004, Rogers *et al.* 2005). The same nutritional exposures in childhood however have the opposite effect on IGF-I

levels measured much later in adulthood (Elias *et al.* 2004, Ben-Shlomo *et al.* 2005). Consistent with our own findings, an inverse association between BMI at age 7 and adult IGF-I levels was reported among 394 Finnish men and women by Kajantie *et al.* (2003), with two additional reports supporting inverse associations of adiposity measured in childhood and IGF-I levels measured later in adult life (Kajantie *et al.* 2003, Martin *et al.* 2006). These studies and the current findings would be compatible with increased nutrition in childhood, resulting in both an increase in adiposity and an increase in hepatic IGF-I production. The latter then acts via pituitary feedback to suppress GH output with a long-term resetting of the GH/IGF-I axis into adulthood and consequently lower adult IGF-I levels. Evidence like that gathered from a small study showing premenopausal IGF-I levels to be related to an elevated breast cancer risk, but primarily in the youngest premenopausal and oldest postmenopausal group in that study (Rollison *et al.* 2006), further indicate that the effect if IGF itself may vary throughout life.

When both parameters are assessed in adulthood, studies tend to support an inverse association between the measures of body shape and IGF-I (Landin-Wilhelmsen *et al.* 1994), similar to our findings, although not all studies have found the association to be linear. For example, one of the largest studies to date (Ben-Shlomo *et al.* 2003) reported inverse associations between adult (age 25, $n=951$) BMI and IGF-I levels. In a recent detailed evaluation among healthy women, BMI was also, albeit weakly, associated with a lower IGF-I/IGFBP-3 ratio (Holmes *et al.* 2001). In two large studies of predominantly Caucasian women, BMI and IGF levels were weakly associated with extreme BMI, on both ends of the spectrum (Holmes *et al.* 2001, Lukanova *et al.* 2002). This has been confirmed in the largest study to date ($n=2139$ women), which reports of lower IGF-I levels in the leanest women (BMI ≤ 22.5 kg/m^2) and those with a BMI >29.2 compared with women with a BMI inside this range (Gram *et al.* 2006, Pischon *et al.* 2006). A study of older women, on the other hand, demonstrated weak to no associations (Goodman-Gruen & Barrett-Connor 1997) and a more detailed evaluation of these data showed a stronger positive association between WHR (Jernstrom & Barrett-Connor 1999) and IGF-I levels in these women (age range 53–90), indicating that the relationship between BMI and IGF levels may shift again in postmenopausal women. Current BMI and IGFBP-1 have consistently been inversely associated in several studies (Janssen *et al.* 1998, Heald *et al.* 2001, Kajantie *et al.* 2003). Studies on associations between WHR or waist circumference and IGF levels have been scarce to date (Holmes *et al.* 2001, Johansson *et al.* 2004, Bezemer *et al.* 2005), and they do not support an association. No studies, to our knowledge, have evaluated the associations of bra cup size with the IGF axis; our findings suggest no important association exists.

As a possible explanation for our findings, it is conceivable that larger body shapes at ages 5 and 10 as well as a higher BMI at age 18 are simply reflections of reduced body growth during adolescence, as growth velocity is linked to GH/IGF-I levels. Thus, the lower IGF-I levels in women with a high adult BMI may have caused slower growth and induced a higher body mass, since it is conceivable that they had lower IGF-I levels already early on in their life. This is further supported by reports of strong correlations between GH and IGF-I and height in prepubertal children and adolescents ($r=0.65$ and 0.78 respectively; Blum *et al.* 1993), further assuming that children who grow fast and are taller also tend to be leaner as well. Alternatively, it is conceivable that obesity in children enhances their response to GH, which in turn may lead to higher IGF-I levels, as suggested by a recent study (Bouhours-Nouet *et al.* 2007). Finally, twin studies (Kao *et al.* 1994, Harrela *et al.* 1996) have shown about half of the interindividual variability in circulating IGF-I and IGFBP-3 levels to be genetically determined.

The strengths of our study include its fairly large size and extensive information on early life correlates collected over more than 15 years. A limitation of our study is its cross-sectional nature, which makes it hard to predict whether factors associated with IGF levels determine those levels, or are in fact determined by them. The one-timed assessment of plasma IGF and, in particular, GH levels represents another potential limitation, as non-differential measurement error may have led to an underestimation of true associations. Finally, while ethnic differences in the relationship between circulating IGF and obesity are likely to exist (Henderson *et al.* 2006), we were unable to address these in our sample of mostly Caucasian women.

In summary, our data suggest that childhood and adult body size may affect premenopausal breast cancer risk differently than birth weight, at least in part through associations with IGF and GH levels. They may also have important implications for other chronic diseases such as cardiovascular disease and type II diabetes.

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