Body shape throughout life and correlations with IGFs and GH

Eva S Schernhammer1,2,3, Shelley S Tworoger1,2, A Heather Eliassen1,2, Stacey A Missmer1,2,4, Jeff M Holly5, Michael N Pollak6 and Susan E Hankinson1,2

1Channing Laboratory, Department of Medicine, Harvard Medical School, Brigham and Women’s Hospital, 181 Longwood Avenue, Boston 02115, Massachusetts, USA
2Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA
3LBI-ACR VIEnna and ACR-ITR VIEnna, Vienna, Austria
4Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Brigham and Women’s Hospital, Boston, Massachusetts, USA
5University Department of Clinical Science at North Bristol, Southmead Hospital, Bristol, UK
6Departments of Medicine and Oncology, McGill University, Montréal, Québec, Canada

(Correspondence should be addressed to E S Schernhammer; Email: eva.schernhammer@channing.harvard.edu)

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/m² at age 18 vs < 19 kg/m², 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 39.4 ng/ml, P for trend 0.002; WHR: 23.0 vs 39.4 mg/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.

Endocrine-Related Cancer (2007) 14 721–732

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 (Renéhan et al. 2005). 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 throughout 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—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 1⁄4 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/m²), 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).
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/m²) than at blood collection (median, 23.8 kg/m²). 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 <0.001). 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 $\geq 30$ 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 1 Baseline characteristics of 592 women

<table>
<thead>
<tr>
<th>All women</th>
<th>Median</th>
<th>Range (10th–90th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.5</td>
<td>37.8–48.5</td>
</tr>
<tr>
<td>BMI at blood draw</td>
<td>23.8</td>
<td>19.9–32.1</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>12.0</td>
<td>11.0–14.0</td>
</tr>
<tr>
<td>BMI at age 18</td>
<td>20.6</td>
<td>18.3–24.0</td>
</tr>
<tr>
<td>Waist circumference (inches, 1986)</td>
<td>66.5</td>
<td>57.2–82.0</td>
</tr>
<tr>
<td>Waist-to-hip ratio (1986)</td>
<td>0.77</td>
<td>0.70–0.87</td>
</tr>
<tr>
<td>Height (inches)</td>
<td>143.0</td>
<td>136.4–149.6</td>
</tr>
<tr>
<td>Number of pregnancies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>1–3</td>
</tr>
<tr>
<td>Plasma levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>245.4</td>
<td>146.5–347.9</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>4765</td>
<td>3297–5896</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>33.6</td>
<td>11.5–67.9</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>0.24</td>
<td>0.14–4.14</td>
</tr>
</tbody>
</table>

Percent

| Birth weight<sup>b,c</sup> | 90.9 |
| Bra cup size at age 20 | | |
| A or less | 32.9 |
| B | 44.4 |
| C | 18.4 |
| D | 4.3 |
| Somatotype at age 5<sup>c</sup> | | |
| 1 | 19.7 |
| 2 | 31.7 |
| 3 | 28.9 |
| 4 | 13.1 |
| 5+ | 6.6 |
| Somatotype at age 10<sup>c</sup> | | |
| 1 | 17.7 |
| 2 | 30.0 |
| 3 | 25.6 |
| 4 | 16.8 |
| 5+ | 9.9 |

<sup>a</sup>Among parous women only.

<sup>b</sup>Thirty women answered ‘Don’t know’ to this question.

<sup>c</sup>Among women ($n = 538$) who were born full-term.

At natural menopause or bilateral oophorectomy.

<sup>a</sup>Among parous women only.

<sup>b</sup>Thirty women answered ‘Don’t know’ to this question.

<sup>c</sup>Among women ($n = 538$) who were born full-term.
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

<table>
<thead>
<tr>
<th>Category definition</th>
<th>$N$</th>
<th>Geometric means, 95% CI</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (pounds) $^a$</td>
<td></td>
<td>IGF-I $^b$</td>
<td>IGFBP-3 $^b$</td>
<td>IGFBP-1 $^c$</td>
<td>GH $^d$</td>
</tr>
<tr>
<td>$&lt;5.5$</td>
<td>17</td>
<td>218 (190–249)</td>
<td>4821 (4493–5173)</td>
<td>23.2 (15.4–34.9)</td>
<td>0.78 (0.42–1.48)</td>
</tr>
<tr>
<td>5.5–6.9</td>
<td>135</td>
<td>228 (217–241)</td>
<td>4632 (4496–4771)</td>
<td>31.8 (26.1–38.7)</td>
<td>0.43 (0.34–0.55)</td>
</tr>
<tr>
<td>7.0–8.4</td>
<td>279</td>
<td>233 (226–241)</td>
<td>4538 (4450–4628)</td>
<td>28.7 (25.4–32.5)</td>
<td>0.50 (0.42–0.59)</td>
</tr>
<tr>
<td>$\geq 8.5$</td>
<td>77</td>
<td>239 (227–251)</td>
<td>4516 (4348–4690)</td>
<td>35.9 (29.1–44.4)</td>
<td>0.50 (0.36–0.68)</td>
</tr>
<tr>
<td>P for difference</td>
<td>508</td>
<td>0.21</td>
<td>0.11</td>
<td>0.04</td>
<td>0.21</td>
</tr>
<tr>
<td>Somatotype at age 5 $^a$</td>
<td></td>
<td>IGF-I</td>
<td>IGFBP-3</td>
<td>IGFBP-1</td>
<td>GH</td>
</tr>
<tr>
<td>1</td>
<td>105</td>
<td>238 (226–250)</td>
<td>4524 (4371–4683)</td>
<td>31.2 (25.4–38.3)</td>
<td>0.47 (0.35–0.63)</td>
</tr>
<tr>
<td>2</td>
<td>169</td>
<td>236 (227–246)</td>
<td>4499 (4379–4623)</td>
<td>28.4 (23.7–34.1)</td>
<td>0.57 (0.46–0.72)</td>
</tr>
<tr>
<td>3</td>
<td>154</td>
<td>243 (233–253)</td>
<td>4506 (4392–4622)</td>
<td>32.4 (27.9–37.6)</td>
<td>0.43 (0.34–0.54)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>211 (197–225)</td>
<td>4821 (4642–5006)</td>
<td>28.6 (22.9–35.6)</td>
<td>0.50 (0.35–0.70)</td>
</tr>
<tr>
<td>5+</td>
<td>35</td>
<td>197 (176–219)</td>
<td>4762 (4555–4978)</td>
<td>33.2 (24.6–44.7)</td>
<td>0.59 (0.36–0.95)</td>
</tr>
<tr>
<td>P for difference</td>
<td>533</td>
<td>0.002</td>
<td>0.08</td>
<td>0.74</td>
<td>0.43</td>
</tr>
<tr>
<td>Somatotype at age 10 $^a$</td>
<td></td>
<td>IGF-I</td>
<td>IGFBP-3</td>
<td>IGFBP-1</td>
<td>GH</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>240 (228–253)</td>
<td>4580 (4421–4744)</td>
<td>33.1 (27.4–40.0)</td>
<td>0.47 (0.35–0.64)</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>241 (231–252)</td>
<td>4515 (4394–4640)</td>
<td>28.2 (23.5–33.9)</td>
<td>0.48 (0.38–0.59)</td>
</tr>
<tr>
<td>3</td>
<td>137</td>
<td>239 (228–250)</td>
<td>4457 (4342–4576)</td>
<td>33.6 (29.0–38.8)</td>
<td>0.47 (0.37–0.60)</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>219 (207–233)</td>
<td>4678 (4527–4835)</td>
<td>29.1 (22.8–37.2)</td>
<td>0.60 (0.43–0.84)</td>
</tr>
<tr>
<td>5+</td>
<td>53</td>
<td>203 (186–221)</td>
<td>4804 (4598–5020)</td>
<td>23.5 (18.4–29.9)</td>
<td>0.52 (0.35–0.77)</td>
</tr>
<tr>
<td>P for difference</td>
<td>536</td>
<td>$&lt;0.001$</td>
<td>0.10</td>
<td>0.03</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI at age 18 (kg/m$^2$)</td>
<td></td>
<td>IGF-I</td>
<td>IGFBP-3</td>
<td>IGFBP-1</td>
<td>GH</td>
</tr>
<tr>
<td>$&lt;19$</td>
<td>117</td>
<td>239 (227–250)</td>
<td>4581 (4464–4701)</td>
<td>33.8 (28.2–40.6)</td>
<td>0.45 (0.35–0.58)</td>
</tr>
<tr>
<td>19–20.9</td>
<td>221</td>
<td>239 (231–248)</td>
<td>4516 (4421–4612)</td>
<td>32.7 (28.8–37.1)</td>
<td>0.46 (0.38–0.56)</td>
</tr>
<tr>
<td>21–22.9</td>
<td>156</td>
<td>235 (225–245)</td>
<td>4541 (4315–4671)</td>
<td>29.4 (24.7–35.1)</td>
<td>0.54 (0.43–0.68)</td>
</tr>
<tr>
<td>23–24.9</td>
<td>60</td>
<td>205 (187–225)</td>
<td>4676 (4484–4877)</td>
<td>22.3 (16.6–29.9)</td>
<td>0.64 (0.43–0.94)</td>
</tr>
<tr>
<td>$\geq 25$</td>
<td>37</td>
<td>210 (192–229)</td>
<td>4780 (4506–5070)</td>
<td>24.0 (17.7–32.5)</td>
<td>0.39 (0.25–0.60)</td>
</tr>
<tr>
<td>P for trend</td>
<td>591</td>
<td>0.005</td>
<td>0.81</td>
<td>0.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Bra cup size at age 20</td>
<td></td>
<td>IGF-I</td>
<td>IGFBP-3</td>
<td>IGFBP-1</td>
<td>GH</td>
</tr>
<tr>
<td>A or less</td>
<td>189</td>
<td>241 (233–249)</td>
<td>4562 (4467–4658)</td>
<td>31.5 (27.5–36.1)</td>
<td>0.49 (0.40–0.61)</td>
</tr>
<tr>
<td>B</td>
<td>255</td>
<td>230 (222–239)</td>
<td>4598 (4504–4693)</td>
<td>31.6 (28.0–35.6)</td>
<td>0.52 (0.44–0.62)</td>
</tr>
<tr>
<td>C</td>
<td>106</td>
<td>227 (214–240)</td>
<td>4520 (4367–4679)</td>
<td>27.1 (21.7–34.0)</td>
<td>0.48 (0.36–0.63)</td>
</tr>
<tr>
<td>D or more</td>
<td>25</td>
<td>220 (192–252)</td>
<td>4549 (4237–4885)</td>
<td>21.5 (14.8–31.4)</td>
<td>0.41 (0.24–0.70)</td>
</tr>
<tr>
<td>P for difference</td>
<td>575</td>
<td>0.21</td>
<td>0.94</td>
<td>0.06</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI at blood draw (kg/m$^2$)</td>
<td></td>
<td>IGF-I</td>
<td>IGFBP-3</td>
<td>IGFBP-1</td>
<td>GH</td>
</tr>
<tr>
<td>$&lt;20$</td>
<td>62</td>
<td>254 (239–271)</td>
<td>4444 (4270–4625)</td>
<td>50.7 (41.6–61.7)</td>
<td>0.51 (0.34–0.77)</td>
</tr>
<tr>
<td>20–22.4</td>
<td>156</td>
<td>235 (226–245)</td>
<td>4522 (4410–4636)</td>
<td>41.1 (36.3–46.5)</td>
<td>0.57 (0.46–0.72)</td>
</tr>
<tr>
<td>22.5–24.9</td>
<td>142</td>
<td>236 (226–245)</td>
<td>4462 (4348–4580)</td>
<td>32.9 (28.0–38.7)</td>
<td>0.55 (0.43–0.72)</td>
</tr>
<tr>
<td>25–27.4</td>
<td>88</td>
<td>244 (230–259)</td>
<td>4578 (4397–4767)</td>
<td>25.4 (21.6–29.9)</td>
<td>0.45 (0.34–0.59)</td>
</tr>
<tr>
<td>27.5–29.9</td>
<td>50</td>
<td>216 (197–238)</td>
<td>4638 (4421–4868)</td>
<td>18.4 (14.2–23.9)</td>
<td>0.51 (0.35–0.73)</td>
</tr>
<tr>
<td>$\geq 30$</td>
<td>90</td>
<td>208 (195–222)</td>
<td>4848 (4704–4996)</td>
<td>16.5 (13.4–20.3)</td>
<td>0.32 (0.26–0.40)</td>
</tr>
<tr>
<td>P for trend</td>
<td>588</td>
<td>$&lt;0.001$</td>
<td>0.23</td>
<td>$&lt;0.001$</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Table 2 continued

<table>
<thead>
<tr>
<th>Category definition</th>
<th>N</th>
<th>IGF-I&lt;sup&gt;b&lt;/sup&gt;</th>
<th>IGFBP-3&lt;sup&gt;b&lt;/sup&gt;</th>
<th>IGFBP-1&lt;sup&gt;c&lt;/sup&gt;</th>
<th>GH&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>95</td>
<td>238 (225–252)</td>
<td>4560 (4407–4717)</td>
<td>40.0 (34.8–48.3)</td>
<td>0.62 (0.45–0.85)</td>
</tr>
<tr>
<td>Q2</td>
<td>99</td>
<td>241 (229–255)</td>
<td>4452 (4302–4608)</td>
<td>34.5 (29.3–40.5)</td>
<td>0.56 (0.42–0.75)</td>
</tr>
<tr>
<td>Q3</td>
<td>84</td>
<td>239 (227–253)</td>
<td>4481 (4311–4657)</td>
<td>31.6 (27.0–37.1)</td>
<td>0.55 (0.39–0.76)</td>
</tr>
<tr>
<td>Q4</td>
<td>103</td>
<td>222 (210–235)</td>
<td>4757 (4621–4988)</td>
<td>14.5 (12.1–17.4)</td>
<td>0.37 (0.29–0.48)</td>
</tr>
<tr>
<td>P for trend</td>
<td>381</td>
<td>0.66</td>
<td>0.19</td>
<td>0.0005</td>
<td>0.13</td>
</tr>
<tr>
<td>Waist-to-hip ratio&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>89</td>
<td>243 (230–256)</td>
<td>4538 (4381–4700)</td>
<td>39.4 (33.2–46.8)</td>
<td>0.67 (0.48–0.93)</td>
</tr>
<tr>
<td>Q2</td>
<td>97</td>
<td>229 (217–242)</td>
<td>4565 (4413–4723)</td>
<td>30.5 (25.4–36.6)</td>
<td>0.53 (0.40–0.69)</td>
</tr>
<tr>
<td>Q3</td>
<td>93</td>
<td>243 (229–258)</td>
<td>4490 (4335–4650)</td>
<td>30.7 (25.1–37.6)</td>
<td>0.46 (0.34–0.63)</td>
</tr>
<tr>
<td>Q4</td>
<td>101</td>
<td>227 (215–240)</td>
<td>4658 (4507–4813)</td>
<td>18.3 (14.7–22.7)</td>
<td>0.44 (0.33–0.58)</td>
</tr>
<tr>
<td>P for trend</td>
<td>380</td>
<td>0.57</td>
<td>0.77</td>
<td>0.002</td>
<td>0.16</td>
</tr>
<tr>
<td>Height (1976)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>100</td>
<td>231 (219–244)</td>
<td>4616 (4466–4772)</td>
<td>31.6 (27.0–36.9)</td>
<td>0.54 (0.40–0.71)</td>
</tr>
<tr>
<td>Q2</td>
<td>162</td>
<td>225 (215–237)</td>
<td>4626 (4501–4755)</td>
<td>27.8 (23.4–33.0)</td>
<td>0.48 (0.39–0.60)</td>
</tr>
<tr>
<td>Q3</td>
<td>158</td>
<td>239 (230–249)</td>
<td>4557 (4451–4666)</td>
<td>31.6 (26.9–37.2)</td>
<td>0.46 (0.38–0.57)</td>
</tr>
<tr>
<td>Q4</td>
<td>172</td>
<td>234 (224–244)</td>
<td>4495 (4391–4601)</td>
<td>30.7 (26.4–35.7)</td>
<td>0.50 (0.40–0.63)</td>
</tr>
<tr>
<td>P for trend</td>
<td>592</td>
<td>0.96</td>
<td>0.41</td>
<td>0.35</td>
<td>0.86</td>
</tr>
</tbody>
</table>

<sup>a</sup>All factors are adjusted for analysis batch, age, fasting status, time of day blood drawn, drawn month, luteal difference, and duration of OC use. P<sub>s</sub> 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 Z<sub>1</sub> vs Z<sub>5</sub>).

<sup>b</sup>Models are mutually adjusted for IGF-I/IGFBP-3.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>Among women (n=538) who were born full-term.

<sup>f</sup>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 (Juel et al. 1994b), 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 (Juel et al. 1994a) 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/m²) 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.

Acknowledgements

This research was supported by National Cancer Institute (NCI) Grants CA67262 and CA50385 and by the NCI Specialized Program of Research Excellence (SPORE) in breast cancer at the Channing Laboratory. Dr Pollak was partially supported by...
grants from the Translational Acceleration Program of the Canadian Breast Cancer Research Alliance. Dr Eliassen was supported by Cancer Education and Career Development Grant R25 CA 098566-2 from the National Cancer Institute. We are indebted to the participants of the ongoing NHS II for their continuing outstanding dedication to the study. We would like to express our thanks for the valuable input and insights of Drs Graham Colditz, David Hunter (Project Director of the NHSII cohort) and Walter Willett (Principal Investigator of the NHSII). We are also indebted to Helena Ellis, Ellen Hertzmark, and Victor Pontes for their technical assistance. No authors have declared a financial interest in a company whose product was studied in the work presented in this paper.

References


Jernstrom H & Barrett-Connor E 1999 Obesity, weight change, fasting insulin, proinsulin, C-peptide, and insulin-like growth factor-I levels in women with and without breast cancer: the Rancho Bernardo Study. *Journal of Women’s Health and Gender-Based Medicine* 8 1265–1272.


Juul A, Main K, Blum WF, Lindholm J, Ranke MB & Skakkebaek NE 1994b The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. *Clinical Endocrinology* 41 85–93.


composition, size at birth, and childhood growth. 


Rogers IS, Gunnell D, Emmett PM, Glynn LR, Dunger DB & Holly JM 2005 Cross-sectional associations of diet and insulin-like growth factor levels in 7- to 8-year-old children. *Cancer Epidemiology, Biomarkers and Prevention* 14 204–212.


Scherhammer ES, Holly JM, Hunter DJ, Pollak MN & Hankinson SE 2006 Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in the Nurses Health Study II. *Endocrine-Related Cancer* 13 583–592.


