Original Contribution

Body Size in Early Life and Adult Levels of Insulin-like Growth Factor 1 and Insulin-like Growth Factor Binding Protein 3

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Body size in early life has been associated with breast cancer risk. This may be partly mediated through the insulin-like growth factor (IGF) pathway. The authors assessed whether birth weight, body fatness at ages 5 and 10 years, and body mass index (BMI; weight (kg)/height $(m)^2$) at age 18 years were associated with plasma concentrations of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 in 6,520 women aged 32–70 years at blood draw from the Nurses' Health Study (1990–2006) and Nurses' Health Study II (1997–2005). Birth weight, body fatness in childhood, and BMI at age 18 years were inversely associated with adult IGF-1 levels. For example, IGF-1 levels were 11.9% lower in women who reported being heaviest at age 10 years than in those who were leanest at age 10 (P-trend < 0.0001). Further, women who reported their birth weight as $\geq$10 pounds ($\geq$4.5 kg) (vs. $<$5.5 pounds ($<$2.5 kg)) had 7.9% lower IGF-1 levels (P-trend $= 0.002$). Women whose BMI at age 18 years was $\geq$30 (vs. $<$20) had 14.1% lower IGF-1 levels (P-trend < 0.0001). Similar inverse associations were observed for insulin-like growth factor binding protein 3. These observations did not vary by adult BMI or menopausal status at blood draw. These findings suggest that altered IGF-1 levels in adulthood may be a mechanism through which early-life body size influences subsequent breast cancer risk.

birth weight; body mass index; breast neoplasms; child; growth; insulin-like growth factor 1; insulin-like growth factor binding protein 3; obesity

Abbreviations: BMI, body mass index; IGF, insulin-like growth factor; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

Body size at birth and at young ages has been consistently associated with breast cancer risk. Greater birth weight is associated with an increased risk of adult breast cancer (reviewed by Michels and Xue (1) and Ruder et al. (2)), while greater body fatness during childhood and adolescence is associated with a decreased breast cancer risk (3) (reviewed by Ruder et al. (2)). These associations appear to be stronger among premenopausal women. The relation of body size in early life with other cancers has been less well-studied. There are no clear associations with youth body size for endometrial or ovarian cancer (4–10), but an increased risk of colorectal cancer among men has been observed (11, 12). The mechanisms underlying these associations are unclear; however, one possibility is that body size in early life may alter cancer risk through the insulin-like growth factor (IGF) pathway.

Insulin-like growth factor 1 (IGF-1) is important for normal growth and development; it has several procarcinogenic properties, such as promoting cell proliferation and inhibiting apoptosis (13). In a recent pooling of 17 cohort studies, women in the highest quintile of IGF-1 had a 28% higher breast cancer risk than those in the lowest quintile (14); there was no difference by menopausal status. Associations for insulin-like growth factor binding protein 3 (IGFBP-3), the major binding protein of IGF-1, were mixed. IGF-1 has also been associated with risks of colon, kidney, ovarian, prostate, and pancreatic cancer (15–19). While early-life body size measures have been associated with IGF-1 levels

measured at birth or in childhood (20–22), little is known about their associations with IGF-1 levels in adulthood.

We previously observed inverse associations between early-life body size and circulating IGF-1 levels in adulthood among premenopausal participants in Nurses' Health Study II (NHSII) (23). In the current analysis, we expand on that study and examine the cross-sectional associations between early-life body size (birth weight, body fatness at ages 5 and 10 years, and BMI at age 18 years) and circulating IGF-1 and IGFBP-3 levels in adulthood among 3,540 premenopausal women and 2,980 postmenopausal women in the Nurses' Health Study (NHS) and NHSII.

MATERIALS AND METHODS

Study populations

The NHS cohort was established in 1976 among 121,700 US female registered nurses aged 30–55 years; NHSII was established in 1989 among 116,430 US female registered nurses aged 25–42 years. All women completed an initial questionnaire about their lifestyle factors, health behaviors, and medical history and have been followed biennially by questionnaire.

From 1989 to 1990, 32,826 NHS participants (ages 43–70 years) provided blood samples and completed a short questionnaire (24). Briefly, women arranged to have their blood drawn and shipped with an ice pack, via overnight courier, to the Channing Laboratory (Boston, Massachusetts), where it was processed and separated into plasma, red blood cell, and white blood cell components.

Between 1996 and 1999, 29,611 NHSII participants (ages 32–54 years) provided blood samples and completed a short questionnaire (25). Briefly, premenopausal women ($n = 18,521$) who had not taken hormones, been pregnant, or lactated within the past 6 months provided blood samples drawn on the third-to-fifth day of their menstrual cycle (follicular phase) and 7–9 days before the anticipated start of their next cycle (luteal phase; called ''timed samples''). Other women ($n = 11,090$) provided a single 30-mL untimed blood sample. Because cyclic variation in IGF-1 levels is modest (26, 27) and the intraclass correlation coefficients were similar for follicular and luteal samples (follicular: 0.69; luteal: 0.83) (28), we analyzed luteal samples from women who gave both luteal and follicular samples. Luteal and untimed samples were shipped and processed identically to the NHS samples. Samples have been stored in liquid nitrogen freezers since collection. These studies were approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital and Harvard School of Public Health (Boston, Massachusetts).

The current analysis included women with blood samples ($n = 6,429$) who were controls from 9 nested case-control studies of plasma IGF-1 and IGFBP-3 levels and risk of various chronic diseases, including benign breast disease (29), breast cancer (30, 31), colorectal cancer (15), colorectal polyps (32), endometriosis (unpublished data), myocardial infarction (33), ovarian cancer (16), pancreatic cancer (17), and type 2 diabetes (unpublished data). We also included baseline samples from a hormone reproducibility study carried out in NHSII over a period of 3 years ($n = 113$) (28). This gave us a total of 6,542 women.

We considered a woman premenopausal at blood collection if 1) she gave timed samples (NHSII only), 2) her menstrual periods had not ceased, or 3) she had at least 1 ovary and was aged 47 years or younger (nonsmokers) or 45 years or younger (smokers) (34). We considered a woman postmenopausal at blood collection if 1) her natural menstrual periods had ceased permanently, 2) she had undergone a bilateral oophorectomy, or 3) she had at least 1 ovary and was aged 56 years or older (nonsmokers) or 54 years or older (smokers). The age cutoffs were chosen because they represented the age at which 90% of women with intact ovaries in the cohorts were premenopausal or postmenopausal, respectively. The remaining women, most of whom had undergone a simple hysterectomy and were aged 48–55 years, were considered to have an unknown menopausal status.

Exposure and covariate information

Information on exposures and covariates was obtained from the questionnaire completed at blood collection and the biennial study questionnaires. Birth weight information was collected in 1992 (NHS) and 1991 (NHSII). Women were asked about their birth weight in the following categories: <5 pounds (<2.3 kg), 5–5.5 pounds (2.3–2.5 kg) (NHS), <5.5 pounds (<2.5 kg) (NHSII), 5.5–6.9 pounds (2.5–3.1 kg), 7–8.4 pounds (3.2–3.8 kg), 8.5–9.9 pounds (3.9–4.4 kg), and ≥10 pounds (≥4.5 kg). The bottom 2 categories in the NHS were collapsed to correspond to the categories used in NHSII. In the NHS, the correlation between the participant's self-reported birth weight and that reported by her mother (considered the gold standard) was 0.77 (35).

In 1988 (NHS) and 1989 (NHSII), women were asked to choose one of 9 diagrams (somatotypes) (36) that best depicted their body fatness at ages 5 and 10 years, with level 9 being the heaviest and level 1 being the leanest (Figure 1). Among older women (ages 71–76 years) in another study population, the correlations between recalled somatotype and measured BMI were 0.57 at age 5 years, 0.70 at age 10 years, and 0.64 at age 20 years; the correlations were similar after controlling for current BMI (37). BMI at blood draw and at age 18 years (asked in 1980 for NHS and in 1989 for NHSII) was calculated as self-reported weight in kilograms divided by self-reported height (collected at baseline) in meters squared. Details about blood collection date, time, fasting status, weight, and use of postmenopausal hormones at the time of blood collection were reported on the blood questionnaire.

Laboratory assays

Total IGF-1 and IGFBP-3 levels were assayed in the laboratory of Dr. Michael Pollak by means of enzyme-linked immunosorbent assay after acid extraction, using reagents from Diagnostic Systems Laboratory (Webster, Texas) in 28 batches from 1997 through 2010. Masked split specimens included within each batch were used to calculate the coefficient of variation within batches; coefficients of

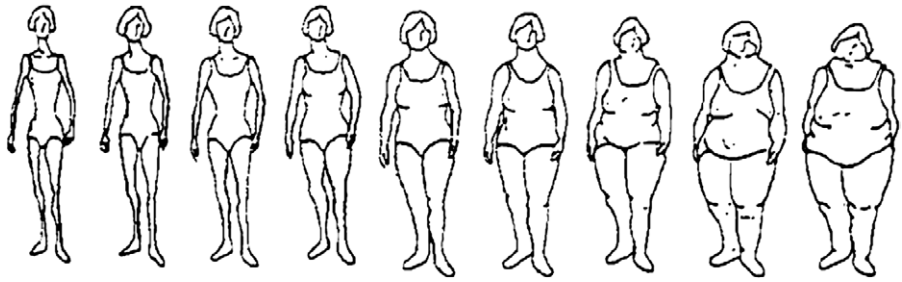

Figure 1. Figure drawing used to assess body fatness at ages 5, 10, and 20 years in the Nurses' Health Study (1988) and Nurses' Health Study II (1989). (Reproduced from Stunkard et al. (36) with permission from Lippincott Williams & Wilkins, Philadelphia, Pennsylvania).

variation were below 15% for 22 of the 28 batches. The highest coefficients of variation were 21.4 and 16.6 for IGF-1 and IGFBP-3, respectively.

Statistical analysis

We identified statistical outliers using the generalized extreme studentized deviate many-outlier detection approach within each batch (38); 2 women with improbable IGF-1 concentrations, 17 women with improbable IGFBP-3 concentrations, and 3 women with improbable values for both IGF-1 and IGFBP-3 were identified as outliers and excluded. Therefore, a total of 6,520 healthy controls were included in these analyses. Mean IGF-1 and IGFBP-3 concentrations in quality control samples differed by batch, indicating that there was some laboratory drift over time. Therefore, we adjusted IGF-1 and IGFBP-3 levels for batch according to the methods described by Rosner et al. (39).

Generalized linear models were used to estimate mean IGF-1 and IGFBP-3 concentrations across categories of predictive variables using natural log-transformed IGF-1 and IGFBP-3 values, adjusting for potential confounders. We exponentiated the results to obtain geometric mean values, and results are reported on the original scale. We conducted tests for trend by modeling exposure measures as continuous variables and calculating the Wald statistic. To assess potential effect modification, we stratified our analyses by birth weight ($<$7 pounds ($<$3.2 kg) vs. $\geq$7 pounds ($\geq$3.2 kg)), body fatness at age 10 years (diagrams 1–4 vs. diagrams $\geq$5), and menopausal status (premenopausal vs. postmenopausal) and tested for interaction using multiplicative terms.

Results of all analyses were adjusted for adult height (inches), age at blood draw (years; continuous), menopausal status/postmenopausal hormone use (postmenopausal/using postmenopausal hormones, postmenopausal/not using postmenopausal hormones, or premenopausal/hormone use unknown), month of blood draw (1–12), time of day of blood draw (8 AM–12 PM, 1 PM–8 PM, or 9 PM–7 AM), and fasting status ($>$8 hours vs. $\leq$8 hours). Because we accounted for laboratory batch using the methods described by Rosner et al. (39), laboratory batch was not included in the model. In secondary analyses, we further adjusted each hormone (IGF-1 and IGFBP-3) for the other and for BMI at blood draw. We considered other potential confounders such as duration of oral contraceptive use, hysterectomy status, history of benign breast disease, family history of breast cancer or colon cancer, parity, smoking, age at menarche, menstrual cycle regularity, breastfeeding, adult diet, and physical activity; however, these factors did not change the results and therefore were not included in the final models. All P values were 2-sided and were considered statistically significant if $\leq$0.05. All analyses were conducted using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The median IGF-1 level was 182 ng/mL (5th–95th percentile range, 89–342), and the median IGFBP-3 level was 4,415 ng/mL (5th–95th percentile range, 2,657–6,298) (Table 1); IGF-1 and IGFBP-3 were moderately correlated ($r = 0.55$, $P < 0.0001$). Median age at blood draw was 51 years. Median BMI at age 18 years was 20.8, and at blood draw it was 24.3. At blood collection, 45.7% of participants were postmenopausal; of these, 48.7% were current users of postmenopausal hormones. Approximately two-thirds of participants were from the NHS cohort.

All 4 measures of early-life body fatness were inversely associated with circulating IGF-1 concentrations. For example, women who reported their body fatness at age 10 years as diagrams 6–9 (heaviest) had 11.9% lower IGF-1 levels than women who reported their size as diagram 1 (leanest) (P-trend < 0.0001; Table 2). Results were similar for body size at age 5 years and for BMI at age 18 years. Women who reported their birth weight as $\geq$10 pounds ($\geq$4.5 kg), versus $<$5.5 pounds ($<$2.5 kg), had 7.9% lower IGF-1 levels (P-trend $= 0.002$). Although the trends remained statistically significant, adjustment for BMI at blood draw attenuated the associations, particularly for birth weight and for BMI at age 18 years (P-trend $= 0.05$ and P-trend $= 0.01$, respectively). Adjustment for IGFBP-3 attenuated the association between IGF-1 and birth weight (P-trend $= 0.07$) but did not alter the associations with the other early-life body size variables (data not shown).

Associations with IGFBP-3 were similar to those for IGF-1: Increased early-life body size was associated with decreased IGFBP-3 levels (Table 3). For example, women who reported a birth weight of $\geq$10 pounds ($\geq$4.5 kg) had

Table 1. Characteristics of Participants at Blood Draw, Nurses' Health Study (1990–2006) and Nurses' Health Study II (1997–2005)

Characteristic	Nurses' Health Study (n = 4,337)				Nurses' Health Study II (n = 2,183)				Both Studies Combined (n = 6,520)			
	No.	%	Median	5th–95th Percentile Range	No.	%	Median	5th–95th Percentile Range	No.	%	Median	5th–95th Percentile Range
Insulin-like growth factor 1, ng/mL			160	83–301			234	119–379			182	89–342
Insulin-like growth factor binding protein 3, ng/mL			4,208	2,540–6,098			4,811	2,951–6,517			4,415	2,657–6,298
Adult height, inches[a]			64	61–68			65	61–69			65	61–69
Age at blood draw, years			57	45–68			44	36–51			51	39–67
Age at menarche, years[b]			13	10–15			12	10–15			12	10–15
Body mass index[c] at age 18 years[b]			21	18–27			21	17–27			21	18–27
Body mass index at blood draw[b]			24	20–34			24	19–38			24	20–35
Birth weight $\geq$7 pounds ($\geq$3.2 kg)[d]	2,006	46.3			1,192	54.6			3,198	59.8		
Somatotype $\geq$6 at age 5 years[b]	72	1.7			38	1.7			110	1.7		
Somatotype $\geq$6 at age 10 years[b]	112	2.6			61	2.8			173	2.7		
Menopausal status/PMH use												
Postmenopausal PMH user	1,238	28.6			212	9.7			1,450	22.2		
Postmenopausal PMH nonuser	1,509	34.8			21	1.0			1,530	23.5		
Premenopausal/PMH use unknown	1,590	36.7			1,950	89.3			3,540	54.3		

Abbreviations: NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; PMH, postmenopausal hormone.

[a] 1 inch = 2.5 cm.

[b] Data were missing for 0–211 NHS participants and 5–40 NHSII participants (total n's ranged from 6,290 to 6,515).

[c] Weight (kg)/height $(m)^2$.

[d] Data were missing for 942 NHS participants and 232 NHSII participants (total n = 5,346).

Table 2. Associations Between Early-Life Body Size and Adult Insulin-like Growth Factor 1 Levels in 6,520 Women From the Nurses' Health Study (1990–2006) and Nurses' Health Study II (1997–2005)

Variable	No. of Participants	Model 1[a]			Model 2[b]		
		Geometric Mean, ng/mL	95% CI	*P*-Trend	Geometric Mean, ng/mL	95% CI	*P*-Trend
Birth weight, pounds (kg)							
<5.5 (<2.3)	517	190	182, 198		191	183, 199	
5.5–6.9 (2.5–3.1)	1,631	191	185, 197		191	185, 198	
7–8.4 (3.2–3.8)	2,490	185	179, 191		187	182, 194	
8.5–9.9 (3.9–4.4)	587	185	178, 193		188	181, 196	
≥10 (≥4.5)	121	175	164, 187	0.002	181	169, 194	0.05
Somatotype at age 5 years							
1 (leanest)	2,088	191	179, 204		191	179, 204	
2	1,691	189	176, 202		189	177, 202	
3	1,342	186	174, 199		189	176, 202	
4	741	182	170, 195		185	173, 198	
5	323	176	163, 190		180	167, 194	
≥6 (heaviest)	110	174	162, 186	<0.0001	182	170, 195	<0.001
Somatotype at age 10 years							
1 (leanest)	1,638	193	183, 203		192	182, 203	
2	1,790	189	180, 200		189	180, 200	
3	1,290	187	177, 197		189	179, 199	
4	935	182	172, 192		185	175, 196	
5	505	176	166, 187		180	170, 191	
≥6 (heaviest)	173	170	160, 180	<0.0001	178	168, 188	<0.0001
Body mass index[c] at age 18 years							
<20	2,215	192	187, 198		190	185, 196	
20–22.9	2,809	186	183, 190		188	184, 192	
23–24.9	704	182	177, 187		187	181, 193	
25–29.9	469	173	167, 179		182	175, 188	
≥30	93	165	154, 177	<0.0001	180	167, 193	0.01

Abbreviation: CI, confidence interval.

[a] Results were adjusted for age at blood draw, adult height (inches), month and time of day of blood draw, fasting status, menopausal status/postmenopausal hormone use at blood draw, and cohort. Laboratory batch was accounted for using statistical methods described by Rosner et al. (39).

[b] Results were adjusted for the variables in model 1 and body mass index at blood draw (continuous).

[c] Weight (kg)/height $(m)^2$.

5.6% lower IGFBP-3 levels than women who reported a birth weight of <5.5 pounds (<2.5 kg) (P-trend = 0.004). Similar associations were observed for the other body size variables. Adjustment for BMI at the time of blood draw tended to strengthen the associations. Adjustment for IGF-1 attenuated all of the observed associations with IGFBP-3 such that there were no longer statistically significant trends (data not shown).

Associations between early-life body size and adult IGF-1 or IGFBP-3 level did not differ by menopausal status (all P's for interaction > 0.16), although the trends were suggestively stronger in premenopausal women (Table 4). For example, for diagrams 6–9 at age 10 years as compared with diagram 1, IGF-1 levels were 8.6% lower among premenopausal women versus 2.6% lower among postmenopausal women. Similar differences were noted when data were stratified by either cohort (stronger in NHSII) or age (stronger in younger women; data not shown). The differences in association by study cohort, age at blood draw, and menopausal status were very similar because women in NHS were predominantly older and postmenopausal at blood draw, whereas NHSII participants were predominantly younger and premenopausal at blood draw. The associations for body size at ages 5 and 10 years, as well as BMI at age 18 years, were similar for women who weighed <7 pounds (<3.2 kg) at birth and women who weighed ≥7 pounds (≥3.2 kg) at birth (data not shown). Further, the associations for birth weight, body size at age 5 years, and BMI at age 18 years were similar when results were stratified by body size at age 10 years (data not shown). We observed no interactions with BMI at the time of blood draw, nor was there an interaction with postmenopausal hormone use among postmenopausal women (data not shown).

Table 3. Associations Between Early-Life Body Size and Adult Insulin-like Growth Factor Binding Protein 3 Levels in 6,520 Women From the Nurses' Health Study (1990–2006) and Nurses' Health Study II (1997–2005)

Variable	No. of Participants	Model 1[a]			Model 2[b]		
		Geometric Mean, ng/mL	95% CI	*P*-Trend	Geometric Mean, ng/mL	95% CI	*P*-Trend
Birth weight, pounds (kg)							
<5.5 (<2.3)	517	4,298	4,191, 4,407		4,306	4,198, 4,416	
5.5–6.9 (2.5–3.1)	1,631	4,250	4,164, 4,337		4,258	4,172, 4,346	
7–8.4 (3.2–3.8)	2,490	4,218	4,136, 4,301		4,229	4,146, 4,314	
8.5–9.9 (3.9–4.4)	587	4,197	4,096, 4,301		4,206	4,104, 4,311	
≥10 (≥4.5)	121	4,059	3,897, 4,227	0.004	4,075	3,910, 4,248	0.007
Somatotype at age 5 years							
1 (leanest)	2,088	4,261	4,092, 4,436		4,274	4,103, 4,452	
2	1,691	4,210	4,043, 4,384		4,222	4,052, 4,399	
3	1,342	4,215	4,046, 4,390		4,219	4,048, 4,397	
4	741	4,230	4,056, 4,411		4,227	4,051, 4,410	
5	323	4,086	3,906, 4,275		4,093	3,911, 4,284	
≥6 (heaviest)	110	4,232	4,056, 4,415	0.01	4,205	4,028, 4,389	0.002
Somatotype at age 10 years							
1 (leanest)	1,638	4,267	4,131, 4,408		4,283	4,142, 4,428	
2	1,790	4,216	4,082, 4,355		4,229	4,091, 4,371	
3	1,290	4,227	4,090, 4,368		4,230	4,091, 4,374	
4	935	4,215	4,075, 4,358		4,220	4,078, 4,366	
5	505	4,103	3,959, 4,252		4,099	3,953, 4,249	
≥6 (heaviest)	173	4,178	4,036, 4,326	0.002	4,155	4,010, 4,304	<0.001
Body mass index[c] at age 18 years							
<20	2,215	4,258	4,182, 4,336		4,283	4,205, 4,363	
20–22.9	2,809	4,230	4,181, 4,280		4,233	4,183, 4,284	
23–24.9	704	4,223	4,149, 4,298		4,208	4,130, 4,287	
25–29.9	469	4,164	4,080, 4,251		4,126	4,034, 4,219	
≥30	93	4,089	3,917, 4,269	0.02	4,012	3,834, 4,197	<0.001

Abbreviation: CI, confidence interval.

[a] Results were adjusted for age at blood draw, adult height (inches), month and time of day of blood draw, fasting status, menopausal status/postmenopausal hormone use at blood draw, and cohort. Laboratory batch was accounted for using statistical methods described by Rosner et al. (39).

[b] Results were adjusted for the variables in model 1 and body mass index at blood draw (continuous).

[c] Weight (kg)/height $(m)^2$.

DISCUSSION

In this study, body size in early life was inversely associated with circulating IGF-1 and IGFBP-3 concentrations in adulthood. Women in the highest categories of body fatness had approximately 10% lower IGF-1 levels than women who were leanest in youth and adolescence. After adjustment for BMI at blood draw, these associations were somewhat attenuated but persisted. Associations were more modest for IGFBP-3. We observed no strong evidence that the association between early-life body size and IGF-1 or IGFBP-3 differed by menopausal status, age, or study cohort.

Several groups have examined the relation between birth weight and adult IGF-1 levels (40–44). Although most reported no association between birth weight and circulating IGF-1, Jernström and Olsson (44) reported an inverse association, in agreement with our findings. However, this study was small ($n = 40$) and the women were aged 19–25 years. Notably, in our previous analysis of early-life body size and adult hormone levels (23), we observed a suggestion of a positive association between birth weight and adult IGF-1, a finding which was not replicated with the larger sample size here. It is possible that a large sample size is needed to detect the modest inverse association between birth weight and IGF-1 that we observed here. To our knowledge, fewer inquiries into the association between early-life body size and adult IGF-1 and IGFBP-3 levels have been conducted (40, 43, 45). One study found no association with adiposity at age 1 year or 5 years (40), while another found an inverse association only among persons who were lean as adults

Table 4. Associations Between Early-Life Body Size and Adult Geometric Mean IGF-1 and IGFBP-3 Levels, by Menopausal Status, in 6,520 Women From the Nurses' Health Study (1990–2006) and Nurses' Health Study II (1997–2005)[a]

	Premenopausal Women			Postmenopausal Women		
	No.	IGF-1, ng/mL	IGFBP-3, ng/mL	No.	IGF-1, ng/mL	IGFBP-3, ng/mL
Birth weight, pounds (kg)						
<5.5 (<2.3)	226	195	4,261	241	154	4,226
5.5–6.9 (2.5–3.1)	817	191	4,221	659	157	4,162
7–8.4 (3.2–3.8)	1,217	191	4,201	1,029	150	4,101
8.5–9.9 (3.9–4.4)	293	189	4,180	241	154	4,078
≥10 (≥4.5)	42	177	3,997	68	145	3,958
P-trend		0.16	0.09		0.08	0.01
Somatotype at age 5 years						
1	750	195	4,263	1,147	152	4,105
2	853	190	4,196	690	154	4,102
3	693	189	4,204	535	152	4,058
4	373	187	4,231	303	149	4,083
5	141	186	4,159	146	141	3,830
≥6	48	186	4,244	50	139	4,012
P-trend		0.01	0.31		0.03	0.01
Somatotype at age 10 years						
1	586	198	4,269	898	151	4,127
2	862	191	4,198	778	153	4,113
3	631	189	4,191	559	151	4,097
4	462	187	4,245	380	150	4,060
5	252	187	4,175	203	139	3,829
≥6	83	181	4,217	70	147	4,041
P-trend		0.001	0.37		0.03	0.001
Body mass index[b] at age 18 years						
≤19.9	1,099	192	4,235	907	153	4,171
20–22.9	1,209	192	4,237	1,341	151	4,069
23–24.9	307	191	4,257	339	151	4,036
25–29.9	210	188	4,213	212	145	3,919
≥30	47	183	4,024	40	147	3,917
P-trend		0.44	0.55		0.08	<0.001

Abbreviations: IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3.

[a] Results were adjusted for age at blood draw, adult height (inches), month and time of day of blood draw, fasting status, cohort, and body mass index at blood draw (continuous). Laboratory batch was accounted for using statistical methods described by Rosner et al. (39).

[b] Weight (kg)/height $(m)^2$.

(43). In a study of 728 participants, nonsignificant inverse associations between childhood BMI and adult IGF-1 (P-trend = 0.09) and IGFBP-3 (P-trend = 0.13) were observed (45). In this study, the adults were, on average, about 20 years older (mean age = 71 years) than the adults in the present study when their IGF-1 and IGFBP-3 levels were measured, suggesting that the inverse relation between childhood size and adult IGF-1 levels persists into old age.

In utero and early-life exposures have been the subjects of much investigation. Birth weight, a proxy for in utero exposures, has been linked consistently to increased premenopausal breast cancer risk. In a recent meta-analysis, Michels and Xue (1) estimated the relative risk in the highest birth weight category (vs. the lowest) to be 1.25 (95% confidence interval: 1.14, 1.38) for premenopausal women, but they found no association among postmenopausal women. By contrast, increasing body fatness in childhood and adolescence has been associated with decreased breast cancer risk in a number of studies (3) (reviewed by Ruder et al. (2)). In the NHS and NHSII, women in the highest body fatness categories (somatotypes 6–9) at age 5 years had a statistically significant decrease in breast cancer risk compared with those in the lowest category (3). Similar relations were observed for body fatness at ages 10 and 20 years (for all associations, P-trend < 0.0001). These results suggest that early-life body size plays an important role in future breast

cancer risk; however, the mechanisms through which early-life body size may act are unclear.

One possible mechanism is that early-life exposures may be involved in establishing set points of hormone levels later in life (reviewed by Michels and Xue (1) and Schernhammer et al. (23)). Although greater adiposity in childhood has been associated with increased IGF-1 measured concurrently (22, 46), the inverse association with circulating IGF-1 in adulthood suggests that the association between body size and IGF-1 levels may change over time. This suggests that early-life exposures could have long-term effects on the IGF pathway, which, in turn, could influence later cancer risk. For example, it has been hypothesized that decreased nutrition to the fetus causes permanent reprogramming of IGF signaling (47). However, the mechanism driving the change in the direction of the association between childhood size and IGF-1 levels measured in childhood and adulthood is unclear. One hypothesis may be that increased adiposity in childhood causes negative feedback via the pituitary gland, resulting in lower long-term growth hormone/IGF levels (23).

Early-life body size and the IGF pathway also may act via mammographic density. Mammographic density is associated with greatly increased breast cancer risk (48), but the mechanisms that link mammographic density and breast cancer are not well understood (49). In the NHS, increased childhood body fatness was inversely associated with mammographic density ($P < 0.001$) (50). In addition, increased adult IGF-1 levels have been associated with increased breast density, particularly among premenopausal women (51–54). Although it is plausible that early-life exposures have independent associations with IGF-1 and mammographic density in adulthood, our findings suggest that childhood body size may act through the IGF pathway to influence mammographic density, which in turn is associated with increased breast cancer risk.

Other mechanisms through which early-life body size may act on breast cancer risk are also plausible. Although early-life exposures may affect sex steroid hormone levels in adults, few associations between early-life body size and adult circulating sex steroid hormone levels were observed in NHSII (55). Increasing body fatness at ages 5 and 10 years was associated with decreased plasma prolactin levels in postmenopausal women (56) but not premenopausal women (55). Prolactin, a growth hormone, has been linked to breast cancer risk (57), indicating that altering prolactin concentrations may be another pathway through which early-life body size may affect breast cancer.

The major strength of this study was its large sample size, with adequate power to detect modest associations and to evaluate effect modification; however, there were several limitations. First, IGF-1 and IGFBP-3 were measured in multiple batches over several years, with substantially different mean levels across batches, even when adjusted for age. However, the associations were consistent across batches, indicating that batch-to-batch variability did not influence the results. Further, the single measurements of IGF-1 and IGFBP-3 limited our ability to evaluate associations over time within the same woman. However, the intraclass correlation coefficient over 2–3 years in premenopausal women was high (the range of intraclass correlation coefficients was 0.69–0.83 for IGF-1 and 0.69–0.76 for IGFBP-3 over the course of the menstrual cycle) (28), indicating that a single measure is a good approximation of long-term IGF-1 and IGFBP-3 levels. In addition, IGF-1 and IGFBP-3 values were correlated, so results from the mutually adjusted analyses may have been unstable because of collinearity. However, the correlation was moderate and the sample size was large, so collinearity is unlikely to have had a substantial effect on the observed associations. The association between IGF-1 and early-life body size changed very little when adjusting for IGFBP-3, although the association between IGFBP-3 and early-life body size was attenuated after adjustment for IGF-1. As such, it is possible that the relation with IGF-1 is the more important biologic association.

Self-reported childhood body fatness may be subject to misclassification because of the amount of time elapsed between childhood and response to the questionnaire. In addition, self-reported size may be influenced by current body size; women may report a size more closely related to their current size than their childhood size. However, in a validation study of self-reported childhood body fatness, the correlation between reported and measured childhood body fatness ranged from 0.48 to 0.68 and did not change substantially when adjusted for current BMI (37), indicating only modest misclassification due to poor recall or current BMI. Any error due to misclassification would likely be nondifferential with respect to IGF-1 and IGFBP-3 and would therefore underestimate the true associations. Nevertheless, misclassification may be an important source of error in this study. Additionally, we could not account for many important factors in our analysis—namely, genetic variability (58–60), glucose levels (60), and stress (61, 62). These factors should be accounted for in future studies.

In summary, our results suggest that birth weight and body size during childhood and adolescence are associated with circulating IGF-1 and IGFBP-3 concentrations in adulthood. This may help to explain the mechanism underlying the association between childhood body fatness and breast cancer risk. However, the relation between birth weight and adult IGF-1 suggests that the biologic mechanisms between in utero exposures and cancer risk in later life are complex. Future studies, with repeated samples taken at defined intervals in childhood, adolescence, and adulthood, will help to elucidate the biologic pathways through which body size, particularly in early life, may affect cancer risk.

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