Height and Body Size in Childhood, Adolescence, and Young Adulthood and Breast Cancer Risk According to Molecular Subtype in the Nurses’ Health Studies

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Abstract
Height and body size in childhood and young adulthood have been consistently associated with breast cancer risk; whether associations differ across molecular subtypes is unclear. In a pooled analysis of the Nurses’ Health Studies, we prospectively examined the association of four exposures: height, body mass index (BMI) at the age of 18 years, childhood and adolescent somatypes, with breast cancer risk according to molecular subtypes defined by immunohistochemical markers. We used multivariable-adjusted Cox proportional hazards regression to estimate HRs and 95% confidence intervals (CI). We identified 2,983 luminal A, 1,281 luminal B, 318 HER2-enriched, 408 basal-like, and 128 unclassified tumors. Height was positively associated with all subtypes ($P_{\text{heterogeneity}} = 0.78$). BMI at the age of 18 ($P_{\text{heterogeneity}} = 0.001$), childhood ($P_{\text{heterogeneity}} = 0.51$), and adolescent somatotype ($P_{\text{heterogeneity}} = 0.046$) were inversely associated, but with differences in magnitude of association. BMI at the age of 18 of $\geq 25$ kg/m² (compared with $20–21.9$ kg/m²) was associated with a 52% decreased risk of HER2-enriched (HR, 0.48; 95% CI, 0.26–0.91; $P_{\text{trend}} < 0.0001$) and 39% reduced risk of basal-like tumors (HR, 0.61; 95% CI, 0.36–1.02; $P_{\text{trend}} = 0.008$). Compared with the lowest category, women in the highest adolescent body size category were 71% less likely to develop HER2-enriched (HR, 0.29; 95% CI, 0.10–0.85; $P_{\text{trend}} = 0.0005$) and 60% less likely to develop basal-like (HR, 0.40; 95% CI, 0.17–0.95; $P_{\text{trend}} = 0.0008$). Height was positively associated with risk of all breast cancer molecular subtypes. BMI at 18 years and childhood and adolescent were inversely associated with risk of most breast cancer molecular subtypes with somewhat stronger associations with HER2-enriched and basal-like subtypes. Cancer Prev Res; 9(9); 732–8. ©2016 AACR.

Introduction
Body size in childhood and adolescence, body mass index (BMI) in young adulthood, and height are established risk factors for pre- and postmenopausal breast cancer (1–3). However, breast cancer is a heterogeneous disease with multiple subtypes of differing prognosis defined by tumor characteristics such as estrogen receptor (ER) and progesterone receptor (PR) status (4, 5). Inverse associations between childhood and adolescent body fatness, BMI in young adulthood and breast cancer have been observed for estrogen receptor–positive (ER+) tumors (4, 16); refs. 1, 2) and negative (ER-) breast cancer. Height is positively associated with ER+ tumors, whereas associations with ER- tumors have been inconsistent, with both positive (6), and null associations (7) observed. Beyond ER and PR, molecular subtypes defined by gene expression or immunohistochemical markers have been explored with respect to breast cancer etiology and prognosis (6–10) and their relationships with risk factors differ (11). Molecular subtypes include luminal A and B, human epidermal growth factor receptor 2 (HER2)-enriched, basal-like and unclassified cancers (4, 12, 13). Few studies have examined associations between body fatness in childhood and adolescence, BMI in young adulthood, and height, and molecular subtypes (7, 14).

Animal data, epidemiologic studies including examinations of effects of radiation exposure on breast cancer risk (15, 16), and risk prediction models (17, 18), have shown that breast tissue is particularly susceptible to exposures in early life, with the period between menarche and first birth most vulnerable (19). This is because the mammary gland goes through extensive morphological changes during early life. Ducts that were developed before birth grow and branch rapidly as a result of hormonal stimulation...
with final differentiation achieved during pregnancy and lactation (20, 21). The consistency of association between early life and young adulthood body fatness and breast cancer risk across strata of age and menopausal status suggests that greater body fatness at young ages may be associated with permanent changes to breast tissue during this important development period that results in a long-term reduction in breast cancer risk. Similarly, adult height is attained during adolescence or young adulthood and may reflect the concentration of growth factors during that phase of life and beyond (22).

We prospectively examined the association between body fatness in childhood and adolescence, BMI at the age of 18, and incidence of breast cancer according to molecular subtype in a pooled analysis of women in the Nurses’ Health Study (NHS) and the Nurses’ Health Study II (NHSII).

Materials and Methods

Study population

NHS and NHSII are two ongoing prospective cohort studies of primarily white (>95%) female registered nurses across the United States. NHS began in 1976 with 121,701 female registered between the ages of 30 and 55 years at baseline. NHSII began in 1989 with 116,430 female registered nurses ages 25 to 42 years. Women are sent follow-up questionnaires every 2 years to obtain information about health behaviors, disease status, medical care, and treatment. Cumulative follow-up rates are high (>90%) in both cohorts.

Exposure assessment

Height and BMI at age 18. Women self-reported height in 1976 (NHS) or 1989 (NHSII) and weight at age 18 in 1980 (NHS) or 1989 (NHSII). Using records from physical examinations conducted at college or nursing school entrance from 118 NHSII participants, the validity of recalled weight at age 18 and self-reported current height was previously assessed (23). On average, participants underestimated weight at age 18 by 1.4 kg. The correlation between recalled and measured weight at age 18 was 0.87.

Childhood and adolescent somatotype. In 1988 (NHS) and 1989 (NHSII), women were asked to select the figure from a validated 9-figure drawing which best corresponded to their body fatness at age 5, 10, and 20 (24, 25). The Third Harvard Growth Study compared women’s recalled figure at 15 with measured BMI at age 15. They found that BMI at age 15 increased linearly (19 to 32 kg/m²) with each level of the figure (levels 1–7; no participants selected figure 8 or 9; ref. 26). We averaged somatotypes across 2 ages to create measures for childhood (ages 5 and 10) and adolescent (ages 10 and 20) body fatness. Because of sparse data, we collapsed the top 5 categories of each measure creating a top figure 5 through 9.

Breast cancer case assessment

Incident breast cancer diagnoses on each biennial questionnaire are, with participant or next of kin permission, confirmed through medical record review. From each woman, we request pathology reports and abstract information on tumor characteristics including grade, histologic type, metastases, and hormone receptor status. Pathology reports were available for >95% of the breast cancer cases in this study. Cases among deceased respondents are identified via review of death certificates and medical records. Nearly all (99%) of self-reported breast cancers are confirmed after medical record review. In-situ cases were censored at date of diagnosis and only invasive cases were included in the analysis.

Subtype classification

Tissue block collection and tissue microarray (TMA) construction were described in detail previously (27, 28). In brief, we obtained archived formalin-fixed, paraffin-embedded tissue blocks for approximately 70% of incident primary breast cancer cases from 1976 to 2006. Women with available tissue blocks were similar with respect to breast cancer risk factors and tumor characteristics compared with the women without available tissue blocks (27, 29). In brief, hematoxylin and eosin sections from cases with pathology samples were reviewed to confirm the diagnosis, classify the histologic type and grade of the breast cancer, and identify the area from which the TMA cores would be taken. TMs contained three 0.6-mm diameter cores from each breast cancer sample. Immunostaining was performed on 5-µm paraffin sections cut from TMA blocks. Antibodies used for ER, PR, HER2, cytokeratin 5/6 (CK5/6), and EGFR staining are described elsewhere (11). A pathologist manually assessed ER, PR, HER2, CK5/6, and EGFR expression on each available core. We used the grade assigned by study pathologists except when not available, in which case we used grade collected from the participant’s pathology report. A case was considered ER-positive (ER+) or PR-positive (PR+) if any of their tissue cores showed any nuclear staining for ER or PR, respectively. A case was deemed ER- and/or PR- if there was complete absence of staining for ER and/or PR in all tissue cores. HER2 protein overexpression was defined as moderate or strong membrane staining (2+ or 3+) in >10% of the cells in any of the tissue cores. Cases were considered CK5/6+ or EGFR+ if any cytoplasmic and/or membranous staining was detected in the tumor cells in any of the cores. Luminal A tumors were defined as ER+ and/or PR+, with no HER2 overexpression and grade 1 (low) or grade 2 (intermediate). Luminal B tumors were either: (i) ER+ and/or PR+ and HER2-overexpressed or (ii) ER- and/or PR- and did not overexpress HER2 and grade 3 (high grade). In secondary analyses, we looked separately at luminal B tumors that over expressed HER2 and those that were high grade. Cases that were ER+, PR+, HER2-overexpressed were classified as HER2-enriched. Basal-like cases were ER-, PR-, did not overexpress HER2, and were positive for CK5/6 and/or EGFR. Unclassified tumors lacked expression of all 5 markers. As many studies lack information on CK5/6 and EGFR needed to define the basal-like subtype, we present estimates for triple-negative (ER-, PR-, and HER2-) breast cancer as well (Supplementary Table S3).

Statistical analysis

As each exposure was assessed in different survey cycles, and we excluded women missing data on the primary exposure from each analysis, the analytic sample and length of follow-up differ for each exposure. Sample sizes are as follows: height (n = 233,214); BMI at age 18 (n = 207,490); childhood and adolescent somatotype (n = 188,689). Women stopped contributing person-time when they reported a breast cancer diagnosis, reported a diagnosis of any other cancer (excluding non-melanoma skin cancer), date of death or the study cutoff date June 1, 2006, whichever occurred first. Follow-up continued through 2006, the most recent year tissue data were available. Our analyses included a maximum of 233,214 women contributing...
Results

Women who were taller had higher alcohol intake, lower BMI at age 18, lower current BMI, greater weight gain since age 18, older age at menar-ché, higher BMI at age 18 and current BMI, and lower prevalence of benign breast disease (Table 2).

Height was positively associated with all molecular subtypes ($P_{\text{heterogeneity}} = 0.78$; Table 3). Women who were $\geq 67$ inches tall, compared to those $\leq 62$ inches tall, were 52% more likely to develop luminal A tumors (HR, 1.52; 95% CI, 1.34–1.73; $P_{\text{trend}} < 0.0001$). 48% more likely to develop HER2-enriched tumors (HR, 1.48; 95% CI, 1.02–2.15; $P_{\text{trend}} = 0.004$), and 2 times more likely to develop unclassified tumors (HR, 2.00; 95% CI, 1.08–3.70; $P_{\text{trend}} = 0.02$). Height was positively associated with all subtypes in pre- and postmenopausal women, although associations were generally stronger in premenopausal women (Supplementary Table S1). For example, for luminal A tumors, each one inch increase in height was associated with a 8% increase in risk for premenopausal women and a 5% increase among postmenopausal women.

BMI at age 18 was inversely associated with all molecular subtypes, although associations were strongest for HER2-enriched and basal-like ($P_{\text{heterogeneity}} = 0.001$; Table 3). Compared with women with a BMI at age 18 or 20 to 21.9 kg/m$^2$, those with a BMI at age 18 of $\geq 25$ kg/m$^2$ were between 52% (HER2-enriched; $P_{\text{trend}} < 0.0001$) and 21% (luminal A; $P_{\text{trend}} < 0.0001$) less likely to develop breast cancer. Each one unit increase in BMI at age 18 was associated with a 2% decrease in risk of luminal B tumors overall; however, this varied between those that overexpressed HER2 (3% per kg/m$^2$) versus those that were high grade (no association; data not shown). Associations were generally stronger for pre- versus postmenopausal women, although we observed inverse associations in both groups (Supplementary Table S2).

Overall, we observed inverse associations between childhood ($P_{\text{heterogeneity}} = 0.51$) and adolescent ($P_{\text{heterogeneity}} = 0.046$) somatotype and most subtypes (Table 4). Compared with lowest category of childhood somatotype, risk reductions for women in the highest category ranged from 29% (luminal A) to 65% (basal-like). For adolescent somatotype, the same contrast was associated with from a 20% reduced risk for luminal A tumors up to a 71% decrease for HER2-enriched tumors. There was no association with unclassified tumors for either childhood or adolescent somatotype. Inverse associations were generally stronger for

### Table 1. Age and age-standardized baseline characteristics according height (inches) among participants in the NHS ($N = 118,072$) and NHSII ($N = 115,142$)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$\leq 62$ in.</td>
<td>$64$ in.</td>
</tr>
<tr>
<td></td>
<td>$n = 26,729$</td>
<td>$n = 19,965$</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.8 (7.3)</td>
<td>42.4 (7.3)</td>
</tr>
<tr>
<td>Height, in</td>
<td>61.3 (10.0)</td>
<td>64.0 (0.0)</td>
</tr>
<tr>
<td>Age at first birth, b y</td>
<td>25.1 (3.3)</td>
<td>25.1 (3.3)</td>
</tr>
<tr>
<td>Parity</td>
<td>3.6 (7.0)</td>
<td>3.6 (6.9)</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>5.6 (10.0)</td>
<td>6.4 (10.4)</td>
</tr>
<tr>
<td>Current BMI, kg/m$^2$</td>
<td>24.1 (4.3)</td>
<td>23.8 (4.3)</td>
</tr>
<tr>
<td>Weight change since age 18, kg</td>
<td>5.7 (9.2)</td>
<td>6.3 (9.5)</td>
</tr>
<tr>
<td>Age at menarché, y</td>
<td>12.3 (1.5)</td>
<td>12.5 (1.5)</td>
</tr>
</tbody>
</table>

Percentages

| History of benign breast disease | 18 | 18 | 19 | 8 | 8 | 8 |
| Irregular menstrual cycles ages 18–22 | 23 | 23 | 23 | 24 | 23 | 24 |
| Current hormone therapy usec | 32 | 34 | 35 | 82 | 82 | 81 |
| Former smoker | 47 | 45 | 40 | 20 | 21 | 23 |
| Excurrent smoker | 32 | 32 | 35 | 14 | 13 | 14 |
| Birth weight $\geq 8.5$ lbs | 5 | 7 | 12 | 5 | 9 | 16 |
| Parous | 93 | 94 | 92 | 72 | 72 | 69 |
| Premenopausal | 71 | 72 | 72 | 97 | 97 | 97 |
| Ever oral contraceptive use | 46 | 48 | 48 | 82 | 84 | 83 |
| Family history of breast cancer | 6 | 5 | 6 | 5 | 6 | 6 |

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population.

a Value is not age adjusted.

b Among parous women.

c Among postmenopausal women.
premenopausal women than postmenopausal women; however, there were small numbers of cases particularly for ER subtypes among premenopausal women (Supplementary Table S2).

**Discussion**

In this prospective pooled analysis of two large cohorts, we observed significant positive associations between adult height and risk of all breast cancer subtypes and inverse associations between BMI at age 18 and childhood and adolescent somatotype and risk of most subtypes. We observed heterogeneity in associations across subtypes for BMI at age 18 and adolescent somatotype. For BMI at age 18, there was a strong inverse association for HER2-enriched and basal-like tumors. The strongest inverse associations with body fatness in adolescence were observed among HER2-enriched, basal-like, and, to a lesser extent, luminal B

**Table 1.** Height, BMI at age 18, and risk of breast cancer according to molecular subtype, NHS and NHSII

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2-enriched</th>
<th>Basal-like</th>
<th>Unclassified</th>
<th>P heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>0.78</td>
<td>0.78</td>
<td>0.78</td>
<td>0.78</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>BMI at age 18, kg/m²</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>18.5-20.0</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>20.1-21.9</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>≥22</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Models adjusted for age (months), time period, cohort, recent alcohol consumption (continuous), age at menarche (<12, 13, 14, >14), age at menopause (years), menstrual status, and PMH use (premenopausal, postmenopausal–never PMH, postmenopausal–past PMH, postmenopausal–current PMH, postmenopausal–unknown PMH), birth index (continuous), history of benign breast disease (yes/no), first-degree family history of breast cancer (yes/no), birth weight (<5.5, 5.5–6.9, 7–8.4, ≥8.5 lbs), weight at age 18 (kg), weight change since age 18 (kg), interaction between menopausal status and weight change since 18, and cumulative average physical activity (quintiles).

*Model for height also adjusted for weight at age 18 (in kg).
Consistent with previous studies, we found that greater adult height was associated with an increased risk of luminal tumors, and young adulthood body size measures and risk of HER2-enriched and basal-like tumors than with luminal tumors. We also found stronger inverse associations with luminal B tumors that overexpressed HER2 compared with those that were high grade. This builds upon previous work in our cohorts that found that height and breast cancer share genetic risk variants (33). We found stronger inverse associations between our adolescent and young adulthood body size measures and risk of HER2-enriched and basal-like tumors than with luminal tumors. We also found stronger inverse associations with luminal B tumors that overexpressed HER2 compared with those that were high grade. This builds upon previous work in our cohorts that found that height and breast cancer share genetic risk variants (33).

There are several possible mechanisms through which height may impact breast cancer risk. Greater body fatness in early life may be associated with higher levels of estrogen which could induce early breast differentiation thereby making breast cells less susceptible to malignant transformation (36). However, in girls age 8–10, higher BMI was associated with higher levels of dehydroepiandrosterone sulfate and sex hormone–binding globulin; there was no difference in circulating levels of estrogen or progesterone (37). It is possible; however, that early life body size affects breast differentiation through a different mechanism.

There are several possible mechanisms through which height and early life body size may impact breast cancer risk. Greater body fatness in childhood, adolescence, and young adulthood may reflect slower growth and lower IGF1 levels, which are associated with lower breast cancer risk (38, 39). IGF1 regulates growth beginning in utero and throughout childhood and adolescence (40). It also induces endothelial growth factor, promotes.

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**Table 4. Childhood and adolescent somatotype and risk of breast cancer according to molecular subtype, NHS and NHS II**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Luminal A HR (95% CI)</th>
<th>Luminal B HR (95% CI)</th>
<th>HER2-Enriched HR (95% CI)</th>
<th>Basal-like HR (95% CI)</th>
<th>Unclassified HR (95% CI)</th>
<th>$P_{\text{heterogeneity}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>1</td>
<td>606 1.00 (reference)</td>
<td>283 1.00 (reference)</td>
<td>66 1.00 (reference)</td>
<td>84 1.00 (reference)</td>
<td>13 1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>15–2</td>
<td>632 1.00 (0.89–1.12)</td>
<td>284 0.93 (0.79–1.10)</td>
<td>69 1.04 (0.73–1.47)</td>
<td>69 0.74 (0.53–1.02)</td>
<td>16 1.45 (0.68–3.05)</td>
<td>0.0001</td>
</tr>
<tr>
<td>2.5–3</td>
<td>360 0.75 (0.66–0.86)</td>
<td>206 0.89 (0.74–1.07)</td>
<td>44 0.86 (0.60–1.22)</td>
<td>57 0.82 (0.59–1.16)</td>
<td>7 0.84 (0.53–1.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>3.5–4.5</td>
<td>315 0.79 (0.69–0.91)</td>
<td>153 0.78 (0.64–0.95)</td>
<td>23 0.55 (0.34–0.90)</td>
<td>32 0.54 (0.35–0.87)</td>
<td>8 0.88 (0.54–2.27)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥5</td>
<td>118 0.77 (0.63–0.94)</td>
<td>45 0.60 (0.44–0.83)</td>
<td>8 0.52 (0.26–1.09)</td>
<td>8 0.35 (0.17–0.74)</td>
<td>7 2.33 (0.90–6.06)</td>
<td>0.06</td>
</tr>
<tr>
<td>Per 1 unit increase</td>
<td>2.03</td>
<td>0.93 (0.87–0.96)</td>
<td>97</td>
<td>0.91 (0.86–0.96)</td>
<td>111</td>
<td>0.84 (0.74–0.94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adolescent&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>0.046</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198 1.00 (reference)</td>
<td>90 1.00 (reference)</td>
<td>21 1.00 (reference)</td>
<td>23 1.00 (reference)</td>
<td>8 1.00 (reference)</td>
<td>0.0001</td>
</tr>
<tr>
<td>15–2</td>
<td>660 1.00 (0.85–1.38)</td>
<td>322 1.02 (0.81–1.29)</td>
<td>84 1.21 (0.75–1.97)</td>
<td>87 1.06 (0.66–1.68)</td>
<td>6 0.24 (0.08–0.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>2.5–3</td>
<td>607 0.90 (0.76–1.06)</td>
<td>299 0.91 (0.72–1.16)</td>
<td>64 0.89 (0.54–1.47)</td>
<td>60 0.93 (0.57–1.49)</td>
<td>15 0.69 (0.28–1.67)</td>
<td>0.0003</td>
</tr>
<tr>
<td>3.5–4.5</td>
<td>461 0.85 (0.69–0.98)</td>
<td>220 0.80 (0.62–1.02)</td>
<td>37 0.64 (0.47–1.03)</td>
<td>53 0.73 (0.44–1.21)</td>
<td>15 0.80 (0.52–1.96)</td>
<td>0.0005</td>
</tr>
<tr>
<td>≥5</td>
<td>105 0.80 (0.62–1.01)</td>
<td>40 0.60 (0.41–0.88)</td>
<td>4 0.29 (0.10–0.85)</td>
<td>7 0.40 (0.17–0.95)</td>
<td>6 1.08 (0.36–3.25)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Per 1 unit increase</td>
<td>2.03</td>
<td>0.93 (0.89–0.97)</td>
<td>97</td>
<td>0.88 (0.83–0.93)</td>
<td>111</td>
<td>0.79 (0.70–0.90)</td>
</tr>
</tbody>
</table>

*All estimates are adjusted for age (months), period, cohort, recent alcohol consumption (0, 0.1–0.5, 0.6–1.4, >1.5 g/d), age at menarche (<12, 12.5, 13, 14, >14), age at menopause (years), height (inches), menopausal status and PMH use (premenopausal, postmenopausal–never PMH, postmenopausal–past PMH, postmenopausal–current PMH, postmenopausal–unknown PMH), birth index (control, oral contraceptive duration (years), history of benign breast disease (yes/no), first-degree family history of breast cancer (yes/no), breast weight (<5.5, 5.5–6.9, 7–8.4, >8.5 lbs), weight change since age 18 kg), interaction between menopausal status and weight change since 18, cumulative average physical activity (quintiles).

<sup>a</sup>Average of somatotype at ages 5 and 10.

<sup>b</sup>Average of somatotype at ages 10 and 20.
tumor growth, and inhibits apoptosis (41). Genome-wide association studies have demonstrated that genes in the IGF signaling pathway are also associated with adult height (42, 43). Rapid growth in childhood and adolescence is associated with increased risk of breast cancer (39, 44), independent of adult height. In our data, childhood and adolescent somatotype were not associated with adult height, whereas there was a weak inverse association between height and BMI at age 18. Age at attained height was also not associated with breast cancer risk (45) in NHS. Women with higher birth weight and higher BMI at age 18 had lower circulating IGFI levels in adulthood compared with women who were leaner at early ages (46). Body fatness during childhood and adolescence has also been associated with lower premenopausal breast density (47). Thus, height and body size in early life and young adulthood may reflect the concentration of growth factors during that phase of life, which then has long-term health effects via growth factors in adulthood and breast tissue composition.

This study’s strengths include its large size, prospective design, detailed and repeated assessment of known breast cancer risk factors, long follow-up, and comprehensive case ascertainment. Although the somatotype pictogram and BMI at age 18 have been validated (26), the measures rely on participant recall, and there is potential for misclassification. The somatotype figure has also been criticized because, while it queries about body size in childhood and adolescence, the pictures presented are of adult women (48). Yet, because the analysis is prospective, any potential misclassification is likely to be nondifferential with respect to disease status and if anything leads to an underestimation of association. In addition, the somatotype figure has been consistently associated with breast cancer and other outcomes (49–51). It is also important to note that studies with measured height and weight in adolescence have also observed significant inverse associations, albeit of lesser magnitude (44). Small case numbers among the rare subtypes (e.g., HER2-enriched, basal-like, and unclassified) limited our power and introduced some instability in effect estimates. In the future, pooled studies should assess associations with these less common breast cancer subtypes. Our study population was predominately lean in childhood and young adulthood and white. The prevalence of overweight and obesity has increased over time, and the distribution of body size in this study is not representative of today’s population (52). In addition, it is possible that the mechanisms for larger body size are different today than they were for earlier birth cohorts included in this analysis. Finally, it is important to study these associations in non-White populations where the distribution of early life body size and molecular subtype is different than observed here (52, 53).

In conclusion, we found that height was positively associated with risk of all breast cancer molecular subtypes, whereas childhood and adolescent somatotype and BMI at age 18 were inversely associated with risk of most subtypes. Adolescent and young adult body sizes were more strongly associated with HER2-enriched and, to a lesser extent, basal-like tumors, than other subtypes. Despite the consistent inverse associations observed between early life body fatness, BMI at age 18, and breast cancer risk, there are many well-known negative health consequences of overweight and obesity throughout the life course. However, these results provide additional evidence of the importance of early life exposures in breast cancer etiology. The observed associations across molecular subtypes suggest that these factors act either through multiple pathways or through a common nonhormonal or HER2-driven pathway to influence breast cancer risk in adulthood.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


38. Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1) and IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010;11:S30.
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