HHS Public Access

Author manuscript

Cancer Prev Res (Phila). Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Cancer Prev Res (Phila). 2016 September ; 9(9): 732–738. doi:10.1158/1940-6207.CAPR-16-0085.

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

Erica T. Warner[1,2,3], **Rong Hu**[3], **Laura C. Collins**[4], **Andrew H. Beck**[4], **Stuart Schnitt**[4], **Bernard Rosner**[3,5], **A. Heather Eliassen**[2,3], **Karin B. Michels**[2,3,6], **Walter C. Willett**[2,3,7], and **Rulla M. Tamimi**[2,3]

[1]Clinical Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA

[2]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

[3]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA

[4]Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[5]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

[6]Department of Obstetrics, Gynecology and Reproductive Biology, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[7]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

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 age 18, childhood and adolescent somatotypes, with breast cancer risk according to molecular subtypes defined by immunohistochemical markers. We used multivariable-adjusted Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI).We identified 2983 luminal A, 1281 luminal B, 318 HER2-enriched, 408 basal-like and 128 unclassified tumors. Height was positively associated with all subtypes (p-heterogeneity=0.78). BMI at age 18 (p-heterogeneity=0.001), childhood (p-heterogeneity=0.51) and adolescent somatotype (p-heterogeneity=0.046) were inversely associated, but with differences in magnitude of association. BMI at age 18 of ≥25 kg/m^2 (compared to 20-21.9 kg/m^2) was associated with a 52% decreased risk of HER2-enriched (HR: 0.48, 95%CI: 0.26-0.91; p-trend <0.0001) and 39% reduced risk of basal-like tumors (HR: 0.61, 95% CI: 0.36-1.02; p-trend=0.008). Compared to 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-trend=0.0005) and 60% less likely to develop basal-like (HR: 0.40, 95%CI: 0.17-0.95; p-trend=0.0008). Height was positively associated with risk of all breast cancer

Corresponding author: Erica T. Warner, 55 Fruit Street, Bartlett 9, Boston, MA 02114, phone: 617-724-9516, fax: 617-726-0040.

Conflicts of interest: The authors have no potential conflicts of interest to disclose.

molecular subtypes. BMI at age 18 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.

Keywords

height; BMI at age 18; childhood; adolescence; molecular subtype

Introduction

Body size in childhood and adolescence, BMI in young adulthood, and height, are established risk factors for pre- and post-menopausal breast cancer (1-3). However, breast cancer is a heterogeneous disease with multiple subtypes of differing prognosis defined by tumor characteristics such as estrogen (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+) (1, 2) and negative (ER−) (1)breast cancer. Height is positively associated with ER+ tumors, while 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 (8-10) 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, body mass index (BMI) at age 18, height, 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

The Nurses' Health Studies (NHS and NHS II) 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 at baseline. NHS II began in 1989 with 116,430 female registered nurses ages 25 to 42. Women are sent follow-up questionnaires every two 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 underreported weight at age 18 by 1.4kg. 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 nine-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/m^2) with each level of the figure (levels 1-7; no participants selected figure 8 or 9) (26). We averaged somatotypes across two ages to create measures for childhood (ages 5 & 10) and adolescent (ages 10 & 20) body fatness. Due to sparse data, we collapsed the top five categories of each measure creating a top category that included anyone that selected figure five through nine.

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 non-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 microarrays (TMAs) 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 1976-2006. Women with available tissue blocks were similar with respect to breast cancer risk factors and tumor characteristics compared to 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 histological type and grade of the breast cancer, and identify the area from which the TMA cores would be taken. TMAs 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), epidermal growth factor receptor (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-negative if there was complete absence of staining for ER and/or PR in all tissue cores. HER2 protein over-expression was defined as moderate or strong membrane staining (2+ or 3+) in more than 10% of the cells in any of the tissue cores. Cases were considered CK5/6-positive or EGFR positive 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 over-expression and grade 1 (low) or grade 2 (intermediate). Luminal B tumors were either: 1) ER+ and/or PR+ and HER2-overexpressed; or 2) ER+ and/or PR+, did not over-express 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 over-expressed were classified as HER2-enriched. Basal-like cases were ER−, PR −, did not over-express HER2 and were positive for CK 5/6 and/or EGFR. Unclassified tumors lacked expression of all five markers. As many studies lack information on CK 5/6 and EGFR needed to define the basal-like subtype, we present estimates for triple negative (ER, PR and HER2 negative) breast cancer as well (Supplementary Table 3).

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 analytical sample and length of follow-up differs 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 was available. Our analyses included a maximum of 233,214 women contributing 6,129,327 person-years of follow-up. Through the study cutoff date there were the following numbers of cases: luminal A (N=2,983), luminal B (N=1,281), HER2-enriched (N=316), basal-like (N=408), and unclassified (N=128).

Cox proportional hazards regression models were used to estimate incidence rate ratios and 95% confidence intervals for breast cancer subtypes associated with adult height (≤ 62, 63, 64, 65, 66, ≥67 inches), BMI at age 18 (<18.5, 18.5-20, 20-21.9, 22-24.9, ≥ 25 kg/m^2) and childhood and adolescent somatotype (1,1.5-2, 2.5-3, 3.5-4.5, ≥5). Age-adjusted and multivariate adjusted models are presented. Multivariate models include covariates selected based on their association with breast cancer in previous analyses. In secondary analyses

(Supplementary Tables 1 and 2) we present estimates for each exposure stratified by menopausal status (pre- or post-menopausal). To evaluate the consistency of risk estimates across molecular subtypes, we performed a competing risks analysis to estimate separate associations of each exposure with the relative hazard of each type of subtype (30-32). Analyses were performed using SAS version 9.3 (SAS, Cary, NC, USA). All statistical tests were two-sided, and 0.05 was the threshold for statistical significance. The Institutional Review Board at Brigham and Women's Hospital approved this investigation.

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 menarche, and higher birth weight (Table 1a). Greater adolescent somatotype was associated with earlier age at menarche, higher BMI at age 18 and current BMI, and lower prevalence of benign breast disease (Table 1b).

Height was positively associated with all molecular subtypes (p-heterogeneity=0.78; Table 2). Women who were ≥67 inches tall, compared to those ≤62 inches tall, were 52% more likely to develop luminal A tumors (HR: 1.52, 95% CI: 1.34–1.73; p-trend: <0.0001), 48% more likely to develop HER2-enriched tumors (HR: 1.48, 95% CI: 1.02–2.15; p-trend: 0.004), and two times more likely to develop unclassified tumors (HR: 2.00, 95% CI: 1.08–3.70; p-trend: 0.02). Height was positively associated with all subtypes in pre- and post menopausal women, though associations were generally stronger in premenopausal women (Supplementary Table 1). 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, though associations were strongest for HER2-enriched and basal-like (p-heterogeneity=0.001; Table 2). Compared to women with a BMI at age 18 or 20-21.9 kg/m^2, those with a BMI at age 18 of ≥25 kg/m^2 were between 52% (HER2-enriched; p-trend <0.0001) and 21% (luminal A; p-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 over-expressed HER2 (3% per kg/m^2) vs. those that were high grade (no association; data not shown). Associations were generally stronger for pre- vs. postmenopausal women, though we observed inverse associations in both groups (Supplementary Table 2).

Overall, we observed inverse associations between childhood (p-heterogeneity=0.51) and adolescent (p-heterogeneity=0.046) somatotype and most subtypes (Table 3). Compared to lowest category of childhood somatotype, risk reductions for women in the highest category ranged from 23% (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 premenopausal women than postmenopausal women; however there were small numbers of cases particularly for ER− subtypes among premenopausal women (Supplementary Table 2).

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 tumors. In addition to differences by subtype, we also found that compared to postmenopausal women, associations were similar, but generally stronger among premenopausal women.

Consistent with previous studies we found that greater adult height was associated with an increased risk of luminal tumors, but we also observed strong positive associations between height and risk of HER2-enriched, basal-like and unclassified tumors, which has not been consistently seen in other studies (6, 7). A recent meta-analysis of 159 prospective cohorts that included 5,216,302 women and 9,732 breast cancer cases with known ER status, found a positive association between height and risk of ER+ tumors (HR: 1.18, 95% CI: 1.13-1.23 per 10cm increase), but no association with ER− tumors (HR: 1.00, 95% CI: 0.86-1.14). Interestingly, when tumors were classified jointly by ER and progesterone receptor (PR) status, there was a borderline significant association with ER−/PR− tumors (HR: 1.08, 95% CI: 0.99-1.18) (33). They also conducted a Mendelian randomization analysis using a genetic risk score derived from 168 height-associated variants and found strong positive associations with ER+ and ER+/PR+ tumors and no association with ER− or ER−/PR− tumors. However, this study comes with several caveats. There was significant heterogeneity across studies overall ($P_{\text{heterogeneity}} < .001$, $I^2 = 61\%$) and ER status was only available on 8.7% (9792/113178) of cases. Importantly, determination of ER and PR status was based on pathology reports and cases were diagnosed over a wide period (late 1960’s through 2000’s) in many different countries. A major strength of our study is uniform staining and scoring of immunohistochemical markers. Additionally, the genetic risk score used Zhang et al.’s Mendelian randomization analysis only explained 10% of the variation in height among people of European ancestry. The authors do not draw conclusions regarding the association of height with breast cancer risk according to ER/PR status. Instead, they conclude that their results demonstrate that height is causally implicated in breast cancer etiology and 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 over-expressed HER2 compared to those that were high grade. This builds upon previous work in our cohorts that found stronger inverse associations with ER− tumors and a suggestion of stronger associations with tumors that over-expressed HER2 (1). Two other studies, also found that the inverse association between childhood body size and breast cancer was strongest for triple negative tumors and those that over-expressed HER2 (34). While associations have also been observed only among ER+/PR+ (2) or ER+/PR− tumors (35),

overall, the body of literature suggests that body size in early life may reduce risk of breast cancer in adulthood through sex hormone dependent and independent mechanisms. It was previously postulated that higher 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 insulin-like growth factor 1 (IGF-1) levels, which are associated with lower breast cancer risk (38, 39). IGF-1 regulates growth beginning in utero and throughout childhood and adolescence (40). It also induces endothelial growth factor, promotes 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, while 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 IGF-1 levels in adulthood compared to 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. Though 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 non-differential with respect to disease status and if anything lead to an underestimation of association. Additionally, 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).

Additionally, it is possible that the mechanisms for larger body size are different today than they were for earlier birth cohorts included in this analysis. Lastly, it is important to study these associations in non-white populations where the distribution of both early-life body size and molecular subtype is different than observed here (52, 53).

In conclusion, we found that height was positively associated with all risk of breast cancer molecular subtypes, while 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 non-hormonal or HER2 driven pathway to influence breast cancer risk in adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work is supported by National Cancer Institute (NCI) grants P01 CA87969, UM1 CA176726 and UM1 CA186107. Dr. Warner was supported by National Cancer Institute grant K01 CA188075. We would like to thank the participants and staff of the Nurses' Health Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

References

1. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. Am J Epidemiol. 2010; 171:1183–94. [PubMed: 20460303]
2. Fagherazzi G, Guillas G, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S. Body shape throughout life and the risk for breast cancer at adulthood in the French E3N cohort. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2013; 22:29. [PubMed: 22694827]
3. Engel P, Fagherazzi G, Boutten A, Dupré T, Mesrine S, Boutron-Ruault M-C, et al. Serum 25 (OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiology Biomarkers & Prevention. 2010; 19:2341–50.
4. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences. 2001; 98:10869.
5. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res. 2009; 11:R31. [PubMed: 19463150]
6. Ritte R, Lukanova A, Tjønneland A, Olsen A, Overvad K, Mesrine S, et al. Height, age at menarche and risk of hormone receptor-positive and-negative breast cancer: A cohort study. International Journal of Cancer. 2013; 132:2619. [PubMed: 23090881]
7. Horn J, Alsaker MD, Opdahl S, Engstrom MJ, Tretli S, Haugen OA, et al. Anthropometric factors and risk of molecular breast cancer subtypes among postmenopausal Norwegian women.

International journal of cancerJournal international du cancer. 2014; 135:2678. [PubMed: 24752603]

8. Engstrøm MJ, Opdahl S, Hagen AI, Romundstad PR, Akslen LA, Haugen OA, et al. Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients. Breast cancer research and treatment. 2013; 140:463–73. [PubMed: 23901018]
9. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA : the journal of the American Medical Association. 2006; 295:2492. [PubMed: 16757721]
10. O'Brien KM, Cole SR, Tse CK, Perou CM, Carey LA, Foulkes WD, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clinical cancer research : an official journal of the American Association for Cancer Research. 2010; 16:6100–10. [PubMed: 21169259]
11. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, Rosner B, et al. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast cancer research and treatment. 2011
12. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000; 406:747–52. [PubMed: 10963602]
13. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular Classification and Molecular Forecasting of Breast Cancer: Ready for Clinical Application? Journal of Clinical Oncology. 2005; 23:7350–60. [PubMed: 16145060]
14. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008; 17:2078.
15. McGregor H, Land CE, Choi K, Tokuoka S, Liu PI, Wakabayashi T, et al. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-69. Journal of the National Cancer Institute. 1977; 59:799. [PubMed: 894745]
16. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiation research. 2003; 160:707–17. [PubMed: 14640793]
17. Colditz GA, Rosner BA. What can be learnt from models of incidence rates? Breast cancer research : BCR. 2006; 8:208. [PubMed: 16762045]
18. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–64. [PubMed: 11092437]
19. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev. 1995; 4:567–71. [PubMed: 7549816]
20. Dontu G, Liu S, Wicha MS. Stem cells in mammary development and carcinogenesis. Stem cell reviews. 2005; 1:207. [PubMed: 17142857]
21. Biro FM, Deardorff J. Identifying opportunities for cancer prevention during preadolescence and adolescence: puberty as a window of susceptibility. Journal of Adolescent Health. 2013; 52:S15. [PubMed: 23601607]
22. Gelander L, Blum WF, Larsson L, Rosberg S, Albertsson-Wikland K. Monthly measurements of insulin-like growth factor I (IGF-I) and IGF-binding protein-3 in healthy prepubertal children: characterization and relationship with growth: the 1-year growth study. Pediatric research. 1999; 45:377. [PubMed: 10088658]
23. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1995; 19:570.
24. Koprowski C, Coates RJ, Bernstein L. Ability of young women to recall past body size and age at menarche. Obesity research. 2001; 9:478. [PubMed: 11500528]

25. Stunkard AJ, Sorensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. Research publications - Association for Research in Nervous and Mental Disease. 1983; 60:115. [PubMed: 6823524]
26. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. American Journal of Epidemiology. 1993; 138:56. [PubMed: 8333427]
27. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, et al. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast cancer research : BCR. 2008; 10:R67. [PubMed: 18681955]
28. Collins LC, Marotti JD, Baer HJ, Tamimi RM. Comparison of estrogen receptor results from pathology reports with results from central laboratory testing. Journal of the National Cancer Institute. 2008; 100:218. [PubMed: 18230800]
29. Wang J, Zhang X, Beck AH, Collins LC, Chen WY, Tamimi RM, et al. Alcohol Consumption and Risk of Breast Cancer by Tumor Receptor Expression. Horm Cancer. 2015; 6:237–46. [PubMed: 26385458]
30. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995; 51:524. [PubMed: 7662841]
31. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. American Journal of Epidemiology. 2005; 162:975. [PubMed: 16207808]
32. Glynn RJ, Rosner B, Christen WG. Evaluation of risk factors for cataract types in a competing risks framework. Ophthalmic epidemiology. 2009; 16:98. [PubMed: 19353398]
33. Zhang B, Shu XO, Delahanty RJ, Zeng C, Michailidou K, Bolla MK, et al. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. Journal of the National Cancer Institute. 2015; 107 10.1093/jnci/djv219. Print 2015 Nov.
34. Eriksson L, Czene K, Rosenberg L, Humphreys K, Hall P. The influence of mammographic density on breast tumor characteristics. Breast cancer research and treatment. 2012; 134:859–66. [PubMed: 22710708]
35. Bardia A, Vachon CM, Olson JE, Vierkant RA, Wang AH, Hartmann LC, et al. Relative weight at age 12 and risk of postmenopausal breast cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008; 17:374.
36. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. British journal of cancer. 2001; 85:1680. [PubMed: 11742488]
37. Baer HJ, Colditz GA, Willett WC, Dorgan JF. Adiposity and sex hormones in girls. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16:1880.
38. Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. The lancet oncology. 2010; 11:530. [PubMed: 20472501]
39. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer. 1999; 85:2400. [PubMed: 10357411]
40. Rosenfeld RG. Insulin-like growth factors and the basis of growth. New England Journal of Medicine. 2003; 349:2184. [PubMed: 14657423]
41. Brosseau C, Pirianov G, Colston KW. Role of insulin-like growth factor binding protein-3 in 1, 25-dihydroxyvitamin-d 3 -induced breast cancer cell apoptosis. International journal of cell biology. 2013; 2013:960378. [PubMed: 23690781]
42. Okada Y, Kamatani Y, Takahashi A, Matsuda K, Hosono N, Ohmiya H, et al. A genome-wide association study in 19 633 Japanese subjects identified LHX3-QSOX2 and IGF1 as adult height loci. Human molecular genetics. 2010; 19:2303. [PubMed: 20189936]
43. He M, Xu M, Zhang B, Liang J, Chen P, Lee JY, et al. Meta-analysis of genome-wide association studies of adult height in East Asians identifies 17 novel loci. Human molecular genetics. 2015; 24:1791. [PubMed: 25429064]

44. Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA. Growth patterns and the risk of breast cancer in women. New England Journal of Medicine. 2004; 351:1619. [PubMed: 15483280]
45. Baer HJ, Rich-Edwards JW, Colditz GA, Hunter DJ, Willett WC, Michels KB. Adult height, age at attained height, and incidence of breast cancer in premenopausal women. International journal of cancerJournal international du cancer. 2006; 119:2231. [PubMed: 16823843]
46. Poole EM, Tworoger SS, Hankinson SE, Schernhammer ES, Pollak MN, Baer HJ. Body size in early life and adult levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3. American Journal of Epidemiology. 2011; 174:642. [PubMed: 21828371]
47. Bertrand KA, Baer HJ, Orav EJ, Klifa C, Shepherd JA, Van Horn L, et al. Body fatness during childhood and adolescence and breast density in young women: a prospective analysis. Breast Cancer Research. 2015; 17:1. [PubMed: 25567532]
48. Magnusson C, Roddam AW. Breast cancer and childhood anthropometry: emerging hypotheses. Breast Cancer Res. 2005; 7:83. [PubMed: 15987435]
49. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. Human reproduction (Oxford, England). 2010; 25:1325.
50. Nimptsch K, Giovannucci E, Willett WC, Fuchs CS, Wei EK, Wu K. Body fatness during childhood and adolescence, adult height, and risk of colorectal adenoma in women. Cancer prevention research (Philadelphia, Pa). 2011; 4:1710.
51. Bertrand KA, Giovannucci E, Zhang SM, Laden F, Rosner B, Birmann BM. A prospective analysis of body size during childhood, adolescence, and adulthood and risk of non-Hodgkin lymphoma. Cancer prevention research (Philadelphia, Pa). 2013; 6:864.
52. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, et al. Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. JAMA. 2016; 315:2292–9. [PubMed: 27272581]
53. John EM, Sangaramoorthy M, Hines LM, Stern MC, Baumgartner KB, Giuliano AR, et al. Body size throughout adult life influences postmenopausal breast cancer risk among hispanic women: the breast cancer health disparities study. Cancer Epidemiol Biomarkers Prev. 2015; 24:128–37. [PubMed: 25352523]

Table 1a

Age and age-standardized baseline characteristics according height (inches) among participants in the Nurses' Health Study (N=118,072) and Nurses' Health Study II (N=115,142)

	NHS (1976)			NHSII (1989)		
	≤ 62 in. (n=26729)	**64 in. (n=19965)**	**≥67 in. (n=23943)**	**≤ 62 in. (n=21856)**	**64 in. (n=18448)**	**≥67 in. (n=30614)**
Means (SD)						
Age [a]	42.8 (7.3)	42.4 (7.3)	41.7 (7.1)	34.1(4.6)	34.0(4.6)	33.7(4.7)
Height (inches)	61.3 (1.0)	64.0 (0.0)	67.9 (1.2)	61.2 (1.2)	64.0 (0.0)	68.1 (1.3)
Age at first birth (years) [b]	25.1 (3.3)	25.1 (3.3)	25.3(3.4)	25.4 (4.1)	25.4 (4.1)	25.6 (4.0)
Parity	3.6 (7.0)	3.6 (6.9)	3.5 (6.9)	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)
Alcohol intake (g/day)	5.6 (10.0)	6.4 (10.4)	6.9 (11.1)	2.6 (5.0)	3.0 (5.9)	3.3 (6.0)
BMI at age 18 (kg/m2)	21.7 (3.0)	21.4 (3.0)	21.1 (3.1)	21.4 (3.9)	21.2 (3.8)	20.7 (4.1)
Current BMI (kg/m2)	24.1 (4.3)	23.8 (4.1)	23.6 (4.0)	24.2 (4.7)	24.1 (4.7)	23.8 (4.8)
Weight change since age 18, kg	5.7 (9.2)	6.3 (9.5)	7.2 (10.7)	6.7 (9.6)	7.5 (10.5)	8.7 (11.7)
Age at menarche (years)	12.3 (1.5)	12.5 (1.4)	12.8 (1.5)	12.2 (1.5)	12.3 (1.4)	12.6 (1.4)
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 use [c]	32	34	35	82	82	81
Former smoker	47	45	40	20	21	23
Current smoker	32	32	35	14	13	14
Birth weight ≥ 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	6	7	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

Table 1b

Age and age-standardized baseline characteristics according to childhood somatotype among participants in the Nurses' Health Study (N=76,299) and Nurses' Health Study II (N=112,390)

	NHS (1988)			NHS II (1989)		
	1 (leanest) (n=23208)	**3 (n=14643)**	**≥5 (heaviest) (n=5387)**	**1 (leanest) (n=19691)**	**3 (n=28052)**	**≥5 (heaviest) (n=7144)**
Mean (SD)						
Age*	55.3 (6.9)	53.7 (7.2)	53.7 (7.1)	34.3 (4.8)	33.8 (4.6)	34.5 (4.6)
Height	64.5(2.5)	64.5 (2.4)	64.6 (2.5)	64.9 (2.7)	64.8 (2.6)	65.1 (2.6)
Age at first birth (years)**	25.1 (3.3)	25.1 (3.2)	25.2 (3.3)	25.3 (4.0)	25.5 (4.0)	25.4 (4.1)
Parity	3.5 (5.6)	3.4 (5.2)	3.3 (5.0)	2.1 (0.9)	2.1 (0.9)	2.0 (0.9)
Alcohol intake (g/day)	6.1 (10.5)	6.2 (10.7)	6.1 (11.0)	3.1 (5.8)	3.0 (5.6)	3.1 (6.2)
BMI at age 18 (kg/m2)	19.8 (2.2)	21.9 (2.6)	24.6 (3.9)	19.4 (2.1)	21.5 (2.8)	24.8 (4.7)
Current BMI (kg/m2)	24.5 (4.0)	26.0 (4.8)	27.6 (5.6)	24.2 (4.7)	24.1 (4.7)	23.9 (4.8)
Weight change since age 18, kg	12.5 (10.5)	11.1 (12.0)	9.1 (15.0)	7.4 (8.2)	7.9 (10.8)	7.6 (15.3)
Age at menarche (years)	12.8 (1.4)	12.4 (1.4)	12.2 (1.4)	12.8 (1.5)	12.3 (1.4)	12.0 (1.5)
Percentage						
History of benign breast disease	17	15	14	10	8	6
Irregular menstrual cycles ages 18-22	24	22	25	24	23	26
Current hormone therapy use^	32	31	28	87	81	77
Former smoker	35	38	40	20	22	23
Current smoker	18	18	24	13	13	20
Birth weight ≥ 8.5 lbs	7	11	16	8	11	15
Parous	94	94	93	71	72	63
Premenopausal	29	30	30	97	97	96
Ever oral contraceptive use	50	50	49	85	83	81
Family history of breast cancer	11	10	10	6	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

Table 2

Height, BMI at age 18 and Risk of Breast Cancer According to Molecular Subtype, Nurses' Health Study and Nurses' Health Study II

		Luminal A		Luminal B		HER2-enriched		Basal-like		Unclassified	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	p-het
Height (inches)[a,b]											0.78
≤62	539	1.00 (reference)	243	1.00 (reference)	71	1.00 (reference)	71	1.00 (reference)	20	1.00 (reference)	
63	342	1.19 (1.04–1.37)	137	1.00 (0.81–1.24)	32	0.94 (0.62, 1.43)	44	1.17 (0.80, 1.71)	17	1.67 (0.87, 3.20)	
64	515	1.32 (1.17–1.50)	234	1.21 (1.00–1.45)	39	0.85 (0.57, 1.27)	76	1.50 (1.08, 2.09)	19	1.38 (0.73, 2.60)	
65	450	1.41 (1.24–1.60)	167	1.05 (0.86–1.29)	52	1.41 (0.97, 2.05)	61	1.47 (1.04, 2.09)	16	1.38 (0.70, 2.70)	
66	452	1.45 (1.27–1.65)	198	1.20 (0.99–1.46)	56	1.65 (1.14, 2.39)	63	1.58 (1.11, 2.25)	25	2.20 (1.19, 4.08)	
≥ 67	685	1.52 (1.34–1.73)	302	1.19 (0.98–1.43)	68	1.48 (1.02, 2.15)	93	1.59 (1.13, 2.24)	31	2.00 (1.08, 3.70)	
HR per 1 inch increase	2983	1.07 (1.05, 1.08)	1281	1.02 (1.00, 1.05)	318	1.08 (1.02, 1.13)	408	1.07 (1.02, 1.11)	128	1.10 (1.02, 1.19)	
P_{trend}		<0.0001		0.05		0.004		0.004		0.02	
BMI at age 18 (kg/m^2)[a]											0.001
<18.5	373	1.10 (0.98–1.25)	136	0.83 (0.68, 1.01)	52	1.77 (1.24, 2.53)	52	1.35 (0.96, 1.90)	20	2.00 (1.11, 3.61)	
18.5-20.0	593	1.05 (0.95–1.16)	258	0.95 (0.81, 1.11)	84	1.75 (1.28, 2.38)	93	1.46 (1.10, 1.94)	22	1.37 (0.78, 2.42)	
20-21.9	922	1.0 (reference)	419	1.00 (reference)	79	1.00 (reference)	101	1.00 (reference)	27	1.00 (reference)	
22.0-24.9	492	0.89 (0.79–0.99)	223	0.88 (0.74, 1.03)	47	0.96 (0.67, 1.38)	79	1.29 (0.96, 1.73)	25	1.51 (0.87, 2.60)	
≥ 25	205	0.79 (0.68–0.92)	82	0.69 (0.54, 0.87)	11	0.48 (0.26, 0.91)	17	0.61 (0.36, 1.02)	9	1.11 (0.52, 2.38)	
HR per 1 kg/m^2 increase	2585	0.96 (0.95, 0.98)	1118	0.98 (0.96, 1.00)	201	0.88 (0.83, 0.92)	342	0.94 (0.90, 0.98)	103	0.95 (0.88, 1.02)	
P_{trend}		<0.0001		0.10		<0.0001		0.008		0.29	

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

[b]Model for height also adjusted for weight at age 18 (in kg)

Table 3

Childhood and Adolescent Somatotype and Risk of Breast Cancer According to Molecular Subtype, Nurses' Health Study and Nurses' Health Study II

		Luminal A		Luminal B		HER2-Enriched		Basal-like		Unclassified	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	p-het
Childhood[a,b]											0.51
1	606	1.00 (reference)	283	1.00 (reference)	66	1.00 (reference)	84	1.00 (reference)	13	1.00 (reference)	
1.5-2	632	1.00 (0.89-1.12)	284	0.93 (0.79-1.10)	69	1.04 (0.73-1.47)	69	0.74 (0.53, 1.02)	16	1.45 (0.68, 3.05)	
2.5-3	360	0.75 (0.66-0.86)	206	0.89 (0.74-1.07)	44	0.89 (0.60-1.32)	57	0.82 (0.58, 1.16)	7	0.84 (0.33, 2.15)	
3.5-4.5	315	0.79 (0.69-0.91)	153	0.78 (0.64-0.95)	23	0.55 (0.34-0.90)	32	0.54 (0.35, 0.81)	7	0.88 (0.34, 2.27)	
≥ 5	118	0.77 (0.63, 0.94)	45	0.60 (0.44-0.83)	8	0.52 (0.26-1.09)	8	0.35 (0.17, 0.74)	7	2.33 (0.90, 6.06)	
Per 1 unit increase	2031	0.93 (0.87, 0.96)	971	0.91 (0.86, 0.96)	210	0.84 (0.74, 0.94)	250	0.83 (0.74, 0.92)	50	1.06 (0.86, 1.31)	
P_{trend}		<0.0001		0.0003		0.003		0.0007		0.57	
Adolescent [a,c]											0.046
1	198	1.00 (reference)	90	1.00 (reference)	21	1.00 (reference)	23	1.00 (reference)	8	1.00 (reference)	
1.5-2	660	1.00 (0.85-1.18)	322	1.02 (0.81-1.29)	84	1.21 (0.75, 1.97)	87	1.06 (0.66, 1.68)	6	0.24 (0.08, 0.71)	
2.5-3	607	0.90 (0.76-1.06)	299	0.91 (0.72-1.16)	64	0.89 (0.54, 1.47)	80	0.93 (0.57, 1.49)	15	0.69 (0.28, 1.67)	
3.5-4.5	461	0.83 (0.69-0.98)	220	0.80 (0.62-1.03)	37	0.64 (0.67, 1.10)	53	0.73 (0.44, 1.21)	15	0.80 (0.32, 1.96)	
≥ 5	105	0.80 (0.62-1.01)	40	0.60 (0.41-0.88)	4	0.29 (0.10, 0.85)	7	0.40 (0.17, 0.95)	6	1.08 (0.36, 3.25)	
Per 1 unit increase	2031	0.93 (0.89, 0.97)	971	0.88 (0.83, 0.93)	210	0.79 (0.70, 0.90)	250	0.82 (0.73, 0.92)	50	1.12 (0.89, 1.40)	
P_{trend}		0.0002		<0.0001		0.0005		0.0008		0.33	

[a] All estimates are adjusted for age (months), time period, cohort, recent alcohol consumption (0, 0.1-1.4, 1.5-4.9, 5.0-9.9, ≥ 10 g/day), age at menarche (<12, 12, 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 (cont), oral contraceptive duration (years), history of benign breast disease (yes/no), first degree family history of breast cancer (yes/no), birth weight (< 5.5 lbs, 5.5-6.9 lbs, 7-8.4 lbs, ≥ 8.5 lbs), weight change since age 18 (kg), interaction between menopausal status and weight change since 18, cumulative average physical activity (quintiles).

[b] Average of somatotype at ages 5 and 10;

[c] Average of somatotype at ages 10 and 20;