Early-Life and Adult Adiposity, Adult Height, and Benign Breast Tissue Composition

Hannah Oh[1,2], Lusine Yaghjyan[3], Rebecca J. Austin-Datta[3], Yujing J. Heng[4], Gabrielle M. Baker[4], Korsuk Sirinukunwattana[4,5], Adithya D. Vellal[4], Laura C. Collins[4], Divya Murthy[6], A. Heather Eliassen[6,7], Bernard A. Rosner[6,8], and Rulla M. Tamimi[9]

ABSTRACT

Background: Early-life and adult anthropometrics are associated with breast density and breast cancer risk. However, little is known about whether these factors also influence breast tissue composition beyond what is captured by breast density among women with benign breast disease (BBD).

Methods: This analysis included 788 controls from a nested case–control study of breast cancer within the Nurses' Health Study BBD subcohorts. Body fatness at ages 5 and 10 years was recalled using a 9-level pictogram. Weight at age 18, current weight, and height were reported via questionnaires. A deep-learning image analysis was used to quantify the percentages of epithelial, fibrous stromal, and adipose tissue areas within BBD slides. We performed linear mixed models to estimate beta coefficients (β) and 95% confidence intervals (CI) for the relationships between anthropometrics and the log-transformed percentages of individual tissue type, adjusting for confounders.

Results: Childhood body fatness (level ≥ 4.5 vs. 1), BMI at age 18 (≥23 vs. <19 kg/m^2), and current adult BMI (≥30 vs. <21 kg/m^2) were associated with higher proportions of adipose tissue [β (95% CI) = 0.34 (0.03, 0.65), 0.19 (−0.04–0.42), 0.40 (0.12, 0.68), respectively] and lower proportions of fibrous stromal tissue [−0.05 (−0.10, 0.002), −0.03 (−0.07, 0.003), −0.12 (−0.16, −0.07), respectively] during adulthood (all $P_{trend} < 0.04$). BMI at age 18 was also inversely associated with epithelial tissue ($P_{trend} = 0.03$). Adult height was not associated with any of the individual tissue types.

Conclusions: Our data suggest that body fatness has long-term impacts on breast tissue composition.

Impact: This study contributes to our understanding of the link between body fatness and breast cancer risk.

See related commentary by Oskar et al., p. 590

Introduction

Anthropometric measures including body fatness (1–9) and height (1, 8, 10) are associated with the risk of breast cancer, the most commonly diagnosed cancer in women worldwide (11). Among both pre- and postmenopausal women (12–17), early-life and adult body fatness have also been consistently associated with percent mammographic density (PMD; refs. 12–18), a strong breast cancer risk factor (19–21), suggesting a potential mechanism through which these factors may influence breast cancer risk. Adult height was associated with PMD in some studies (17, 18, 22), but not in others (15, 23).

PMD indicates the relative amount of dense (fibroglandular) versus nondense (adipose) tissue in the breast. Fibroglandular tissue includes both epithelial and fibrous stromal tissues. While many studies have examined the factors associated with PMD, few studies have specifically measured the amount of specific tissue types in the breast and examined the relationships with epithelial, fibrous stromal, and adipose tissue. As most breast cancers arise from epithelial tissues (24) and studies suggest independent roles of both epithelial and stromal tissue on breast cancer risk (25), the investigation of the risk factor associations with specific breast tissue types in cancer-free women may provide additional insights into the mechanisms through which these factors influence breast cancer risk.

In the Nurses' Health Study (NHS) and NHSII, we have quantified the percentages of individual breast tissue types (epithelial, fibrous stromal, adipose) on benign breast biopsies using deep-learning computer analysis. In this study, we examined the relationships of early-life and adult anthropometric measures [childhood body fatness, body mass index (BMI) at age 18, current adult BMI, change in BMI since age 18, and adult height] with breast tissue composition on benign breast biopsies among women with biopsy-confirmed benign breast disease (BBD) in the NHS and NHSII.

Materials and Methods

Study population

This analysis included participants who served as controls in the nested case–control study of breast cancer that was conducted within the Nurses' Health Study (NHS) and NHSII BBD subcohorts. Details of this nested case–control study have been described previously (26, 27). The NHS and NHSII are ongoing cohort studies. The NHS began in 1976 among 121,700 female nurses aged 30–55 years. The NHSII began in 1989 among 116,429 female nurses aged 25–42 years. In both cohorts, information on

[1]Interdisciplinary Program in Precision Public Health, Department of Public Health Sciences, Graduate School of Korea University, Seoul, Republic of Korea. [2]Division of Health Policy and Management, College of Health Sciences, Korea University, Seoul, Republic of Korea. [3]Department of Epidemiology, College of Public Health and Health Professions and College of Medicine, University of Florida, Gainesville, Florida. [4]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. [5]Department of Engineering Science, Institute of Biomedical Engineering (IBME), University of Oxford, Oxford, United Kingdom. [6]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [8]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [9]Department of Population Health Sciences, Weill Cornell Medicine, New York, New York.

Corresponding Author: Hannah Oh, Korea University, Hana Science Building B358, 145 Anam-ro, Seongbuk-gu, Seoul, Republic of Korea. Phone: 822-3290-5678; E-mail: hannahoh@korea.ac.kr

Cancer Epidemiol Biomarkers Prev 2021;30:608–15

doi: 10.1158/1055-9965.EPI-20-1348

participants' health behaviors, anthropometric factors, medical histories, and disease diagnosis (e.g., BBD) were collected via self-administered questionnaires (28). Both cases and controls reported biopsy-confirmed BBD diagnosis in 1950–1998. Cases were women who developed breast cancer following their BBD diagnosis. Among women who remained free of breast cancer at the time each case was diagnosed, up to four controls (1:4 matching) were selected matching to the case on year of birth and year of benign breast biopsy. For all cases and controls, we attempted to obtain BBD pathology records and archived benign biopsy specimen from their hospital pathology department.

This analysis was restricted to the controls from this nested case–control study because controls were selected to represent the exposure distribution in the study base. To reduce potential reverse causation due to clinical and subclinical tissue change, we excluded all cases and women with *in situ* or invasive carcinoma at benign breast biopsy. Among 1,908 controls, we excluded women with missing information on age at benign biopsy ($n = 1$) and breast tissue composition (unable to obtain biopsy specimen, unable to digitize the biopsy slides; $n = 924$). The characteristics of study participants were similar between those with versus without missing information on breast tissue composition, except that women with missing information were younger and had slightly lower current adult BMI. We also excluded women with missing information on anthropometrics (childhood and adolescent body fatness: $n = 145$; BMI at age 18 years: $n = 36$; current adult BMI: $n = 14$). A total of 788 women were included in this analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Consent was obtained or implied by return of questionnaires. The study was conducted in accordance with recognized ethical guidelines (Declaration of Helsinki).

Exposure assessment

Body fatness at ages 5, 10, and 20 years were recalled in 1988 (NHS) and 1989 (NHSII) using Stunkard's nine-level pictogram (level 1: most lean; level 9: most overweight; ref. 29). Recalled body fatness using this pictogram has shown a good correlation with measured BMI in a previous validation study (Pearson $r = 0.60$–0.66; ref. 30). Average body fatness at ages 5 and 10 years was used to represent childhood body fatness. For childhood body fatness measures, we collapsed the levels 4.5 or higher because there were few women with extreme values. Height and weight at age 18 were reported via the baseline questionnaire and were used to estimate BMI at age 18 (kg/m^2). We also estimated current adult BMI (kg/m^2) using current weight that was reported via follow-up questionnaires administered around the time of benign breast biopsy. Change in BMI since age 18 (kg/m^2) was estimated by subtracting BMI at age 18 from current adult BMI. All continuous exposure variables (BMI at age 18, current adult BMI, change in BMI since age 18, and adult height) were categorized into quintiles based on the distribution in the study sample.

Breast tissue composition

Hematoxylin and eosin (H&E)-stained benign breast biopsy slides were independently reviewed by study pathologists and classified according to BBD subtypes (nonproliferative, proliferative without atypia, atypical ductal or lobular hyperplasia; ref. 27). Whole-slide images were digitized (Panoramic SCAN 150, 3DHISTECH Ltd.) and processed to quantify the percentages of epithelial, fibrous stromal, and adipose tissues using deep-learning computational pathology method. Details of the method are described elsewhere (31, 32). Briefly, our method generated binary tissue masks for each whole-slide image using color thresholding. After locating the tissue-containing areas, each whole-slide image was split into 2048 × 2048 patches and tissue segmentation was performed. Each pixel on a patch is classified as epithelial (comprising of normal terminal duct lobular units and benign lesions), fibrous stroma (inter- and intralobular), fat, or background. Pixels classified per tissue region were summed across patches; values from the patches were summed to the whole-slide image level. We averaged across all available slides for a woman (median = 3, range 1–4), weighted by the total tissue area of the slides.

Statistical analysis

Percentages of epithelial, fibrous stromal, and adipose tissues were log-transformed to improve normality of the residuals. To account for correlations among the controls within the matched sets, we performed linear mixed models with a compound symmetry correlation structure to estimate beta coefficients (β) and 95% confidence intervals (CI) for the relationships between anthropometrics and log-transformed percentages of individual breast tissue type (epithelial, fibrous stromal, adipose). Multivariable models included age at BBD, menopausal status/hormone therapy (HT) use, BBD subtype, BBD diagnosis year, family history of breast cancer, parity/age at first birth, total breastfeeding, smoking, alcohol use, and physical activity. Additional adjustment for age at menopause and age at menarche did not change the results and thus these variables were not included in the final models. For change in BMI since age 18, models additionally adjusted for BMI at age 18. For all analyses, we used covariate information reported via questionnaires assessed prior to but around the time of benign breast biopsy. We performed tests for trend by modeling exposures as continuous variables using category-specific median values. For early-life body fatness measures, we also evaluated the role of potential mediators by comparing the models with and without adjustment for weight change since age 18. To reduce collinearity, we adjusted for weight change since age 18 instead of current adult BMI. We also stratified the analyses by menopausal status and BBD subtype to assess the variation in associations by these variables. We performed tests for interaction using Wald test for interaction terms. To confirm the robustness of results, logistic regression models on binary outcomes (above vs. below median; 7.5% epithelial, 74.5% fibrous stromal, 15.3% adipose) were additionally performed as sensitivity analyses. In separate sensitivity analyses, we also repeated analyses after excluding outliers (0 for epithelial, 9 values for fibrous stromal, and 9 values for adipose tissue measure) identified using the extreme Studentized deviate many-outlier procedure (33). All analyses were conducted with SAS software 9.3 (SAS Institute Inc.).

Results

The mean age at benign breast biopsy was 46.0 years among 788 women who were included in our analysis. The majority of women were premenopausal (64%). The mean BMI at benign breast biopsy was 24.2 kg/m^2. On average, women with higher levels of childhood body fatness were younger and more likely to have nonproliferative lesions, higher BMI at age 18 and current adult BMI, younger age at menarche, family history of breast cancer, and, among postmenopausal women, younger age at menopause (**Table 1**).

Childhood body fatness (level ≥ 4.5 vs. 1) was statistically significantly associated with higher proportions of adipose tissue [$\beta = 0.34$; 95% CI = 0.03, 0.65; $P_{trend} = 0.02$) and lower proportions of fibrous stromal tissue ($\beta = -0.05$; 95% CI = −0.10, 0.002; $P_{trend} = 0.03$; **Table 2**). After additional adjustment for weight change since age 18,

Table 1. Age and age-adjusted characteristics of 788 study participants in the Nurses' Health Study (NHS) and the NHSII, according to self-reported average body fatness at ages 5–10 years.

	Childhood body fatness (average at ages 5–10 years)				
	Level 1 (*N* = 263)	**Level 1.5–2 (*N* = 240)**	**Level 2.5–3 (*N* = 135)**	**Level 3.5–4 (*N* = 92)**	**Level ≥4.5 (*N* = 58)**
	Mean (SD) or percentage				
Age at biopsy[a], years	47.4 (10.5)	45.8 (10.6)	44.8 (10.3)	44.6 (10.8)	45.5 (7.9)
Height, inches	64.7 (2.6)	64.7 (2.4)	64.7 (2.3)	65.0 (2.6)	64.8 (2.5)
BMI at age 18, kg/m^2	19.7 (2.3)	20.7 (2.2)	21.8 (2.5)	22.3 (2.2)	23.4 (2.8)
Current adult BMI[b], kg/m^2	23.1 (3.4)	23.8 (3.9)	25.0 (4.6)	25.4 (4.3)	26.9 (5.2)
Age at menarche, years	13.0 (1.3)	12.6 (1.3)	12.5 (1.2)	12.5 (1.3)	12.0 (1.2)
Alcohol intake[b], g/d	5.9 (8.7)	5.4 (10.2)	3.9 (6.8)	5.8 (9.3)	4.4 (4.6)
Physical activity[b], MET-hr/wk	14.3 (17.1)	16.4 (19.0)	14.4 (15.1)	13.2 (15.8)	13.9 (15.1)
Current smoking[b], %	20.7	11.7	18.8	15.8	16.9
BBD subtype[b]					
Nonproliferative, %	27.7	36.1	25.5	37.9	34.0
Proliferative without atypia, %	58.7	50.6	55.8	52.6	55.3
Atypical hyperplasia, %	13.6	13.4	18.8	9.5	10.8
Calendar year of BBD diagnosis					
1950–1969, %	8.4	5.1	3.9	3.4	0.0
1970–1979, %	27.2	25.0	16.9	16.7	27.2
1980–1989, %	45.2	47.3	48.2	54.8	45.8
1990–1998, %	19.2	22.5	30.9	25.1	27.0
Parity/age at first birth[b]					
Nulliparous, %	9.4	8.5	8.9	9.2	6.1
Parous/<25 years, %	46.9	50.4	43.4	54.6	51.9
Parous/25–29 years, %	34.9	32.5	35.5	31.6	35.7
Parous/≥30 years, %	8.9	8.6	12.1	4.7	6.2
Total breastfeeding[b] (among parous women)					
<1 month, %	46.9	39.6	42.5	52.5	23.7
1–6 months, %	21.1	22.8	20.5	14.1	45.1
7–12 months, %	15.0	13.1	16.7	19.3	11.3
≥13 months, %	17.0	24.5	20.3	14.2	19.9
Menopausal status/HT use[b]					
Premenopausal, %	63.1	64.4	69.6	66.3	65.8
Postmenopausal/non-HT users, %	14.5	15.0	15.6	19.3	11.7
Postmenopausal/current HT users, %	10.7	12.3	7.5	6.3	10.5
Unknown/missing, %	11.8	8.3	7.3	8.2	11.9
Age at menopause[b,c], years	49.0 (3.9)	48.1 (5.1)	47.6 (6.0)	46.5 (5.8)	45.1 (6.2)
Family history of breast cancer, %	8.9	13.7	11.2	12.8	17.4

Note: Values are means (SD) or percentages, standardized to the age distribution of the study population, except for age. Values of polytomous variables may not sum to 100% due to rounding.

Abbreviations: BBD, benign breast disease; BMI, body mass index; HT, hormone therapy; MET, metabolic equivalent task.

[a]Value is not age adjusted.

[b]At the time of benign biopsy.

[c]Among postmenopausal women only.

both associations did not change and remained statistically significant (adipose: $\beta = 0.34$; 95% CI = 0.03, 0.64; $P_{trend} = 0.02$; fibrous stromal: $\beta = -0.05$; 95% CI = −0.10, 0.004; $P_{trend} = 0.02$). No association was found between childhood body fatness and epithelial tissue ($\beta = 0.02$; 95% CI = −0.16, 0.21; $P_{trend} = 0.87$).

BMI at age 18 (≥23.0 vs. <19.0 kg/m^2) was positively associated with proportions of adipose tissue ($\beta = 0.19$; 95% CI = −0.04, 0.42; $P_{trend} = 0.02$) and inversely associated with proportions of epithelial ($\beta = -0.15$; 95% CI = −0.29, −0.01; $P_{trend} = 0.03$) and fibrous stromal tissue ($\beta = -0.03$; 95% CI = −0.07, 0.003; $P_{trend} = 0.04$; **Table 2**). After additional adjustment for weight change since age 18, these associations remained statistically significant (all $P_{trend} < 0.05$).

Current adult BMI (≥30.0 vs. <21.0 kg/m^2) was positively associated with proportions of adipose tissue ($\beta = 0.40$; 95% CI = 0.12, 0.68; $P_{trend} < 0.001$) and inversely associated with proportions of fibrous stromal tissue ($\beta = -0.12$; 95% CI = −0.16, −0.07; $P_{trend} < 0.0001$; **Table 2**). The associations did not materially change after additional adjustment for childhood body fatness (adipose: $\beta = 0.34$; 95% CI = 0.04, 0.63; $P_{trend} = 0.003$; fibrous stromal: $\beta = -0.11$; 95% CI = −0.16, −0.06; $P_{trend} < 0.0001$). No association was found for epithelial tissue. Similar positive association with adipose tissue and inverse association with fibrous stromal tissue were also observed with change in BMI since age 18. However, adult height was not associated with any of the individual tissue types (**Table 2**).

When stratified by menopausal status, current adult BMI (per 1 kg/m^2 increase) was positively associated with epithelial tissue in postmenopausal women (non-HT users: $\beta = 0.05$; 95% CI = 0.01, 0.08; current HT users: $\beta = 0.03$; 95% CI = −0.01, 0.08), but inversely associated in premenopausal women ($\beta = -0.01$; 95% CI = −0.02, 0.001; $P_{interaction} = 0.003$; **Table 3**). Similar interactions by menopausal

Table 2. Associations of early-life and adult anthropometric measures with log-transformed percentages of individual breast tissue types (epithelial, fibrous stroma, adipose) on benign breast biopsies in the Nurses' Health Study (NHS) and the NHSII.

		Beta coefficient (95% confidence interval)					
		Epithelial tissue		Fibrous stromal tissue		Adipose tissue	
	N	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Childhood body fatness (average at ages 5–10 years)							
Level 1	263	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Level 1.5–2	240	0.04 (−0.08 to 0.15)	0.04 (−0.07 to 0.16)	−0.01 (−0.04 to 0.03)	−0.01 (−0.04 to 0.02)	−0.05 (−0.24 to 0.14)	−0.04 (−0.23 to 0.15)
Level 2.5–3	135	−0.08 (−0.21 to 0.06)	−0.07 (−0.21 to 0.06)	−0.003 (−0.04 to 0.03)	−0.01 (−0.04 to 0.03)	0.12 (−0.11 to 0.34)	0.13 (−0.10 to 0.35)
Level 3.5–4	92	0.07 (−0.09 to 0.22)	0.08 (−0.08 to 0.23)	−0.04 (−0.08 to 0.01)	−0.04 (−0.08 to −0.0003)	0.12 (−0.13 to 0.38)	0.14 (−0.12 to 0.40)
Level ≥4.5	58	0.02 (−0.16 to 0.21)	0.02 (−0.17 to 0.20)	−0.05 (−0.10 to 0.002)	−0.05 (−0.10 to 0.004)	0.34 (0.03 to 0.65)	0.34 (0.03 to 0.64)
P_{trend}[c]	788	0.87	0.84	0.03	0.02	0.02	0.02
BMI at age 18 years, kg/m^2							
<19.0	186	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
19.0–19.9	129	−0.04 (−0.18 to 0.11)	−0.03 (−0.18 to 0.12)	0.02 (−0.02 to 0.06)	0.01 (−0.03 to 0.05)	−0.17 (−0.41 to 0.07)	−0.15 (−0.39 to 0.09)
20.0–20.9	137	−0.05 (−0.19 to 0.10)	−0.04 (−0.18 to 0.10)	−0.01 (−0.05 to 0.03)	−0.02 (−0.06 to 0.02)	0.07 (−0.17 to 0.31)	0.09 (−0.15 to 0.33)
21.0–22.9	176	−0.07 (−0.20 to 0.07)	−0.06 (−0.20 to 0.07)	−0.003 (−0.04 to 0.03)	−0.01 (−0.04 to 0.03)	0.10 (−0.13 to 0.32)	0.11 (−0.11 to 0.33)
≥23.0	160	−0.15 (−0.29 to -0.01)	−0.14 (−0.28 to 0.002)	−0.03 (−0.07 to 0.003)	−0.04 (−0.08 to −0.01)	0.19 (−0.04 to 0.42)	0.22 (−0.005 to 0.45)
P_{trend}[c]	788	0.03	0.05	0.04	0.01	0.02	0.01
Current adult BMI, kg/m^2							
<21.0	174	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
21.0–22.9	203	0.05 (−0.09 to 0.18)	0.05 (−0.09 to 0.18)	−0.005 (−0.04 to 0.03)	−0.003 (−0.04 to 0.03)	−0.11 (−0.33 to 0.11)	−0.13 (−0.35 to 0.09)
23.0–24.9	159	−0.09 (−0.23 to 0.06)	−0.09 (−0.23 to 0.06)	−0.01 (−0.05 to 0.03)	−0.01 (−0.05 to 0.03)	−0.05 (−0.28 to 0.19)	−0.07 (−0.30 to 0.17)
25.0–29.9	168	0.03 (−0.11 to 0.17)	0.03 (−0.11 to 0.18)	−0.05 (−0.09 to −0.01)	−0.05 (−0.09 to −0.01)	0.17 (−0.06 to 0.40)	0.14 (−0.09 to 0.38)
≥30.0	84	0.05 (−0.12 to 0.22)	0.05 (−0.13 to 0.23)	−0.12 (−0.16 to −0.07)	−0.11 (−0.16 to −0.06)	0.40 (0.12 to 0.68)	0.34 (0.04 to 0.63)
P_{trend}[c]	788	0.57	0.59	<0.0001	<0.0001	<0.001	0.003
Change in BMI since age 18, kg/m^2							
≤0	112	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
0.1–2.0	224	−0.08 (−0.23 to 0.08)	−0.07 (−0.22 to 0.08)	−0.03 (−0.07 to 0.01)	−0.03 (−0.07 to 0.01)	0.15 (−0.10 to 0.40)	0.16 (−0.09 to 0.41)
2.1–4.0	184	−0.14 (−0.30 to 0.01)	−0.14 (−0.30 to 0.02)	−0.05 (−0.09 to −0.01)	−0.05 (−0.09 to −0.01)	0.15 (−0.11 to 0.42)	0.16 (−0.10 to 0.43)
4.1–7.0	156	−0.03 (−0.20 to 0.14)	−0.03 (−0.19 to 0.14)	−0.08 (−0.12 to −0.04)	−0.08 (−0.13 to −0.04)	0.33 (0.05 to 0.60)	0.33 (0.06 to 0.61)
>7.0	112	0.04 (−0.14 to 0.21)	0.04 (−0.13 to 0.22)	−0.12 (−0.16 to −0.07)	−0.12 (−0.16 to −0.07)	0.43 (0.14 to 0.71)	0.43 (0.14 to 0.72)
P_{trend}[c]	788	0.27	0.27	<0.0001	<0.0001	0.002	0.002
Height, inches							
<63.0	180	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
63.0–64.9	201	−0.05 (−0.18 to 0.08)	−0.05 (−0.18 to 0.08)	0.01 (−0.03 to 0.04)	0.01 (−0.03 to 0.04)	−0.04 (−0.25 to 0.18)	−0.04 (−0.25 to 0.18)
65.0–65.9	105	0.02 (−0.14 to 0.17)	0.02 (−0.14 to 0.17)	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.02)	−0.09 (−0.35 to 0.17)	−0.09 (−0.35 to 0.17)
66.0–66.9	116	0.09 (−0.06 to 0.24)	0.09 (−0.06 to 0.24)	−0.003 (−0.04 to 0.04)	−0.002 (−0.04 to 0.04)	−0.13 (−0.39 to 0.12)	−0.14 (−0.39 to 0.11)
≥67.0	186	−0.001 (−0.13 to 0.13)	−0.0004 (−0.13 to 0.13)	−0.02 (−0.05 to 0.02)	−0.02 (−0.06 to 0.02)	0.20 (−0.03 to 0.42)	0.20 (−0.02 to 0.42)
P_{trend}[c]	788	0.60	0.60	0.23	0.22	0.12	0.11

Abbreviations: BBD, benign breast disease; BMI, body mass index; HT: hormone therapy; MET, metabolic equivalent task.

[a]Model 1 included age at benign biopsy (years, continuous), BBD subtype (nonproliferative, proliferative without atypia, atypical hyperplasia), BBD diagnosis year (1950–1969, 1970–1979, 1980–1989, 1990–1998), menopausal status/HT use (premenopausal, postmenopausal/non-HT users, postmenopausal/current HT users, other), family history of breast cancer (yes, no), parity/age at first birth (nulliparous, parous/<25 years, parous/25–29 years, parous/≥30 years), total breastfeeding (nulliparous, <1, 1–6, 7–12, ≥13 months), current smoking (yes, no), alcohol intake (g/d), and physical activity (MET-hr/wk). For change in BMI since age 18, models additionally adjusted for BMI at age 18 (kg/m^2, continuous).

[b]Model 2 additionally included weight change since age 18 (kg, continuous) for childhood body fatness and BMI at age 18 exposures, and included childhood body fatness (level 1–5+, continuous) for current adult BMI, change in BMI since age 18, and height exposures in Model 1.

[c]P_{trend} was estimated by modeling exposures as continuous variables using category-specific median values.

Table 3. Associations of early-life and adult anthropometric measures with log-transformed percentages of individual breast tissue types (epithelial, fibrous stroma, adipose) on benign breast biopsies in the Nurses' Health Study (NHS) and the NHSII, stratified by menopausal status.

			Beta coefficient (95% confidence interval)		
		N	Epithelial	Fibrous stromal	Adipose
Childhood body fatness					
Premenopausal	Per 1-level increase	501	−0.02 (−0.06 to 0.02)	−0.01 (−0.02 to 0.001)	0.08 (−0.001 to 0.15)
Postmenopausal/non-HT users	Per 1-level increase	125	0.09 (−0.03 to 0.21)	0.0003 (−0.03 to 0.03)	−0.06 (−0.19 to 0.07)
Postmenopausal/current HT users	Per 1-level increase	88	0.14 (−0.01 to 0.28)	−0.05 (−0.09 to −0.01)	0.23 (−0.07 to 0.53)
$P_{interaction}$		714	0.03	0.09	0.35
BMI at age 18					
Premenopausal	Per 1-kg/m^2 increase	501	−0.02 (−0.04 to 0.0002)	−0.01 (−0.01 to −0.001)	0.04 (0.01 to 0.07)
Postmenopausal/non-HT users	Per 1-kg/m^2 increase	125	0.01 (−0.04 to 0.07)	−0.001 (−0.02 to 0.01)	−0.03 (−0.09 to 0.03)
Postmenopausal/current HT users	Per 1-kg/m^2 increase	88	−0.01 (−0.09 to 0.08)	−0.03 (−0.06 to −0.01)	0.13 (−0.05 to 0.30)
$P_{interaction}$		714	0.91	0.03	0.45
Current adult BMI					
Premenopausal	Per 1-kg/m^2 increase	501	−0.01 (−0.02 to 0.001)	−0.01 (−0.01 to −0.004)	0.04 (0.02 to 0.06)
Postmenopausal/non-HT users	Per 1-kg/m^2 increase	125	0.05 (0.01 to 0.08)	−0.01 (−0.02 to 0.001)	−0.002 (−0.05 to 0.04)
Postmenopausal/current HT users	Per 1-kg/m^2 increase	88	0.03 (−0.01 to 0.08)	−0.01 (−0.02 to −0.002)	0.002 (−0.08 to 0.09)
$P_{interaction}$		714	0.003	0.26	0.24
Change in BMI since age 18					
Premenopausal	Per 1-kg/m^2 increase	501	−0.01 (−0.02 to 0.01)	−0.01 (−0.01 to −0.004)	0.04 (0.01 to 0.06)
Postmenopausal/non-HT users	Per 1-kg/m^2 increase	125	0.05 (0.01 to 0.09)	−0.01 (−0.02 to 0.001)	0.01 (−0.04 to 0.05)
Postmenopausal/current HT users	Per 1-kg/m^2 increase	88	0.05 (0.0004 to 0.10)	−0.005 (−0.02 to 0.01)	−0.04 (−0.14 to 0.06)
$P_{interaction}$		714	0.005	0.53	0.25
Height					
Premenopausal	Per 1-inch increase	501	0.003 (−0.02 to 0.02)	−0.002 (−0.01 to 0.003)	0.02 (−0.02 to 0.06)
Postmenopausal/non-HT users	Per 1-inch increase	125	0.003 (−0.05 to 0.06)	−0.02 (−0.03 to 0.001)	0.05 (−0.01 to 0.11)
Postmenopausal/current HT users	Per 1-inch increase	88	0.01 (−0.05 to 0.08)	−0.002 (−0.02 to 0.02)	0.02 (−0.12 to 0.15)
$P_{interaction}$		714	0.46	0.47	0.98

Note: Adjusted for age at benign biopsy (years, continuous), BBD subtype (nonproliferative, proliferative without atypia, atypical hyperplasia), BBD diagnosis year (1950–1969, 1970–1979, 1980–1989, 1990–1998), menopausal status/HT use (premenopausal, postmenopausal/non-HT users, postmenopausal/current HT users, other), family history of breast cancer (yes, no), parity/age at first birth (nulliparous, parous/<25 years, parous/25–29 years, parous/≥30 years), total breastfeeding (nulliparous, <1, 1–6, 7–12, ≥13 months), current smoking (yes, no), alcohol intake (g/d), and physical activity (MET-hr/wk). For change in BMI since age 18, models additionally adjusted for BMI at age 18 (kg/m^2, continuous).
Abbreviations: BBD, benign breast disease; BMI, body mass index; HT, hormone therapy; MET, metabolic equivalent task.

status were found for the associations between change in BMI since age 18 and epithelial tissue ($P_{interaction} = 0.005$) and between childhood body fatness and epithelial tissue ($P_{interaction} = 0.03$). Although the interaction was not statistically significant ($P_{interaction} = 0.24$), the positive association between current adult BMI and adipose tissue was restricted to premenopausal women ($\beta = 0.04$; 95% CI = 0.02, 0.06). When stratified by BBD subtype, the associations were similar across BBD subtypes (**Table 4**).

In sensitivity analyses, results were similar when logistic regression models were performed on binary outcomes and after excluding outliers.

Discussion

To date, this study is the first to comprehensively examine early-life and adult anthropometric measures in relation to epithelial, fibrous stromal, and adipose tissue composition in pre- and postmenopausal women with BBD. In this study, both early-life and adult body fatness were associated with higher percentages of adipose tissue and lower percentages of fibrous stromal tissue on benign breast biopsies. These associations for early-life and adult body fatness did not change after adjustment for each other, providing evidence for independent effects. With BMI at age 18, we additionally observed an inverse association with epithelial tissue. Current adult BMI and change in BMI since age 18 were positively associated with epithelial tissue in postmenopausal women only. Adult height was not associated with any of the breast tissue composition measures.

Our findings of strong positive associations between body fatness measures and adipose tissue are consistent with those from previous studies of PMD (13, 17, 18, 34–38). Including our previous report from the NHS and NHSII (18), studies have consistently reported that higher levels of body fatness are associated with lower levels of PMD, indicating higher amount of nondense (adipose) tissue compared with that of dense tissue (epithelial and fibrous stromal tissues combined). These studies suggested that the excess adipose tissue in the body may contribute to a higher amount of adipose tissue in the breast. In this study of benign breast biopsies, we also observed lower proportions of fibrous stromal tissue, as well as higher proportions of adipose tissue, in women with higher levels of body fatness. Our findings provided additional information regarding breast tissue composition in relation to body fatness across the lifecourse. Our data suggest that an increase in the amount of adipose tissue in the breast may occur by replacing fibrous stromal tissue but not epithelial tissue. In this study, the inverse association for epithelial tissue was observed with BMI at age 18 only and not with childhood or current adult body fatness, suggesting that body fatness at a certain age period (e.g., during puberty) may differentially influence breast tissue composition and have lifelong impact on age-related lobular involution (the age-related process of

Table 4. Associations of early-life and adult anthropometric measures with log-transformed percentages of individual breast tissue types (epithelial, fibrous stroma, adipose) on benign breast biopsies in the Nurses' Health Study (NHS) and the NHSII, stratified by BBD subtype.

			Beta (95% confidence interval)		
		N	Epithelial	Fibrous stromal	Adipose
Childhood body fatness					
Nonproliferative lesion	Per 1-level increase	245	−0.01 (−0.09 to 0.07)	−0.02 (−0.04 to −0.0005)	0.19 (0.07 to 0.31)
Proliferative lesion without atypia	Per 1-level increase	442	−0.003 (−0.05 to 0.04)	−0.002 (−0.01 to 0.01)	0.02 (−0.07 to 0.10)
Proliferative lesion with atypia	Per 1-level increase	101	0.05 (−0.06 to 0.16)	−0.03 (−0.05 to −0.01)	0.10 (−0.01 to 0.22)
$P_{interaction}$		788	0.79	0.10	0.12
BMI at age 18					
Nonproliferative lesion	Per 1-kg/m^2 increase	245	−0.02 (−0.05 to 0.01)	−0.01 (−0.02 to −0.01)	0.07 (0.02 to 0.12)
Proliferative lesion without atypia	Per 1-kg/m^2 increase	442	−0.01 (−0.03 to 0.01)	0.0002 (−0.01 to 0.01)	0.01 (−0.02 to 0.05)
Proliferative lesion with atypia	Per 1-kg/m^2 increase	101	−0.03 (−0.09 to 0.02)	−0.01 (−0.03 to −0.003)	0.08 (0.01 to 0.14)
$P_{interaction}$		788	0.98	0.003	0.15
Current adult BMI					
Nonproliferative lesion	Per 1-kg/m^2 increase	245	−0.01 (−0.03 to 0.01)	−0.01 (−0.02 to −0.005)	0.05 (0.02 to 0.08)
Proliferative lesion without atypia	Per 1-kg/m^2 increase	442	0.003 (−0.01 to 0.02)	−0.01 (−0.01 to −0.003)	0.03 (0.004 to 0.05)
Proliferative lesion with atypia	Per 1-kg/m^2 increase	101	−0.0005 (−0.03 to 0.03)	−0.01 (−0.01 to −0.001)	0.01 (−0.02 to 0.05)
$P_{interaction}$		788	0.93	0.69	0.80
Change in BMI since age 18					
Nonproliferative lesion	Per 1-kg/m^2 increase	245	0.004 (−0.02 to 0.03)	−0.01 (−0.01 to −0.0001)	0.03 (−0.01 to 0.07)
Proliferative lesion without atypia	Per 1-kg/m^2 increase	442	0.01 (−0.01 to 0.03)	−0.01 (−0.02 to −0.01)	0.04 (0.004 to 0.07)
Proliferative lesion with atypia	Per 1-kg/m^2 increase	101	0.01 (−0.02 to 0.04)	−0.005 (−0.01 to 0.002)	−0.004 (−0.04 to 0.03)
$P_{interaction}$		788	0.99	0.29	0.44
Height					
Nonproliferative lesion	Per 1-inch increase	245	0.02 (−0.01 to 0.06)	0.003 (−0.01 to 0.01)	0.01 (−0.04 to 0.06)
Proliferative lesion without atypia	Per 1-inch increase	442	−0.01 (−0.03 to 0.01)	−0.01 (−0.01 to −0.001)	0.03 (−0.01 to 0.07)
Proliferative lesion with atypia	Per 1-inch increase	101	0.03 (−0.03 to 0.08)	−0.01 (−0.02 to 0.01)	0.02 (−0.05 to 0.08)
$P_{interaction}$		788	0.36	0.10	0.74

Note: Adjusted for age at benign biopsy (years, continuous), BBD subtype (nonproliferative, proliferative without atypia, atypical hyperplasia), BBD diagnosis year (1950–1969, 1970–1979, 1980–1989, 1990–1998), menopausal status/HT use (premenopausal, postmenopausal/non-HT users, postmenopausal/current HT users, other), family history of breast cancer (yes, no), parity/age at first birth (nulliparous, parous/<25 years, parous/25–29 years, parous/≥30 years), total breastfeeding (nulliparous, <1, 1–6, 7–12, ≥13 months), current smoking (yes, no), alcohol intake (g/d), and physical activity (MET-hr/wk). For change in BMI since age 18, models additionally adjusted for BMI at age 18 (kg/m^2, continuous).

Abbreviations: BBD, benign breast disease; BMI, body mass index; HT, hormone therapy; MET, metabolic equivalent task.

atrophy of epithelial structures and replacement with adipose tissue in the breast). Further studies are needed to confirm the influence of body fatness at different ages on breast tissue composition, particularly fibrous stromal versus epithelial composition.

In our stratified analyses, we observed some variation in associations by menopausal status. Among premenopausal women, we observed that current adult BMI was positively associated with adipose tissue and inversely associated with both epithelial and fibrous stromal tissues. However, among postmenopausal women, current adult BMI was positively associated with epithelial tissue and not associated with adipose tissue. The differential associations we observed in pre- versus postmenopausal women are in line with the evidence on relationship with breast cancer risk. In many studies, premenopausal BMI is inversely associated with breast cancer risk (3, 39), whereas postmenopausal BMI is positively associated (1, 7–9). Similarly, higher proportions of epithelial tissue as we observed in postmenopausal women have been associated with an increased breast cancer risk (40–42), whereas higher proportions of adipose tissue have been associated with a reduced breast cancer risk (19–21). Our findings support breast tissue composition as a potential link between body fatness and breast cancer risk.

With adult height, we did not observe an association with benign breast tissue composition. Studies have shown inconsistent findings for the relationship between height and PMD (15, 17, 18, 22, 23). In our previous report from the NHS (18), we observed that height was positively associated with PMD in premenopausal women but not in postmenopausal women. However, in this study of benign biopsies, we did not observe an association in either pre- or postmenopausal women. The discrepancy in results may be due to the differences in population characteristics (women with vs. without BBD) and methodologic issues (mammography vs. biopsies). While most studies of PMD included healthy women, our study was restricted to women with biopsy-confirmed BBD. Although BBD is not cancerous, surrounding tissues of benign lesions may not be similar to those of healthy women who have never had a breast biopsy. Our breast tissue measures also reflect available tissue from a biopsy, which may include the benign lesion and may not be representative of the entire breast. Furthermore, while PMD reflects dense versus nondense tissue area or volume composition at macroscopic levels (entire breast), our biopsy-based measures reflect breast tissue composition at microscopic levels (lesion area). Although a previous study from women with BBD has reported positive correlations between PMD and biopsy-based epithelial content measures (43, 44), little is known about the relationship between microscopic versus macroscopic levels of breast tissue composition. Further investigations may be needed to clarify the role of height in breast tissue composition.

We acknowledge this study has limitations. First, anthropometric measures were self-reported and thus are subject to measurement

error. However, we used information collected prior to benign breast biopsy and thus any resulting measurement error is likely to be nondifferential in respect to outcomes. Second, we quantified the percentages of epithelial, fibrous stromal, and adipose tissues in the available benign breast biopsy slides from each woman (median: 3 slides per woman). As these biopsy slides may represent a small portion of the entire breast, these measures may include measurement error when there is some heterogeneity in breast tissue composition throughout the breast. However, a study from Mayo BBD cohort has shown a large concordance in lobular involution across all four quadrants of the breast (44), suggesting little heterogeneity in epithelial contents throughout the breast. We also observed largely consistent results with our benign tissue measures compared with those from PMD. Furthermore, our study excluded women with missing information on breast tissue composition due to technical issues [unable to obtain biopsy specimen, unable to digitize slides that were poor quality, too thick to fit into a scanner (>4 mm), or old style (e.g., embedded in cubes and not tissue cassette)]. However, we confirmed that the study characteristics were generally similar between those who were included versus excluded from the analysis. Finally, as the tissue composition was measured in women with BBD, our results may not be generalizable to women without BBD.

Despite these limitations, this study has a number of strengths. This is the first to examine early-life factors in relation to breast tissue composition. We included body fatness measures at different ages: body fatness at ages 5–10 years, BMI at age 18, and current adult BMI. With careful adjustment for breast cancer risk factors, we also reduced potential confounding. Furthermore, by using a deep-learning computer analysis system, we were able to perform high-throughput analyses on large data and reduced observer error in assessment of breast tissue composition.

In summary, we observed positive associations of early-life and adult body fatness with proportion of adipose tissue and inverse associations with proportions of fibrous stromal tissue in the breast. Our data suggest that both early-life and adult body fatness may influence breast tissue composition. These findings contribute to our understanding of breast cancer biology and suggest that these risk factors may influence breast cancer risk by altering tissue composition even before cancer develops.

Authors' Disclosures

K. Sirinukunwattana is a cofounder of Ground Truth Labs, an Oxford University spin-off company. The company has neither financial interest nor involvement in the work. A.H. Eliassen reports grants from NIH during the conduct of the study. B.A. Rosner reports grants from NIH during the conduct of the study. R.M. Tamimi reports grants from NIH/NCI during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

H. Oh: Conceptualization, formal analysis, methodology, writing–original draft. **A.H. Eliassen:** Writing–review and editing. **B.A. Rosner:** Methodology, writing–review and editing. **R.M. Tamimi:** Conceptualization, supervision, methodology, writing–review and editing. **L. Yaghjyan:** Funding acquisition, methodology, writing–review and editing. **R.J. Austin-Datta:** Writing-review and editing. **Y.J. Heng:** Data curation, writing–review and editing. **G.M. Baker:** Data curation, writing–review and editing. **K. Sirinukunwattana:** Data curation, writing–review and editing. **A.D. Vellal:** Data curation, writing–review and editing. **L.C. Collins:** Writing-review and editing. **D. Murthy:** Data curation, writing–review and editing.

Acknowledgments

We would like to thank the participants and staff of the Nurses' Health Study and Nurses' Health Study II 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. This work was supported by the NCI at the NIH (to L. Yaghjyan, grant number R01CA240341; to R.M. Tamimi, grant number CA131332, CA175080, and P01 CA087969; to A.H. Eliassen, grant number U01 CA176726 and UM1 CA186107), Avon Foundation for Women, and Susan G. Komen for the Cure. H. Oh was supported by the National Research Foundation of Korea (NRF) grants (2019R1G1A1004227, 2019S1A3A2099973) and Korea University grants (K2001271, L1906811). A.D. Vellal was supported by the Beth Israel Deaconess Medical Center High School Summer Research Program.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 14, 2020; revised November 16, 2020; accepted December 2, 2020; published first December 7, 2020.

References

1. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514–27.
2. 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.
3. Premenopausal Breast Cancer Collaborative G, Schoemaker MJ, Nichols HB, Wright LB, Brook MN, Jones ME, et al. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol 2018;4:e181771.
4. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. N Engl J Med 2004;351:1619–26.
5. 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. Eur J Cancer Prev 2013;22:29–37.
6. Weiderpass E, Braaten T, Magnusson C, Kumle M, Vainio H, Lund E, et al. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1121–7.
7. Gaudet MM, Carter BD, Patel AV, Teras LR, Jacobs EJ, Gapstur SM. Waist circumference, body mass index, and postmenopausal breast cancer incidence in the cancer prevention study-ii nutrition cohort. Cancer Causes Control 2014;25:737–45.
8. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer 2013;132:1125–32.
9. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 2015;1:611–21.
10. 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. J Natl Cancer Inst 2015;107:djv219.
11. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
12. Jeffreys M, Warren R, Gunnell D, McCarron P, Smith GD. Life course breast cancer risk factors and adult breast density (United Kingdom). Cancer Causes Control 2004;15:947–55.
13. McCormack VA, dos Santos Silva I, De Stavola BL, Perry N, Vinnicombe S, Swerdlow AJ, et al. Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. Br J Cancer 2003;89:852–9.
14. Sellers TA, Vachon CM, Pankratz VS, Janney CA, Fredericksen Z, Brandt KR, et al. Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. Am J Epidemiol 2007;166:456–64.
15. Andersen ZJ, Baker JL, Bihrmann K, Vejborg I, Sorensen TI, Lynge E. Birth weight, childhood body mass index, and height in relation to mammographic

density and breast cancer: a register-based cohort study. Breast Cancer Res 2014; 16:R4.
16. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N. High-risk mammographic parenchymal patterns and anthropometric measures: a case-control study. Br J Cancer 1999;81:1257–61.
17. Dorgan JF, Klifa C, Shepherd JA, Egleston BL, Kwiterovich PO, Himes JH, et al. Height, adiposity and body fat distribution and breast density in young women. Breast Cancer Res 2012;14:R107.
18. Oh H, Rice MS, Warner ET, Bertrand KA, Fowler EE, Eliassen AH, et al. Early-life and adult anthropometrics in relation to mammographic image intensity variation in the nurses' health studies. Cancer Epidemiol Biomarkers Prev 2020;29:343–51.
19. Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, Salane M, et al. Mammographic densities and risk of breast cancer. Cancer 1991;67:2833–8.
20. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995;87:670–5.
21. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
22. Sung H, Ren J, Li J, Pfeiffer RM, Wang Y, Guida JL, et al. Breast cancer risk factors and mammographic density among high-risk women in urban China. NPJ Breast Cancer 2018;4:3.
23. Rice MS, Bertrand KA, Lajous M, Tamimi RM, Torres-Mejia G, Biessy C, et al. Body size throughout the life course and mammographic density in Mexican women. Breast Cancer Res Treat 2013;138:601–10.
24. Dimri G, Band H, Band V. Mammary epithelial cell transformation: insights from cell culture and mouse models. Breast Cancer Res 2005;7:171–9.
25. Ginsburg OM, Martin LJ, Boyd NF. Mammographic density, lobular involution, and risk of breast cancer. Br J Cancer 2008;99:1369–74.
26. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the nurses' health study. Cancer 2006;107:1240–7.
27. Tamimi RM, Colditz GA, Wang Y, Collins LC, Hu R, Rosner B, et al. Expression of IGF1R in normal breast tissue and subsequent risk of breast cancer. Breast Cancer Res Treat 2011;128:243–50.
28. Bao Y, Bertoia ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, et al. Origin, methods, and evolution of the three nurses' health studies. Am J Public Health 2016;106:1573–81.
29. Stunkard AJ, Sorensen T, Schulsinger F. Use of the danish adoption register for the study of obesity and thinness. Res Publ Assoc Res Nerv Ment Dis 1983;60: 115–20.
30. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol 1993;138:56–64.
31. Heng YJ, Vellal AD, Sirinukunwattana K, Baker GM, Stancu AL, Pyle ME, et al. Developing a deep learning image analysis pipeline for benign breast disease (Abstract 1639). Mod Pathol 2018;31:589.
32. Vellal AD, Sirinukunwattana K, Kensler KH, Baker GM, Stancu AL, Pyle ME, et al. Deep learning image analysis of benign breast disease to identify subsequent risk of breast cancer. JNCI Cancer Spectrum 2021. pkaa119, https://doi.org/10.1093/jncics/pkaa119.
33. Rosner B. Percentage points for a generalized ESD many-outlier procedure. Technometrics 1983;25:165–72.
34. Irwin ML, Aiello EJ, McTiernan A, Bernstein L, Gilliland FD, Baumgartner RN, et al. Physical activity, body mass index, and mammographic density in postmenopausal breast cancer survivors. J Clin Oncol 2007;25:1061–6.
35. Athilat S, Joe C, Rodriguez CB, Terry MB, Tehranifar P. Childhood body size and midlife mammographic breast density in foreign-born and U.S.-born women in New York City. Ann Epidemiol 2018;28:710–6.
36. Schoemaker MJ, Jones ME, Allen S, Hoare J, Ashworth A, Dowsett M, et al. Childhood body size and pubertal timing in relation to adult mammographic density phenotype. Breast Cancer Res 2017;19:13.
37. Tseng M, Byrne C. Adiposity, adult weight gain and mammographic breast density in US Chinese women. Int J Cancer 2011;128:418–25.
38. Alimujiang A, Imm KR, Appleton CM, Colditz GA, Berkey CS, Toriola AT. Adiposity at age 10 and mammographic density among premenopausal women. Cancer Prev Res 2018;11:287–94.
39. Amadou A, Ferrari P, Muwonge R, Moskal A, Biessy C, Romieu I, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obes Rev 2013;14:665–78.
40. Baer HJ, Collins LC, Connolly JL, Colditz GA, Schnitt SJ, Tamimi RM. Lobule type and subsequent breast cancer risk: results from the nurses' health studies. Cancer 2009;115:1404–11.
41. Figueroa JD, Pfeiffer RM, Brinton LA, Palakal MM, Degnim AC, Radisky D, et al. Standardized measures of lobular involution and subsequent breast cancer risk among women with benign breast disease: a nested case-control study. Breast Cancer Res Treat 2016;159:163–72.
42. Radisky DC, Visscher DW, Frank RD, Vierkant RA, Winham S, Stallings-Mann M, et al. Natural history of age-related lobular involution and impact on breast cancer risk. Breast Cancer Res Treat 2016;155:423–30.
43. Gierach GL, Patel DA, Pfeiffer RM, Figueroa JD, Linville L, Papathomas D, et al. Relationship of terminal duct lobular unit involution of the breast with area and volume mammographic densities. Cancer Prev Res 2016;9:149–58.
44. Ghosh K, Hartmann LC, Reynolds C, Visscher DW, Brandt KR, Vierkant RA, et al. Association between mammographic density and age-related lobular involution of the breast. J Clin Oncol 2010;28:2207–12.