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Height, BMI, BMI change and the risk of estrogen receptor positive, HER2 positive and triple-negative breast cancer among women ages 20 to 44 years

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Abstract

Background—The evidence regarding the relationships between various anthropometric characteristics and breast cancer risk among young women is mixed, and few studies have assessed these associations by its subtype.

Methods—This was a population-based case-control study of 779 estrogen receptor positive (ER+), 182 triple-negative (TN), and 60 ER-negative/human epidermal growth factor-2-overexpressing (HER2) invasive breast cancer cases aged 20-44 years diagnosed from 2004-2010 in the Seattle-Puget Sound metropolitan area, and 939 cancer-free controls. Associations between height and body mass index (BMI) at different time points in relation to breast cancer risk were assessed using polytomous logistic regression.

Results—Height, BMI at age 18, and BMI at reference date were not related to risks of ER+, TN, or HER2-overexpressing breast cancer. BMI change from age 18 to reference date was not related to risk of either ER+ or HER2-overexpressing breast cancer. However, compared to women with a 0-4.9 kg/m^2 change over this interval in their BMI from age 18 to reference date, those who experienced a ≥10 kg/m^2 increase had a 2.0-fold (95% confidence interval [CI]: 1.2-3.3) increased risk of TNBC. For ER+ disease there was some evidence that parity modified the effect of BMI change ($P_{interaction}$=0.002), as an increase of ≥10 kg/m^2 was associated with a reduced risk of ER+ disease only among nulliparous women (odds ratio [OR]=0.3, 95% CI: 0.2-0.6).

Conclusions—The relationships between BMI change and risks of TNBC and ER+ breast cancer appear to differ substantially.

Keywords

Breast cancer; height; body mass index; estrogen receptor; triple-negative; premenopausal

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Introduction

The relationships between anthropometric factors and breast cancer risk have been extensively studied among young women.[1] Briefly, height is positively associated[2, 3] and body mass index (BMI) is negatively associated[3, 4] with breast cancer risk among premenopausal women. Fewer studies have evaluated the impact of weight gain, but of those focused on young women, four[5-8] of the five[4-8] observed no relationship between weight gain and breast cancer risk. However, among the studies evaluating associations between BMI,[9-19] height[9, 12, 15, 16] and risk of different breast cancer subtypes defined by joint estrogen receptor (ER)/progesterone receptor (PR) status, the majority have observed no association between BMI and risk of either ER+/PR+[9-14] or ER−/PR−,[9-19] and no association between height and risk of either ER+/PR+[9, 12, 16] or ER−/PR−[9, 12, 16] breast cancer. Six studies have evaluated associations between anthropometric factors and risk of different breast cancer subtypes defined by ER/PR and HER2-neu (HER2) status among young women.[20-25] These studies have yielded inconsistent results, and five of six studies have been hindered by small sample sizes with the numbers of triple-negative (ER−/PR−/HER2-) cases included ranging from only 19 to 119.[20-24] The largest study included 187 triple-negative cases and observed no association between BMI and risk of triple-negative breast cancer.[25] Given the distinct biologies of different breast cancer subtypes they likely have unique etiologies,[26, 27] and prior studies have identified differences in magnitudes and directions in risk associated with various reproductive and lifestyle characteristics across molecular subtypes of breast cancer.[2829] Studying potentially modifiable risk factors for these cancers in young women is particularly important given that the proportions of two of the more aggressive subtypes, triple-negative and HER2-overexpressing (ER-/HER2+), are inversely associated with age.[21] Toward this goal, we evaluated the associations between height, BMI, and BMI change and risk of different molecular subtypes of breast cancer in a population-based case-control study of women 20-44 years of age.

Material and Methods

The design and methods used in this population-based case-control study have been described previously.[30] Briefly, eligible cases were women 20-44 years of age designed specifically to characterize risk factors for breast cancer among young women diagnosed with invasive breast cancer between January 2004 and June 2010 with no prior history of *in situ* or invasive breast cancer living in the three county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties). Potentially eligible cases were identified thorough the Cancer Surveillance System (CSS), the population-based tumor registry that serves the 13 counties of Western Washington state and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Of the 1,359 eligible cases identified, 1,056 (78%) were interviewed. Of those not enrolled (n=303), 82% refused to be interviewed, 10% could not be located, and 8% died before the interview could be conducted. We obtained basic information on breast cancer diagnosis and a variety of tumor characteristics from the cancer registry and from a centralized review of pathology reports. This review included collection of data on tumor histology, stage, ER, PR, and HER2-neu status. ER and PR positivity were defined as positive staining of ≥1% of cells and negative staining of 0 to <1 % of positive cells. HER2 positivity was based on an

immunohistochemistry (IHC) score of 3+ and/or a fluorescence in situ hybridization (FISH)-positive result and negativity was defined as an IHC score of 0 or 1+ and/or a FISH-negative result. Cases with a 2+ HER2 IHC result without a FISH result were considered to have unknown HER2 status. This information was used to group cases into three defined groups: ER+ (approximating the luminal A and B subtypes), ER-/HER2+ (HER2-neu overexpressing type), and ER−/PR−/HER2- [triple-negative (TN) approximating the basal-like subtype and unclassified]. This approach has been used in our previous work.[30] The 28 cases (2.7%) for whom data on ER, PR, and/or HER2 status were missing were excluded.

We used a combination of list-assisted (purchased randomly generated telephone numbers) and Mitofsky-Waksberg (telephone numbers randomly generated ourselves using a clustering factor of 5)[31] random digit dialing methodologies to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. Controls were frequency matched within 5-year age groups to the cases using one-step recruitment. Of the 1,489 eligible controls identified, 943 (63%) were interviewed by this method.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. Cases and controls were interviewed in their homes by a trained interviewer and asked about their reproductive history, demographics, physical activity, alcohol drinking, cigarette smoking, medical history, history of breast cancer screening, and family history of breast cancer. In addition, women were queried regarding their weight at age 18 (not counting times when women were pregnant or nursing), height, weight one year prior to their reference date. Our questioning was limited to exposures that occurred before each participant's reference date. The reference date/age used for each woman with breast cancer was her diagnosis date/age. Control reference dates/ages were assigned to reflect the expected distribution of reference dates/ages among the cases. The mean time between reference date and interview date was 18 months for cases and 20 months for controls, and the median times were 16 months and 19 months, respectively. This was consistent with our goal of trying to interview women within two years of their reference date. Data on height were missing for four controls and seven cases (five ER+ and two ER−/PR−/HER2- cases). Therefore, our final analytic data set consisted of 939 control women, 779 ER+ cases, 60 ER-/HER2+ cases and 182 ER−/PR−/HER2- cases.

Statistical Analysis

Our primary exposures of interest were height at reference age, BMI at age 18, BMI at reference date, and change in BMI from age 18 to reference date. Weight at reference age (kg) was weight one year before the reference age. Height and weight were also measured at the time of the interview by the trained interviewer. We used measured values of height at the time of interview and self-reported values of weight at reference age and weight at age 18 to calculate exposures. When physically measured height at the interview was not available, self-reported height was used (n=111 for cases, n=132 for controls). When self-reported weight at reference age was not available, physically measured weight at the

interview was used (n=113 for cases, n=150 for controls). BMI at reference age (kg/m^2) was calculated as weight one year prior to reference date (kg) divided by squared height at reference age (m). BMI at age 18 (kg/m^2) was calculated as weight at age 18 (kg) divided by squared height at reference (m). A high level of correlation was observed between self-reported and physically measured anthropometric characteristics (continuous variables: r=0.96 for height, r=0.88 for weight; quartile categorizations: r=0.91 for height, r=0.85 for weight). For height, BMI at age 18, and BMI at reference age, our primary analysis was based on the quartile distributions of these anthropometric characteristics among our control population where the lowest quartile served as the reference category. Additionally, for BMI at reference date we evaluated risk according to clinically relevant categories (≤24.9, 25.0-29.9, ≥30.0). We did not use these same categories for BMI at age 18 because there were few obese women (n=20 controls, 18 cases). For BMI change from age 18 to reference date, we grouped women into four categories (change of: <0.0, 0.0-4.9, 5.0-9.9, ≥10.0 kg/m^2), where those in the 0.0-4.9 category served as the reference group. These evenly spaced categories were selected for ease of interpretation. We used polytomous logistic regression to calculate odds ratios (ORs) and their associated 95% confidence intervals (CIs) to compare ER+, ER−/PR−/HER2-, and ER-/HER2+ breast cancer cases to controls. All analyses were conducted using Stata/SE 13 (StataCorp LP, College Station, TX). All models were adjusted for age (five year categories) and reference year (continuous) since controls were matched to cases on these factors. Several potential confounders and effect modifiers of the relationship between each anthropometric factors and breast cancer risk were assessed including: race/ethnicity, education, first-degree family history of breast cancer, duration of oral contraceptives, parity number, age at first live birth among parous women, age at menarche, alcohol consumption, smoking history, physical activity, and mammography screening history. Age at first live birth and race/ethnicity changed our risk estimates by more than 10% when added to the model, so our final statistical models were adjusted for age, reference year, age at first live birth, and race/ethnicity. Parity was found to be a statistically significant effect modifier of the relationship between BMI change and risk of ER+ breast cancer based on likelihood ratio testing (p-values for interaction were <0.05 for ER+ breast cancer). In the stratified analysis by parity, we collapsed women with BMI change of <0.0 and 0.0-4.9 into one category, where those in the ≤4.9 category served as the reference group. P values for trend were calculated by treating each categorical variable as an ordered continuous variable. Additionally, estimates of trend for continuous values were calculated by treating each variable as continuous variable. For BMI change from age 18 to reference, the trend calculated was limited to those whose BMI stayed the same or increased over this interval. We conducted Wald tests to estimate case-case differences in risk between our ER+ and TN case groups.

Results

Compared to control women, cases as a whole were less likely to be non-Hispanic white and more likely to have a first-degree family history of breast cancer, to be nulliparous, and to ever have had a screening mammogram (**Table 1**). Compared to the ER+ breast cancer cases, the TN cases were somewhat more likely to be younger, to be African American, to have a younger age at first live birth, and less likely to have graduate or professional school

education and to ever have had a screening mammogram. The HER2 cases were more likely to be younger, to have a younger age at first live birth, and to never have had a screening mammogram.

There was some suggestion that women in the upper three height quartiles had slightly elevated risks of ER+ and slightly decreased risks of HER2+ breast cancer compared to women in the lowest quartile, but neither trend was statistically significant (**Table 2**). There was some suggestion that women in the upper three BMI at age 18 quartiles had decreased risks of TN breast cancer compared to women in the lowest quartile, but this trend was also not statistically significant. In contrast, a change in BMI from age 18 to reference date of ≥10.0 kg/m^2 was associated with a 2.0-fold (95%CI: 1.2-3.3) increased risk of TNBC (P_{trend}=0.02), but not with risk of either ER+ or ER-/HER2+ breast cancers. When analyzed on a continuous scale, BMI change from age 18 to reference date was associated with an increased risk of TNBC per 1.0 kg/m^2 unit increase in BMI (OR=1.07, 95% CI: 1.02-1.11).

Parity modified the association between BMI change and ER+ breast cancer risk ($P_{interaction}$=0.002) (**Table 3**). Nulliparous women those whose BMI increased by 5.0-9.9 kg/m^2 or by ≥10 kg/m^2 had decreased risks of ER+ breast cancer (OR=0.5, 95%CI: 0.3-0.9 and OR=0.3, 95%CI: 0.2-0.6, respectively) compared to those women whose BMI changed <5.0 kg/m^2 (P_{trend} <0.001). BMI change was not related to risk of ER+ breast cancer among parous women. Parity did not statistically significantly modify the relationship between BMI change and TN breast cancer ($P_{interaction}$=0.11), though there was some suggestion that the observed increase in risk was primarily limited to parous women.

Discussion

In this population-based case-control study of women 20-44 years of age we observed that height, BMI at reference, and BMI at age 18 were not associated with risk of any of the three breast cancer subtypes evaluated. However, an increase in BMI since age 18 was associated with an increased risk of TNBC, primarily among parous women, as well as a reduced risk of ER+ breast cancer limited to nulliparous women. This study adds to the limited literature[20-25] addressing these relationships. Comparing our results to them is challenging, particularly given that only one study have specifically evaluated change in BMI.[20]

Among studies characterizing risk by ER/PR status, some have observed that BMI at diagnosis[15-19] and BMI at age 18[15] are inversely associated with risk of ER+/PR+ breast cancer, but similar to our results the majority of these studies have observed no association between BMI and risk of either ER+/PR+[9-14] or ER−/PR−[9-19] breast cancer. Five case-control studies[20-23, 25] and one cohort study[24] have assessed risk according to joint ER/PR/HER2 status. The results across these studies have been generally null for each breast cancer subtype as three[20-22] of the four[20-23] studies that evaluated luminal A cancer risk, two[20, 23] of the three[20, 22, 23] studies that evaluated luminal B cancer risk, all four[20, 22-24] of the studies that evaluated HER2-overexpressing breast cancer risk, and five[20, 21, 23-25] of the six[20-25] studies that evaluated TN/basal-like cancer risk found no associations between

different aspects of BMI and cancer risk. Thus, there are no consistently observed positive or negative associations between BMI and different breast cancer subtypes.

Given the paucity of available evidence on the relationships between anthropometric factors and different breast cancer subtypes, our results need to be interpreted cautiously. The inverse association between BMI and premenopausal breast cancer risk overall is thought to be primarily hormonally driven. The greater frequency of anovulatory and irregular menstrual cycles in women with higher BMIs result in reduced endogenous estrogen production.[32] The inverse association between BMI change and risk of ER+ breast cancer among only nulliparous women may reflect that the profound changes in breast tissue induced by pregnancy outweigh the effects of BMI on breast cancer risk.[33] As described above, while there is some evidence that BMI is inversely related to hormone receptor positive breast cancer, studies evaluating the relationship between BMI and hormone receptor negative disease are largely null. The biological mechanisms underlying the relationships observed between BMI change and TN breast cancer are largely unknown. Obesity does exert a range of biological effects beyond its influence on hormones that could potentially explain this finding. For example, BMI is positively related to IGF-I levels,[34] and IGF-I has been shown to enhance breast cancer cell growth irrespective of hormone receptor status.[35] So if our observation is confirmed, further exploration of the biological underpinnings of this association is needed.

It is important to acknowledge the limitations of this study. Given our case-control design, recall bias is a potential concern. However, beyond finding case-control differences we also observed significant case-case differences. Given that recall across case groups should not differ appreciably, the impact of recall bias on our results is likely minimal. With respect to exposure assessment we utilized both self-reported and measured height and weight, and there was high correlation between these measures. We also conducted sensitivity analyses of our BMI data restricted to those women with measured weights and then restricted to those with self-reported weights and our results did not change appreciably with either restriction (data not shown). However, our BMI change variable required recall of body weight at age 18 and is thus potentially subject to recall bias. Our analyses did again though show both case-control and case-case differences suggesting that any differences in recall are likely to be non-differential with only the potential to bias risk estimates toward the null.[36]

In conclusion, this population-based case-control study of young women adds to recent evidence indicating that height, current BMI, and BMI at age 18 are not associated with risk of breast cancer subtypes defined by ER/PR/HER2 status. BMI change from age 18 was observed to be positively related to risk of TNBC and inversely related to risk of ER+ breast cancer among only nulliparous women. These results require confirmation and the underlying biological mechanisms are largely unknown.

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Table 1

Distribution of selected characteristics among controls and cases, ER−/PR−/HER2−, ER−/HER2+, ER+ breast cancer.

	Controls		Cases								
			Total			Subtypes					
	(n=940)		(n=1,021)			ER−/PR−/HER2− (n=182)		ER−/HER2+ (n=60)		ER+[a] (n=779)		
Characteristic	**n**	**%**	**n**	**%**	**p-value[b]**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value[b]**
Age (years)												
20-29	25	3%	24	2%		7	4%	2	3%	15	2%	
30-34	86	9%	83	8%		22	12%	6	10%	55	7%	
35-39	267	28%	279	27%		58	32%	22	37%	199	26%	
40-44	562	60%	635	62%	0.7	95	52%	30	50%	510	66%	0.03
Reference (years)												
2004-2005	306	33%	290	28%		61	34%	17	28%	212	27%	
2006-2007	361	38%	356	35%		57	31%	25	42%	274	35%	
2008-2010	273	29%	375	37%	0.001	64	35%	18	30%	293	38%	0.007
Race/ethinicity												
Non-Hispanic white	768	82%	798	79%		142	78%	48	80%	608	79%	
African American	34	4%	53	5%		17	9%	4	7%	32	4%	
Asian/Pacific Islander	82	9%	119	12%		14	8%	6	10%	99	13%	
Native American	19	2%	27	3%		7	4%	1	2%	19	2%	
Hispanic White	35	4%	19	2%	0.01	2	1%	1	2%	16	2%	0.003
Missing	2		5			0		0		5		
Education												
High school or less	98	10%	121	12%		24	13%	8	13%	89	11%	
Post high-school/some college	306	33%	335	33%		65	36%	16	27%	254	33%	
College graduate	354	38%	375	37%		69	38%	23	38%	283	36%	
Graduate/Professional school	181	19%	190	19%	0.8	24	13%	13	22%	153	20%	0.7
Missing	1		0			0		0		0		
First-degree family history of breast cancer												
No	815	90%	790	80%		140	79%	48	81%	602	80%	
Yes	92	10%	198	20%	<.001	38	21%	11	19%	149	20%	<.001

	Controls		Cases								
			Total			Subtypes					
	(n=940)		(n=1,021)			ER−/PR−/HER2− (n=182)		ER−/HER2+ (n=60)		ER+[a] (n=779)		
Characteristic	**n**	**%**	**n**	**%**	**p-value[b]**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value[b]**
Missing	33		33			4		1		28		
Duration of oral contraceptives use (years)												
Never	103	11%	118	12%		15	8%	11	18%	92	12%	
<5.0	338	36%	362	36%		59	33%	22	37%	281	36%	
5.0-9.9	218	23%	206	20%		39	22%	11	18%	156	20%	
≥10	278	30%	328	32%	0.4	66	37%	16	27%	246	32%	0.4
Missing	3		7			3		0		4		
Parity number												
Nulliparous	191	20%	270	26%		50	27%	11	18%	209	27%	
1	194	21%	206	20%		34	19%	14	23%	158	20%	
2	366	39%	374	37%		68	37%	23	38%	283	36%	
≥3	189	20%	170	17%	0.01	30	16%	12	20%	128	16%	0.1
Missing	0		1			0		0		1		
Age at first live birth among parous women (years)												
<25	219	29%	242	32%		57	43%	17	35%	168	30%	
25-29	225	30%	243	32%		35	27%	20	41%	188	33%	
30-34	205	27%	181	24%		30	23%	8	16%	143	25%	
≥35	100	13%	83	11%	0.2	10	8%	4	8%	69	12%	0.04
Missing	0		1			0		0		1		
Age at menarche (years)												
<12	190	20%	225	22%		44	24%	11	18%	170	22%	
12-13	521	55%	581	57%		100	55%	42	70%	439	56%	
≥14	227	24%	214	21%	0.2	38	21%	7	12%	169	22%	0.2
Missing	2		1			0		0		1		
Alcohol consumption (average number of alcohol drinks/week)												
Never	227	24%	243	24%		45	25%	23	38%	175	23%	
0-1.4	234	25%	238	23%		34	19%	15	25%	189	24%	

	Controls		Cases								
			Total			Subtypes					
	(n=940)		(n=1,021)			ER−/PR−/HER2− (n=182)		ER−/HER2+ (n=60)		ER+[a] (n=779)		
Characteristic	**n**	**%**	**n**	**%**	**p-value[b]**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value[b]**
1.4-3.7	235	25%	254	25%		49	27%	9	15%	196	25%	
≥3.7	237	25%	278	27%	0.7	53	29%	13	22%	212	27%	0.2
Missing	7		8			1		0		7		
Smoking status at refrence date												
Never	639	68%	648	64%		111	61%	42	70%	495	64%	
Current	139	15%	170	17%		37	20%	10	17%	123	16%	
Former	160	17%	202	20%	0.1	34	19%	8	13%	160	21%	0.2
Missing	2		1			0		0		1		
Physical activity (average hours of any physical activity at reference age/week)												
0	448	48%	485	48%		87	48%	31	52%	367	47%	
≤4	319	34%	359	35%		72	40%	21	35%	266	34%	
>4	171	18%	175	17%	0.8	22	12%	8	13%	145	19%	0.4
Missing	2		2			1		0		1		
Ever had a screening mammogram												
Never	478	51%	433	42%		84	46%	34	57%	315	40%	
Ever	462	49%	588	58%	<.001	98	54%	26	43%	464	60%	<.001

Abbreviations: BMI, body mass index. ER, estrogen receptor. PR, progesterone receptor. HER2, human epidermal growth factor receptor-2.

[a] Regardless of PR/HER2 status

[b] Chi-squared

Table 2

Association of height, BMI at age 18, BMI at reference, BMI change and breast cancer risk.

	Controls		Cases																
							Subtypes												$P_{heterongeneity}$ ER−/PR−/HER2− vs ER+
	(n=940)		(n=1,021)				ER−/PR−/HER2− (n=182)				ER−/HER2+ (n=60)				ER+[a] (n=779)				
	n	%	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	
Height (m)																			
<1.60	185	20%	181	18%	1.0	Ref	30	16%	1.0	Ref	17	28%	1.0	Ref	134	17%	1.0	Ref	
1.60-<1.64	240	26%	290	28%	1.3	0.9-1.8	54	30%	1.4	0.8-2.4	15	25%	0.9	0.4-2.1	221	28%	1.3	0.9-1.9	
1.64-<1.70	261	28%	275	27%	1.1	0.8-1.5	48	26%	0.9	0.5-1.6	14	23%	0.6	0.2-1.4	213	27%	1.2	0.9-1.7	
≥1.70	254	27%	275	27%	1.1	0.8-1.5	50	27%	1.0	0.6-1.8	14	23%	0.7	0.3-1.7	211	27%	1.2	0.8-1.7	
P_{trend}						0.99				0.53				0.28				0.63	0.37
Continuous (per 5cm)					1.04	0.96-1.13			1.03	0.88-1.20			0.84	0.66-1.07			1.06	0.97-1.16	
BMI at age 18 (kg/m^2)																			
<18.8	238	26%	299	29%	1.0	Ref	56	31%	1.0	Ref	15	25%	1.0	Ref	228	29%	1.0	Ref	
18.8-<20.4	233	25%	257	25%	0.9	0.7-1.2	47	26%	0.7	0.4-1.2	15	25%	1.0	0.5-2.3	195	25%	0.9	0.7-1.3	
20.4-<22.2	224	24%	237	23%	1.0	0.7-1.3	37	20%	0.7	0.4-1.2	16	27%	1.0	0.4-2.3	184	24%	1.0	0.8-1.4	
≥22.2	232	25%	221	22%	0.9	0.6-1.1	41	23%	0.7	0.4-1.2	14	23%	1.0	0.4-2.3	166	21%	0.9	0.6-1.2	
P_{trend}						0.41				0.17				0.93				0.65	0.28
Continuous (kg/m^2)					0.99	0.96-1.03			0.95	0.89-1.01			0.97	0.89-1.07			1.00	0.97-1.04	
BMI at reference (kg/m^2)																			
<21.7	235	25%	295	29%	1.0	Ref	47	26%	1.0	Ref	13	22%	1.0	Ref	235	30%	1.0	Ref	
21.7-<24.2	231	25%	235	23%	0.9	0.7-1.2	37	20%	0.9	0.5-1.5	20	33%	1.4	0.6-3.1	178	23%	0.8	0.6-1.2	
24.2-<28.3	241	26%	253	25%	0.9	0.7-1.3	42	23%	0.8	0.5-1.4	9	15%	0.8	0.3-1.9	202	26%	1.0	0.7-1.3	
≥28.3	232	25%	238	23%	0.9	0.7-1.2	56	31%	1.2	0.7-2.0	18	30%	1.2	0.5-2.8	164	21%	0.8	0.6-1.2	
P_{trend}						0.68				0.62				1.00				0.5	0.38
Continuous (kg/m^2)					1.00	0.98-1.02			1.02	0.98-1.05			1.01	0.96-1.06			1.00	0.98-1.02	
BMI at reference (kg/m^2)																			
<25	526	56%	600	59%	1.0	Ref	99	54%	1.0	Ref	37	62%	1.0	Ref	464	60%	1.0	Ref	
25-<30	241	26%	243	24%	1.0	0.8-1.3	43	24%	1.0	0.6-1.5	9	15%	0.6	0.3-1.3	191	25%	1.0	0.8-1.4	

	Controls		Cases															
							Subtypes											$P_{heterongeneity}$ ER−/PR−/HER2− vs ER+
	(n=940)		(n=1,021)				ER−/PR−/HER2− (n=182)				ER−/HER2+ (n=60)				ER+[a] (n=779)			
	n	%	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	n	%	OR[d]	95%CI	
≥30	172	18%	178	17%	1.1	0.8-1.4	40	22%	1.2	0.7-2.0	14	23%	1.1	0.5-2.3	124	16%	1.0	0.7-1.4	
P_{trend}						0.81				0.5				0.88				0.94	0.54
BMI change from age 18 to reference (kg/m^2)																			
<0	89	10%	91	9%	0.9	0.6-1.4	14	8%	1.3	0.6-2.7	3	5%	0.7	0.2-2.5	74	10%	0.9	0.6-1.3	
0-<5.0	456	49%	535	53%	1.0	Ref	80	44%	1.0	Ref	33	55%	1.0	Ref	422	55%	1.0	Ref	
5.0-<10.0	259	28%	251	25%	0.9	0.7-1.1	52	29%	1.2	0.7-1.9	12	20%	0.6	0.3-1.4	187	24%	0.9	0.7-1.1	
≥10.0	123	13%	137	14%	1.1	0.8-1.5	35	19%	2.0[c]	1.2-3.3	12	20%	1.1	0.5-2.6	90	12%	0.9	0.7-1.3	
P_{trend}[b]						0.90				0.02				0.88				0.46	0.007
Continuous (kg/m^2)[b]					1.01	0.98-1.04			1.07	1.02-1.11			1.02	0.96-1.09			0.99	0.97-1.02	

Abbreviations: OR, odds ratio. CI, confidence interval.

[a] Regardless of PR/HER2 status.

[b] BMI change ≥0.

[c] P < 0.05.

[d] ORs are adjusted by age at reference, reference year, race/etnicity, age at first bitrh.

Table 3

Association of BMI change and ER+ breast cancer risk stratified by parity.

	Controls (n=927)		Cases								$P_{heterongeneity}$
			ER−/PR−/HER2− (n=181)				ER+[a] (n=772)				
	n	%	n	%	OR[c]	95%CI	n	%	OR[c]	95%CI	
Nulliparous (never had a live birth)											
BMI change from age 18 to reference (kg/m^2)											
<5.0	112	59%	30	60%	1.0	Ref	154	74%	1.0	Ref	
5.0-<10.0	48	25%	16	32%	1.3	0.6-2.6	38	18%	0.5[b]	0.3-0.9	
≥10.0	29	15%	4	8%	0.5	0.2-1.5	15	7%	0.3[b]	0.2-0.6	
P_{trend}						0.4				<0.001	0.08
Continuous (kg/m^2)					0.97	0.91-1.04			0.93	0.89-0.97	
Parous (ever had a live birth)											
BMI change from age 18 to reference (kg/m^2)											
<5.0	433	59%	64	49%	1.0	Ref	342	61%	1.0	Ref	
5.0-<10.0	211	29%	36	27%	1.2	0.8-1.9	148	26%	0.9	0.7-1.2	
≥10.0	94	13%	31	24%	2.1[b]	1.3-3.4	75	13%	1.0	0.7-1.4	
P_{trend}						0.008				0.7	0.0045
Continuous (kg/m^2)					1.06	1.02-1.10			1.00	0.97-1.02	
$P_{interaction}$						0.11				0.002	

[a] Regardless of PR/HER2 status.

[b] P < 0.05.

[c] ORs are adjusted by age at reference, reference year, race/etnicity.