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Adult BMI change and Risk of Breast Cancer: National Health and Nutrition Examination Survey (NHANES) 2005-2010

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Abstract

Objective—Breast cancer is the second leading cause of cancer mortality among women in the developed world. This study assessed the association between occurrence of breast cancer and Body Mass Index (BMI) change from age 25 to age closest to breast cancer diagnosis while exploring the modifying effects of demographic variables.

Methods—The National Health and Nutrition Examination Survey data were used. Women included were ≥50 years, not pregnant and without a diagnosis of any cancer but breast. The total sample included 2,895 women (172 with breast cancer and 2,723 controls with no breast cancer diagnosis). Multivariate logistic regression was used to estimate the OR and 95% CI's and interaction evaluated by including an interaction term in the model.

Results—Women whose BMI increased from normal or overweight to obese compared to those who remained at a normal BMI were found to have a 2 times higher odds (OR=2.1; 95% CI: 1.11-3.79) of developing breast cancer. No significant association was observed for women who increased to overweight. However, a more pronounced association was observed in non-Hispanic black women (OR=6.6; 95% CI: 1.68-25.86) and a significant association observed when they increased from normal to overweight (OR=4.2; 95% CI: 1.02-17.75).

Conclusions—Becoming obese after age 25 is associated with increased risk of breast cancer in women over 50 years old, with non-Hispanic black women being at greatest risk.

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Authors Disclosure Statement

The authors declare that they have no conflict of interest.

Keywords

BMI change; weight gain; breast cancer; Race; NHANES; cancer; epidemiology; prevention

Background

Excessive weight is a growing public health problem and the second most preventable cause of death [1]. Globally, it is estimated that over one billion adults are overweight and 315 million are obese [2]. Developed countries have the highest obesity prevalence; in the US one in three (36%) adults is obese [2]. By 2015, it is estimated that 75% of adults will be overweight or obese and of these, 41% will be obese [3]. Disparities exist in the prevalence of obesity; until recently, Body Mass Index (BMI) has been consistently higher in women compared to men [4]. Also, it is estimated that by 2015 the percent of women who will be overweight will be greatest in African American women (87%) and Hispanic women (80%) compared to Caucasians (69%) [3]. Both the incidence of obesity and breast cancer rates increase with age [5, 6].

Breast cancer is the most common cancer and the second leading cause of cancer mortality among women in the developed world [7, 8]. One factor shown to be related to the development of breast cancer, its recurrence in postmenopausal women [9-11] and breast cancer mortality [12] is obesity. The link between obesity and breast cancer is believed to be related to inflammation which induces aromatase expression and estrogen synthesis [13, 14]. Adipose tissue is a major source of estrogenic hormones and both aromatase expression and estrogen synthesis are linked to increased risk of breast cancer [15]. The gains made in lowering mortality of breast cancer through early detection and better treatment [16-18] may be diminished by the rising obesity pandemic.

While several studies have evaluated the association of breast cancer and weight change over time, [19-22] no study to our knowledge has looked at weight change in terms of BMI change. BMI is a common anthropometric measure and is universally used to measure and define obesity [23]. Measuring weight change relative to an individual's height in form of BMI change may further inform the relationship between excess weight and breast cancer risk. Moreover, this study was based on the National Health and Nutrition Examinations Survey (NHANES), thus is the first study to our knowledge to assess BMI category change on the risk of breast cancer based on a nationally representative sample.

The aim of this study was to investigate the relationship between BMI change and risk of breast cancer using the time period from age 25 until age closest to breast cancer diagnosis. BMI change was a categorical variable with 4 categories: 1) having a normal BMI at both time points, 2) increase to overweight from normal BMI, 3) increase to obesity from normal or overweight and 4) being overweight or obese at both time points. Also, while disparities in the prevalence of obesity among women exist, this study explored the association of demographic factors as modifiers of the association between BMI changes with breast cancer risk. The findings of this research will build on understanding the role of BMI change over a woman's life in affecting their risk of breast cancer perhaps underscoring the need to

maintain a normal BMI throughout life especially for women with certain demographic characteristics.

Methods

Study Design

Data were obtained from the National Health and Nutrition Examination Survey (NHANES). The survey design, questionnaires, and examination methodology of NHANES are described in details at the CDC website [24]. The National Center for Health Statistics-NCHS Ethics Review Board approved the survey protocols and informed consent was obtained from all participants. The Indiana University Internal Review Board considered the study to be exempt from local review since the data were de-identified and publicly accessible. The data used in this study were from the 2005/06, 2007/08 and 2009/10 surveys.

Study population

A total of 2,895 women met the inclusion and exclusion criteria including 172 with breast cancer and 2,723 without breast cancer. Women were included if they were aged 50 years and above and were excluded if they were pregnant (n=5), were missing self-reported weight at age 25 (n=279) and had been diagnosed with other cancers (n=310). In the three surveys, low-income individuals, individuals 60 years of age and older, African Americans and Mexican Americans were oversampled; therefore, sampling weights were added to allow the estimates to be generalizable to the US population. A weight statement and variable were included in the Proc SurveyLogistic model.

Variables

Breast cancer diagnosis was the outcome variable. Participants who reported being diagnosed with breast cancer were defined as the ‘cases’ while those without a diagnosis of cancer were defined as ‘controls’. The cases and controls were not matched on any demographic or clinical characteristics.

In the dataset, weight and height were provided at age 25, 10 years and 1 year prior to interview and at the time of interview. To avoid loss of data for those missing height at age 25 we estimated their height at that time. After age 40, people normally lose about 1 cm every 10 years [25], therefore, for those missing height at age 25 (n=48), their height was estimated by increasing the appropriate amount to their current height. The overall mean height at age 25 remained the same; it was 63.84 inches before adjustment and was 63.82 inches when those missing height were included; thus it was assumed that using the estimated heights did not introduce a bias. BMI was calculated as a ratio of weight in kilograms over height in meters squared (kg/m^2) and grouped into three categories: normal (<25.00), overweight (≥ 25.00-29.99), and obese (≥ 30.00) using the World Health Organization’s criteria for grouping weight status [26].

In calculating the exposure, BMI at age 25 was the baseline BMI for those with breast cancer and those without. BMI measurements were available when the participants were 25 years old and 10 years and 1 year prior to interview as well as at the time of interview. For

those with breast cancer, the change in BMI was determined by the difference in their BMI values at age 25 and the BMI measurement closest to the breast cancer diagnosis (either 1 or 10 years prior to interview mark). Over 90% of the women with breast cancer had diagnosis that was close to the 10 year prior to interview mark and hence the BMI measurement provided a good exposure period before diagnosis. This was further evidenced by the 10 year difference between the mean age (67.6 years) and mean age of breast cancer diagnosis (57.5 years). Since women without breast cancer had no age of diagnosis and because 90% of the cases had a breast cancer diagnosis close to 10 years prior to their interview date, the 10 year prior to interview BMI was used as the risk exposure end point for the controls.

BMI changes were defined as 1) *Normal*-women whose BMI remained normal; 2) *Reduced*-women whose BMI reduced from overweight to normal and from obese to overweight or to normal; 3) Increased to overweight (referred to as Normal to Overweight)- women whose BMI increased from normal to overweight, 4) Increased to obese (referred to as Normal/overweight to obese)-women whose BMI increased from normal to obese or from overweight to obese, and 5) *Overweight/Obese*-women whose BMI remained within the overweight or obese category.

Statistical Analysis

All statistical analyses were conducted using SAS (version 9.3). Descriptive statistics showing the characteristics of the study participants by breast cancer status are provided in Table 1. Chi square and t-test statistics were performed to compare the distribution and means of covariates by breast cancer status. Logistic regression analysis was used to measure the association between occurrence of breast cancer and BMI change while controlling for the covariates (age, race/ethnicity, education, marital status, age at menarche, age at menopause, smoking and total cholesterol). Total cholesterol was measured enzymatically in serum. In regards to the exposure of interest, only 4 BMI change levels (normal throughout, increase to Overweight, increase to Obesity and Overweight/obese throughout) were used; since only a few women experienced a reduction in their weight between the two time periods, this category was dropped from further analysis. *P*-values less than .05 were considered statistically significant.

Interaction was assessed by separately including an interaction term for race, education and age with BMI change in the multivariate logistic regression to assess their joint effect on breast cancer risk. To correct for multiple comparisons in the interaction model, an alpha of .01 instead of .05 was used. The education and BMI change interaction (p-value=0.3557) and the age and BMI change interaction (p-value=0.4010) were not significant and therefore are not reported in this paper. The significant race and BMI change interaction on breast cancer risk is shown in Table 4. In all the models, several confirmed or suspected factors related to the risk of breast cancer were held constant. These included: age, race/ethnicity, education, marital status, age at menarche, age at menopause and smoking and total cholesterol. These covariates met the p-value cutoff criteria of 0.25 for assessing confounding when bivariate analysis was conducted.

A sensitivity analysis was conducted to assess the association of BMI change and risk of breast cancer using data from women (n=102) whose breast cancer diagnosis occurred after

the ten year prior to interview mark. Therefore, BMI change was measured as the difference in BMI change from age 25 to 10 years prior to interview for both groups.

Results

The demographic characteristics, exposure variable and other health related measurements of the study participants are shown in Table 1. Women with breast cancer were older (67.6 years) compared to the controls (63.5 years). There were a higher proportion of women with less than high school education among women with breast cancer when compared to those without breast cancer. There were more non-Hispanic white women among women with breast cancer compared to those without but a higher proportion of non-Hispanic Blacks and Hispanic women among women without breast cancer compared to those without. However, the distribution of marital status and smoking status was similar for both groups. Regarding the exposure of interest, majority of women with breast cancer had a normal BMI at age 25 compared to women without breast cancer. However, they were more likely to have gained weight from age 25 compared to women without breast cancer. The percentage of women with BMI increase from normal to overweight (30.0%) and from normal/overweight to obese (20.4%) was higher among women with breast cancer than those with no breast cancer. For menstrual and reproductive factors, there were no differences among women with breast cancer and those without in respect to age at first menses and age at last menstrual period.

Logistic regression models

As shown in Table 2, the association of BMI at different time points was not significantly associated with risk of breast cancer. However, Table 3 summarizes the model used to evaluate the association of BMI change and breast cancer risk. In the multivariable model, the risk of breast cancer was found to be 2.1 times higher for women whose BMI increased from normal/overweight to obese (OR=2.1, 95% CI, 1.11-3.79) when compared to women who maintained a normal BMI, controlling for the demographic and other health characteristics of the study subjects. The association between breast cancer risk and women whose BMI increased from normal to overweight or women who were overweight or obese when compared with those who remained with a normal BMI were not statistically significant. Table 3 also shows regression results of sensitivity analyses of 102 women with breast cancer whose breast cancer diagnosis occurred after the ten year prior to interview mark; therefore, BMI history shows an exposure prior to diagnosis. Both results (n=172 vs n-102 with breast cancer) showed increased odds when women increased weight from normal/overweight to obese, but the odds ratio was higher when diagnosis occurred after the ten year prior to interview mark (OR=3.4) compared to when BMI measurement was closest to diagnosis (OR=2.1).

Additionally, in the regression model four covariates (age, race/ethnicity, education level and marital status) were also significantly associated with the risk of breast cancer, when controlling for the other variables in the analysis (data not shown). As expected, the risk of breast cancer increased with age (OR=1.06; 95% CI: 1.03-1.08). Breast cancer risk was lower for Hispanics compared to non-Hispanic white women (OR=0.4; 95% CI: 0.22-0.76);

lower for those with less than a high school education compared to those with a college education (OR=0.44; 95% CI: 0.26-0.74); and lower for women who were not married/living with a partner compared to those who were married/living with partner (OR=0.65; 95% CI: 0.43-0.98). All other covariates (age at menarche, age at menopause, smoking and total cholesterol) were not significantly associated with risk of breast cancer.

Interaction of BMI change and Race

The second research question explored whether race/ethnicity and other demographic characteristics modified the association of BMI change with breast cancer risk. As shown in Table 4, there were significant differences in the proportion of BMI change by race/ethnicity. Although the proportion of women who had increased from normal to overweight was similar for non-Hispanic blacks (28.5%) and non-Hispanic whites (27.3%), twice the proportion of non-Hispanic Blacks (23%) compared to non-Hispanic whites (12.1%) increased their BMI from normal/overweight to obese.

The association between BMI change and breast cancer was modified by race/ethnicity, p-value=<.0001 and the results are shown in Table 5. Among non-Hispanic whites, women whose BMI increased from normal/overweight to obese compared to those who remained normal had a 2 times higher odds (OR=2.0) of developing breast cancer. A more pronounced association was found among non-Hispanic Black women. Non-Hispanic Black women were 4-7 times as likely to have breast cancer if they increased their BMI from normal to overweight (OR=4.2) or to obese (OR=6.6) when compared to those who were normal throughout. No significant associations between BMI change and breast cancer risk were observed for Hispanic women. The number of women of other races/ethnicities in the BMI change categories was too small to draw conclusions with confidence. No significant interactions between BMI change and education level or BMI change and age in relation to breast cancer risk were observed. The non-significant interactions are not reported in this paper.

Discussion

In this study, an increase in BMI from normal/overweight to obese and overweight to obese was associated with an increased risk of breast cancer compared to those who remained in the normal BMI (<25.0) category. The associations were stronger for Non-Hispanic Black women (4 to 7 times) who increased in weight from normal to overweight or obese. These results indicate that an increase in BMI to obese after adulthood may be an important marker for increased breast cancer risk.

The findings of this study are consistent with other studies that reported a positive association between weight gain and risk of breast cancer [20, 27-30] among postmenopausal women and especially those not using hormone replacement therapy [31]. While most studies have reported weight gain based on absolute weight at diagnosis, this study used change in weight from baseline of 25. In clinical practice since BMI categories are used conventionally using BMI category change instead of absolute BMI change may be a good strategy for patients and health care providers to understand the risk of developing breast cancer. In our study we used menopausal status by age 50 and hence used age 50 as

an inclusion criteria. Some women did not include their age at menopause; however, 81% had breast cancer diagnosed after menopause. We conducted a sensitivity analysis based only on those whose breast cancer was post-menopausal (n=139) and the results remained the same. Women who had a BMI increase from normal/overweight to obese had a significant and increased odds of breast cancer (OR=2.0, 95% CI, 1.01-3.77) when compared to those who maintained a normal BMI. For women who were diagnosed with breast cancer prior to menopause (pre-menopausal breast cancer), BMI change was not significantly associated with risk of breast cancer.

This may be the first study to show a significant moderating effect of race on the association of adult BMI change and breast cancer risk. The actual mechanism of this moderating effect remains unclear. However several factors may be associated with the higher risk among non-Hispanic blacks. First, racial/ethnic disparities exist in terms of prevalence of obesity and non-Hispanic black women tend to be heavier when compared to non-Hispanic white [3]. Secondly, though the variation is small, genetic risk factors have been shown to predict obesity in non-Hispanic blacks [32, 33]. There is also evidence showing the association of obesity with low socio-economic status [34, 35]. Low socio-economic status in terms of lower income, lower educational attainment and lower literacy levels [36, 37] are associated with poor health outcomes [38]. Likewise, inadequate health literacy is associated with lower knowledge or disease etiology and prevention [39, 40]. Overall, non-Hispanic black women have a lower socio-economic status when compared to non-Hispanic white women.

No association was found between women who increased their BMI from normal to overweight (OR=1.5; 95% CI: 0.90-2.45) or stayed overweight or obese (OR=1.3; 95% CI: 0.54-3.36) when compared to those who remained normal. If increasing BMI from normal/overweight to obese increased risk of breast cancer, then similar results would be expected for those whose BMI remained overweight or obese. However, the lack of an association may partly be attributed to the small number of women with breast cancer who stayed overweight or obese (n=12, 5%). Moreover, no significant relationship was observed between BMI change and breast cancer risk in Hispanic women. This may partly be explained by the small number of Hispanic women in the study (n=693) and of these only 22 had been diagnosed with breast cancer. In addition, breast cancer incidence is lower among Hispanic women (91/100,000) compared to non-Hispanic black (116/100,000) and non-Hispanic white women (125/100,000) [7]. The incidence of breast cancer in Hispanic women has recently decreased while the rates have increased among non-Hispanic blacks but remained stable in other racial groups [41].

The strengths of this study include using data from a large survey (NHANES) that includes a national representative sample, therefore, allowing exploration of the association of many variables with development of breast cancer in the general US population. The study also has a modest sample of women with breast cancer and a large control group. Likewise, the study dataset allowed analysis to control for several potential confounders, beyond the demographic factors, that may influence the association between BMI change and breast cancer risk. In addition, some of the measures such as total cholesterol, current height and weight, etc. were objectively measured reducing recall bias.

The study limitations are those inherent in observational studies. The major limitation of this study design is potential uncontrolled confounding differences between those with breast cancer and those without breast cancer that were not included in the regression model. While the study has a large number of women overall as well as controls, the smaller number of women with breast cancer limits the ability to compare all BMI change categories. In addition, the associations were modeled based on self-reported historical weight and height, which may lead to a recall misclassification of BMI. However, it is likely that the same amount of misclassification (non-differential) occurred in both arms and may have attenuated the results. In addition, using the same data in this study, a validation test of self-reported and objectively measured weight was conducted and a very strong correlation (r=0.97) was established. This suggests that majority of persons in the NHANES survey correctly reported their weight. The use of self-reported height and weight has been advocated previously as an accurate method to define and categorize BMI [42]. It is also important to highlight that the results of this study assess BMI change between two time points but BMI change may have fluctuated within the two time points. Therefore, we were limited by this national data set on other time points that may be important in calculating BMI change over time. Lastly, this analysis is based on breast cancer survivors and therefore, survival bias may exist.

Conclusion

Results from this study suggest that a BMI increase from normal/overweight to obese increases a woman's risk of breast cancer and that this change from normal/overweight to obese and breast cancer risk is much stronger in non-Hispanic Blacks. The results underscore the importance of understanding the relationship between BMI change over time and risk of breast cancer and the role that race may play in this association. Assessing BMI change overtime may be a better predictor of breast cancer risk than weight at a point in time. Weight gain expressed as movement between BMI categories may be more practical and useful in clinical practice. Health care providers may use the findings as a prevention strategy for breast cancer when counseling their patients. Indeed, the American Society of Clinical Oncology has prioritized educating providers and patients on the role of energy balance as one of the strategies to reduce the impact of obesity on cancer [43]. Further, studies with a larger number of women with breast cancer should be conducted to validate the results and to explore the associations of BMI change from normal to overweight and staying overweight or obese throughout and risk of cancer. The role of genetics as potential effect modifiers should also be considered.

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Table 1

Weighted Demographic and Health Related Characteristics of women with Breast Cancer and those without Breast cancer

	Breast Cancer N=172	No Breast Cancer N=2723
	(Mean)	(Mean)
Age	67.6	63.5
Age at menarche	12.7	12.8
Age at menopause	46.6	45.8
	n (%)	n (%)
Education		
Less than high school	91 (65.1)	1181 (52.1)
High school graduate	37 (17.2)	729 (29.5)
College education	44 (17.5)	809 (18.4)
Race		
Non-Hispanic White	111 (85.6)	1316 (75.5)
Non-Hispanic Black	35 (8.3)	628 (11.5)
Hispanic	22 (3.1)	671 (7.4)
Other race	4 (2.9)	108 (5.5)
Marital Status		
Married/Living with partner	100 (65.8)	1447 (61.4)
Not married	72 (34.2)	1275 (38.6)
BMI at age 25		
Underweight/Normal	153 (92.0)	2220 (61.4)
Overweight	13 (4.9)	353 (11.3)
Obese	6 (3.1)	150 (5.1)
BMI Change*		
Normal throughout	63 (44.5)	1122 (52.5)
Normal to Overweight	54 (30.0)	694 (27.4)
Normal/Overweight to Obese	33 (20.4)	357 (12.3)
BMI >25 throughout	12 (5.1)	239 (7.8)
Smoked at least 100 cigarettes in life		
Smoker	76 (41.4)	1140 (43.6)
Non-smoker	96 (58.6)	1582 (56.4)

* The numbers of breast cancer cases whose BMI category reduced from obese to overweight (n=0), from overweight to normal (n=2) and increased from overweight to obese (n=5) were too small to provide reliable comparison. The category of those who reduced was not dropped from further analysis while that of those who increased from overweight to obese was combined with that of those who increased from normal to obese.

Table 2

Association of BMI at different Time points and risk of Breast Cancer

	* Age 25	** Average 10 years ago	** Current
BMI Categories			
Underweight & Normal (<25 Kg.m^2)	Reference	Reference	Reference
Overweight (25-29.99 Kg.m^2)	0.4 (0.18-1.09)	1.6 (0.98-2.51)	0.7 (0.38-1.14)
Obese (≥30 Kg.m^2)	0.9 (0.28-2.85)	1.1 (0.62-2.03)	1.1 (0.69-1.75)

* **Model** was adjusted for variables that were constant at age 25:: age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and Other race), education (less than high school education, high school graduate and college education).

** **Model** was adjusted for all variables that are *confirmed or suspected risk factors* for breast cancer: age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and Other race), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (smoked at least 100 cigarettes in life Yes/No) and total cholesterol (mg/dl).

Table 3

Weighted ORs and 95% CIs of the association between BMI Change and Breast Cancer Risk

	BMI measurement closest to breast cancer diagnosis (n=172)		**Analysis based on 102 breast cancer cases whose BMI measurement was prior to their diagnosis**	
	Model a	**Model b**	**Model a**	**Model b**
BMI Change				
Normal throughout	Reference	Reference	Reference	Reference
Normal to Overweight	1.3 (0.80-2.02)	1.5 (0.90-2.45)	1.1 (0.59-2.17)	1.5 (0.75-2.92)
Normal/Overweight to Obese	**2.0 (1.15-3.56)***	**2.1 (1.11-3.79)***	**3.1 (1.58-5.93)***	**3.4 (1.66-6.99)***
Overweight/Obese throughout	1.0 (0.42-2.38)	1.3 (0.54-3.36)	1.1 (0.44-2.55)	1.5 (0.53-4.01)

** Statistically significant at p<.05.* **Model a** was adjusted for variables that were *significantly different for cases and controls*: age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and Other race), education (less than high school education, high school graduate and college education). **Model b** was adjusted for all variables that are *confirmed or suspected risk factors* for breast cancer: age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and Other race), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (smoked at least 100 cigarettes in life Yes/No) and total cholesterol (mg/dl).

Table 4

Comparison of BMI change categories by Race

	non-Hispanic white	non-Hispanic blacks	Hispanic	Other
BMI Change				
Normal throughout	691 (53.2%)	202 (35.7%)	229 (37.9%)	63 (60.0%)
Normal to Overweight	355 (27.3%)	161 (28.5%)	204 (33.8%)	28 (26.7%)
Normal/Overweight to Obese	157 (12.1%)	133 (23.5%)	94 (15.6%)	6 (5.7%)
Overweight/Obese throughout	96 (7.4%)	70 (12.4%)	77 (12.8%)	8 (7.6%)

χ^2*= 104.7, pvalue=<.0001*

Table 5

Weighted ORs with 95% CIs of the joint effect of Race and BMI Change on Breast Cancer Risk

	non-Hispanic white	**non-Hispanic blacks**	**Hispanic**
BMI Change			
Normal throughout	Reference	Reference	Reference
Normal to Overweight	1.5 (0.86-2.65)	**4.2 (1.02-17.75)**	2.2 (0.59-8.43)
Normal/Overweight to Obese	**2.0 (1.00-4.14)**	**6.6 (1.68-25.86)**	1.1 (0.15-8.42)
Overweight/Obese throughout	1.4 (0.49-4.16)	1.0 (0.10-9.77)	1.4 (0.22-8.61)

* *Race and BMI change interaction term significant (p*<.0001). **Model** was adjusted for all variables that are *confirmed or suspected risk factors* for breast cancer: age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and Other race), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (smoked at least 100 cigarettes in life Yes/No) and total cholesterol (mg/dl).