Optimal Cutoffs of Obesity Measures in Relation to Cancer Risk in Postmenopausal Women in the Women's Health Initiative Study

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Abstract

Background: Obesity is a risk factor for several cancers in postmenopausal women. We attempted to determine cutoffs of adiposity measures in relation to risk of obesity-related cancers among postmenopausal women and to examine the effects of hormone therapy (HT) use on the cutoffs, neither of which has been broadly studied.

Methods: We used data from the Women's Health Initiative cohort ($n = 144,701$) and applied Cox-proportional hazards regressions to each combination of 17 cancer types and 6 anthropometric measures (weight, body mass index [BMI], weight to height ratio, waist circumference, waist to hip ratio [WHR], and waist to height ratio). Interactions between the anthropometric measures and HT use were also examined. Cutoffs were determined by applying a grid search followed by a two-fold cross validation method. Survival ROC analysis of 5- and 10-year incidence followed.

Results: Breast, colorectal, colon, endometrium, kidney, and all cancers combined were significantly positively associated with all six anthropometric measures, whereas lung cancer among ever smokers was significantly inversely associated with all measures except WHR. The derived cutoffs of each obesity measure varied across cancers (e.g., BMI cutoffs for breast and endometrium cancers were 30 kg/m^2 and 34 kg/m^2 , respectively), and also depended on HT use. The Youden indices of the cutoffs for predicting 5- and 10-year cancer incidence were higher among HT never users.

Conclusion: Using a panel of different anthropometric measures, we derived optimal cut-offs categorizing populations into high- and low-risk groups, which differed by cancer type and HT use. Although the discrimination abilities of these risk categories were generally poor, the results of this study could serve as a starting point from which to determine adiposity cutoffs for inclusion in risk prediction models for specific cancer types.

Introduction

OBESITY IS ASSOCIATED WITH INCREASED RISK of numerous diseases including cancer.^{1–3} Obesity or excess accumulation of body fat is often assessed using anthropometric measurements, owing to their low cost, simplicity of use, and the strong correlation with measured body fat.^{4–6} Commonly used anthropometric obesity measures include weight (kg); body mass index (BMI; kg/m^2),⁷ the most widely used anthropometric index; weight-to-height ratio (Wt/Ht);⁸ waist circumference (WC);⁹ waist-to-height ratio (WC/Ht),¹⁰ and waist-to-hip ratio (WHR).¹¹ The former three

measures represent whole body obesity, whereas the latter three represent central obesity.

Most prospective studies of cancer risk related to obesity have, therefore, used one or more of these anthropometric measures.^{3,12,13} The risk assessments are often made in terms of hazard ratios for continuous obesity measures or arbitrarily chosen data-dependent categorizations based on, for example, median, quartiles, or quintiles. The weight status classifications proposed by the United States National Heart Lung and Blood Institute (NHLBI) guideline¹⁴ based on ranges of BMI are also applied in most research settings. While the resulting hazard ratios, whether from continuous or categorical obesity

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measures, may provide clinically useful information about risk groups, they may not necessarily provide information as to what absolute values of body fat measures might serve to identify a high-risk group defined by excess body weight.

When determined in relation to cancer incidence, a single cutoff point can provide the aforementioned information and can be used for identifying low- and high-risk groups with respect to the cancer outcome. In identifying risk groups, however, use of hormone therapy (HT) should be taken into consideration since it is known to modify the association of obesity with certain cancers.^{15–17} To this end, we used the entire Women's Health Initiative (WHI) cohort data from US postmenopausal women to (1) identify cancer sites that are significantly associated with any anthropometric body fat measure; (2) identify obesity measures whose effects on cancer incidence interact with hormone therapies; (3) develop cutoffs for the anthropometric measures for risk of cancer across 17 sites and all cancers combined, and, where necessary, stratified by the HT use since HT can be an effect modifier of the obesity-cancer association^{16–19} and (4) assess the discrimination ability of the cutoffs in terms of sensitivity and specificity of 5- and 10-year cancer incidence.

Methods

Study sample

The WHI is an on-going multi-center prospective cohort study of a large sample of U.S. postmenopausal women aged between 50 and 79 years at enrollment. The WHI was primarily designed to further understanding of the determinants of major chronic diseases including cancer. Participants were recruited at 40 centers across United States between 1993 and 1998, and enrolled into either the clinical trial (WHI-CT) component or the observational study (WHI-OS) component²⁰. Details of the design and reliability of the baseline measures have been published elsewhere²¹.

As of April 2, 2012, a total of 24,309 incident cancers had been diagnosed among the 161,808 participants in the OS ($n=68,132$) and CT ($n=93,676$) after a median of 12.0 years of follow-up. For the analyses conducted here, we excluded subjects with a previous history of cancer, except non-melanoma skin cancer ($n=16,256$), and those missing information on height ($n=851$), which is required for computation of BMI and other derived anthropometric measures. These exclusions left $n=144,701$ subjects among whom 20,928 had one or more cancer diagnosis during follow-up.

Measurements

All participants were measured for weight, height, and waist and hip circumferences by trained staff adhering to standardized protocols at baseline and also during follow-up. For the present study, we used only baseline anthropometric measurements for the development of cutoff points. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Waist circumference at the natural waist or at the narrowest part of the torso and hip circumference at the maximal circumference were recorded to the nearest 0.1 cm. Body mass index (kg/m^2) was computed as weight (kg) divided by the square of height (m). The other ratios are similarly computed: weight-to-height ratio (kg/m), waist-to-hip ratio ($\text{cm/cm} = \text{m/m}$), and waist to height ratio ($\text{cm/cm} = \text{m/m}$).

At baseline, self-administered questionnaires were used to collect information on hormone therapy (HT) use (never, estrogen only, or estrogen plus progesterone); demographics; medical; reproductive and family history; and dietary and lifestyle factors, including smoking history, alcohol consumption, and recreational physical activity. Questions about physical activity included walking and participation in recreational sports or leisure-time activity. A variable "current total leisure-time physical activity" (MET-hours/week) was computed by multiplying the number of hours of leisure-time physical activity per week by the metabolic equivalent (MET) value of the activity and summing the products of all types of activities.^{22,23}

Cancer outcome

New cancer diagnoses and other clinical outcomes were ascertained semi-annually in the WHI-CT and annually in the WHI-OS using in-person, mailed, or telephone questionnaires. When malignancy was self-reported, it was verified by centralized review of medical records and pathology reports by trained physician adjudicators²⁴. We excluded from the analysis of endometrial cancer women who reported a history of hysterectomy at baseline (6 cases; 1107 non-cases), and for the analysis of ovarian cancer women with a history of bilateral oophorectomy (19 cases; 667 non-cases). For the analysis of lung cancer, we stratified subjects by their smoking status: ever or never smoking. Cancers of the colon and rectum were analyzed separately. In sum, we analyzed a total of 17 cancer sites and all cancers combined. In addition, we also analyzed all cancers combined after excluding breast cancer since breast cancer represented about one third of all incident cancers.

Statistical model

The generally applied statistical model is a Cox proportional hazards (PH) model with an anthropometric body fat measure as the main predictor for each cancer site. We converted the obesity measures into their corresponding z-scores, that is, the measures standardized by their standard deviations, in order to compare the magnitudes of hazards ratios (HR) across obesity measures on the same scale. Although sets of specific covariates differed by cancer site, the following covariates were included in the Cox models for all cancer sites: age at enrollment (continuous); years of education (less than high school graduate, high school graduate/some college, college graduate, post-college); pack-years of smoking (continuous); alcohol consumption (drinks per week, continuous); height (continuous); randomization status in clinical trials (treatment arm of each trial, control, placebo, not randomized); and hormone therapy (HT) experience at baseline.

With respect to HT use, we used ever versus never use as the stratifying variable, since distinguishing between use of estrogen only or estrogen plus progesterone yielded similar results. The interaction between HT use and obesity measure on cancer incidence was tested for each and every pair of anthropometric measure and cancer. If an interaction effect was significant, we further stratified by HT use the analysis for the corresponding paired risk category of the obesity measure and the cancer. In this stratified analysis, HT use was not controlled. Other additional covariates pertinent to each

cancer site were added to the models to control for their potential confounding effects (see footnotes to Table 3). Statistical significance was declared if a two-sided p -value is less than 0.05.

Validity of proportionality of hazards was tested by examining the correlation of Schoenfeld residuals²⁵ of a continuous anthropometric measure with ranked survival times. The proportionality assumptions held for all paired risk categories of cancer sites and anthropometric measures except for a relatively few cases with $p < 0.05$ but very weak correlations.

Determination of cutoff points

We restricted the determination of a cutoff to cancers which showed a statistically significant association of a body fat measure. For those cancers, we first conducted a grid search to identify an optimal cutoff point, and then applied a two-fold cross validation method²⁶ to estimate the HR of the optimal cutoff point. Specifically, to determine an optimal cutoff we applied a grid search for which the Cox PH model for a dichotomized anthropometric measure determined by each value of the corresponding continuous anthropometric measure increasing from its 5% quantile to its 95% quantile by an appropriate unit interval, using the entire data set. Then, we determined a value linked to the maximized log-likelihood ratio or equivalently to the minimized p -value as the optimal cutoff point. However, since the resulting p -value of the HR of the optimized dichotomized anthropometric measure is not adjusted for multiple comparisons,²⁷ it yields an upwardly biased HR of the optimal cutoff. Therefore, we applied the two-fold cross-validation method to mitigate this problem and adjust its p -value and HR (“high” versus “low” risk groups) as described in detail in Mazumdar et al.²⁸

Briefly, we randomly divided the whole data set D into two datasets, D_1 and D_2 , with equal sizes. To adjust the p -value and the HR associated with the cutoff obtained from D as above, we first applied the grid search to each of the datasets, D_1 and D_2 , and determined their two corresponding cutoffs, referred to as cutoff₁ and cutoff₂. We then categorized subjects in D_1 into high- and low-risk groups based on cutoff₂ and likewise those in D_2 into high- and low-risk group based on cutoff₁. Then we combined D_1 and D_2 with the high- and low-risk groups defined in this manner into a single dataset and then applied the Cox PH model to estimate HR of the high- versus the low-risk groups and its p -value. We used these as the adjusted p -values and HRs for the optimal cutoff point obtained from the whole data set D . This procedure was applied to every paired risk category combination of cancer sites and anthropometric measures for both unstratified and HT-stratified analyses. It should be noted that the statistical power of HR based on a dichotomized measure based on a cutoff is lower than that of the HR based on its continuous measure.²⁸

Assessment of sensitivity and specificity of the cutoffs

We evaluated discrimination ability of optimal cutoffs by assessing their sensitivities and specificities for 5- and 10- year incidence applying the time-dependent receiver operating characteristic (ROC) curve method developed by Heagerty et al.²⁹. In addition, both the area under curve (AUC) of the ROC curve and Youden index (= sensitivity +

specificity – 1) were calculated. We note that these analyses were performed in a univariate fashion without adjusting for other covariates due to the lack of available methods.

Results

Subject characteristics

Baseline subject characteristics, including anthropometric obesity measures and potential confounding factors, were comparable (data not shown) between the two randomly divided groups used for the two-fold validations. Summary statistics for baseline subject characteristics by BMI status are presented in Table 1, which shows that all variables are significantly different across the BMI categories with all p -values < 0.05 . Correlations among the anthropometric measures except for WHR were high, ranging from 0.74 (between Weight and WC/Ht) to 0.98 (between BMI and Wt/Ht). In contrast, the correlations of WHR with other measures were relatively low ranging from 0.31–0.34 (with Weight, with Wt/Ht, and with BMI) to 0.67–0.68 (with WC and with WC/Ht). All of these correlations were statistically significant.

The site-specific unadjusted (crude) cancer incidence rates per 10,000 persons per year are presented in Table 2. The incidence rate for all cancers combined was 134.8 per 10,000 persons per year. Among the individual cancer sites, the incidence rate of invasive breast cancer was the highest at 42.4 per 10,000 per year, whereas that of cervical cancer was the lowest at 0.5 per 10,000 per year.

Cancer sites associated with anthropometric measures

Table 3 presents the HRs and 95% confidence intervals for the association of the continuous standardized anthropometric measures (i.e., z -scores), with risk of cancer at each site. From the unstratified analyses, the following cancer sites were significantly associated with all of the anthropometric obesity measures: Breast, colorectal, colon, endometrium, kidney, and all cancers combined. Non-Hodgkin lymphoma (NHL) was associated only with WHR whereas lung cancers among ever smokers were associated with all obesity measures except WHR; lung cancer among ever smokers was the only cancer site inversely associated with obesity measures. For the following cancers interactions between HT use and at least one obesity measure were significant: breast, endometrium, pancreas, and all cancers combined. For pancreatic cancer, only the interaction between WHR and HT was significant, whereas for breast cancer that was the only non-significant interaction (Table 3). Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/jwh) shows the HRs for cancers with and without inclusion of breast cancer are made; the significant results are almost identical.

In general, the HR of WHR z -score, if significant, was the smallest regardless of HT use across the cancer sites as well as across the standardized obesity measures. The HRs of the standardized obesity measures were greater for HT never users than for HT ever users. The HR's were greatest for endometrial cancer followed by those for kidney cancer.

Optimal cutoffs of anthropometric measures

From the unstratified analyses, the HR's of the cutoffs were significant ($p < 0.05$) for all cancer sites and all measures except for the WHR cutoff of NHL (HR = 1.07, $p = 0.324$)

TABLE 1. BASELINE CLINICAL AND DEMOGRAPHIC CHARACTERISTICS BY BODY MASS INDEX STATUS

	<i>BMI status (mean $\pm$ SD, %)</i>					<i>p-value^a</i>
	<i>< 18.5</i> (<i>n</i> = 1234)	<i>18.5–24.9</i> (<i>n</i> = 49263)	<i>25–29.9</i> (<i>n</i> = 50189)	<i>30–34.9</i> (<i>n</i> = 26830)	<i>≥ 35</i> (<i>n</i> = 16782)	
Weight (kg)	46.3 $\pm$ 4.7	59.7 $\pm$ 6.2	71.5 $\pm$ 6.76	84.0 $\pm$ 7.5	103.1 $\pm$ 15.0	< 0.0001
Height (cm)	162.1 $\pm$ 6.9	162.3 $\pm$ 6.4	161.7 $\pm$ 6.3	161.4 $\pm$ 6.3	161.0 $\pm$ 7.2	< 0.0001
Wt/Ht (kg/m)	28.5 $\pm$ 2.0	36.7 $\pm$ 2.9	44.2 $\pm$ 2.9	52.0 $\pm$ 3.0	64.0 $\pm$ 8.2	< 0.0001
WC (cm)	65.4 $\pm$ 5.5	74.9 $\pm$ 6.8	85.7 $\pm$ 7.6	96.2 $\pm$ 8.3	108.8 $\pm$ 11.5	< 0.0001
WC/Ht (cm/cm)	0.4 $\pm$ 0.03	0.46 $\pm$ 0.04	0.53 $\pm$ 0.05	0.60 $\pm$ 0.05	0.68 $\pm$ 0.07	< 0.0001
WHR (cm/cm)	0.75 $\pm$ 0.06	0.78 $\pm$ 0.07	0.82 $\pm$ 0.08	0.84 $\pm$ 0.08	0.85 $\pm$ 0.08	< 0.0001
Age at enrollment (years)	64.5 $\pm$ 7.8	63.2 $\pm$ 7.4	63.4 $\pm$ 7.2	63.0 $\pm$ 7.0	61.7 $\pm$ 6.7	< 0.0001
Pack years of smoking	9.7 $\pm$ 18.6	8.7 $\pm$ 16.8	9.6 $\pm$ 17.8	10.2 $\pm$ 18.9	10.3 $\pm$ 19.0	< 0.0001
Red meat intake (median serving/day)	0.46 $\pm$ 0.46	0.55 $\pm$ 0.48	0.68 $\pm$ 0.54	0.82 $\pm$ 0.66	0.98 $\pm$ 0.80	< 0.0001
Alcohol serving per week	2.7 $\pm$ 5.3	3.0 $\pm$ 5.3	2.4 $\pm$ 4.8	1.8 $\pm$ 4.4	1.2 $\pm$ 3.9	< 0.0001
Folate intake (mg/day)	254 $\pm$ 114	254 $\pm$ 113	254 $\pm$ 118	257 $\pm$ 123	266 $\pm$ 142	< 0.0001
MET-hours per week	14.9 $\pm$ 16.1	15.1 $\pm$ 15.1	11.9 $\pm$ 13.3	8.9 $\pm$ 11.6	6.6 $\pm$ 10.0	< 0.0001
Age of menarche > 13 years	23.5%	24.9%	26.6%	27.1%	26.3%	< 0.0001
Age of menopause < 50 years	42.8%	45.0%	46.8%	48.7%	49.4%	< 0.0001
Age at first birth ≥ 30 year	8.6%	8.2%	7.11%	6.8%	6.1%	< 0.0001
Family history of breast cancer ^b	36.7%	39.3%	38.3%	37.2%	36.9%	0.0002
Family history of colorectal cancer ^c	17.6%	15.9%	16.6%	16.8%	16.7%	0.0054
Clinical trial group	22.8%	35.3%	45.7%	53.6%	55.9%	< 0.0001
White	81.3%	87.2%	83.0%	78.7%	73.2%	< 0.0001
Post-college education	34.9%	33.7%	27.9%	23.9%	21.6%	< 0.0001
Null parity	22.6%	12.9%	11.0%	10.4%	11.3%	< 0.0001
Diabetes ever	2.8%	2.3%	4.7%	8.9%	14.6%	< 0.0001
Aspirin use at baseline	20.5%	22.0%	23.0%	22.6%	21.6%	< 0.0001
Oral contraceptive use ever	38.0%	43.9%	41.1%	40.5%	41.6%	< 0.0001
Hormone therapy ever	54.5%	62.6%	57.5%	51.3%	45.2%	< 0.0001
Smoking ever (at least 100 cigarettes ever)	47.1%	48.6%	49.2%	48.4%	49.9%	0.0033

Missing values are excluded for the comparisons.

^a*p*-Values are based on analysis of variance or Chi-squared tests.

^bMale/Female relative had colorectal cancer.

^cFemale relative had breast cancer.

BMI, body mass index; MET, metabolic equivalent; WC, waist circumference; WC/Ht, waist to height ratio; WHR, waist to hip ratio; Wt/Ht, weight to height ratio.

(Table 4). This nonsignificance may be a result of relatively low statistical power due to dichotomization. Unlike the cutoffs of the other measures, the cutoff for WC/Ht was not the lowest for lung cancer among ever smokers. All cutoffs for lung cancer among ever smokers had HR's less than 1, whereas the anthropometric cutoffs for all the other cancer sites in Table 4 had HRs greater than 1. The HR's of all obesity measure cutoffs for endometrial cancer were the greatest except for the WHR cutoff whose HR was largest for kidney cancer.

From the HT-stratified analyses, the HR's of WC and WC/HT cutoffs for endometrial cancer and that of WHR for all cancers combined were not significant among HT ever users whereas HR's all cutoffs were significant among HT never users. The HRs of the cutoffs were higher for HT never users even though the cutoffs were generally lower for the HT never users. In Supplementary Table S2, comparisons of cutoffs and HR's between all cancers with and without inclusion of breast cancer are made; the results are almost identical except for BMI and WC.

Five and ten year sensitivity and specificity

The sensitivities and specificities of the cutoffs derived from survival ROC curves are displayed in Supplementary

Table S3 along with the Youden indices and the AUCs of the corresponding ROC. Unlike the other cancer sites, the sensitivities and specificities of lung cancer among ever smokers were derived so that lower values of obesity measures indicated greater risk.

From the unstratified analyses, in general, the values of all AUC's are small and no greater than 0.6 for 5- or ten-10 incidence. The Youden indices over all combinations of anthropometric measures and cancer sites ranged from -0.02 to 0.18 for 5-year incidence and from -0.01 to 0.16 for 10-year incidence; the average Youden indices are 0.06 and 0.07 , respectively. Likewise, the AUC's are close to 0.55 on average for both 5- and 10-year incidence, and the range of AUCs is narrow like that of the Youden indices (Supplementary Table S3). The similarity between the 5- and 10-year incidence estimates may not be surprising due to the aforementioned supported proportionality of hazards.

From the HT-stratified analysis, the values of both AUC and Youden indices were greater for HT never users than for HT ever users for both 5- and 10-year incidence. In particular, both AUC (as high as 0.68) and Youden indices (as high as 0.28) of the obesity measure cutoffs were greatest for endometrial cancer for HT never users. In sum, minimum, maximum and mean of both AUC and Youden indices were greater for HT never users than those for HT ever users, and

TABLE 2. UNADJUSTED CRUDE CANCER INCIDENCE RATES PER 10,000 PERSONS PER YEAR AMONG THE WOMEN'S HEALTH INITIATIVE PARTICIPANTS

<i>Cancer site</i>	<i>No. of cases</i>	<i>Incidence rate per 10,000 persons per year</i>
Breast	6,798	42.4
Colorectum	1,904	11.6
Lung	1,755	10.7
Ever smoker (ES)	1,466	17.4
Never smoker (NS)	269	3.4
Colon	1,516	9.2
Melanoma	1,169	7.1
Endometrium	1,115	6.8
Non-Hodgkin lymphoma	888	5.4
Ovary	702	4.3
Pancreas	459	2.8
Bladder	457	2.8
Leukemia	447	2.7
Kidney	369	2.2
Multiple myeloma	282	1.7
Thyroid	270	1.6
Rectum	257	1.6
Brain	176	1.1
Stomach	152	0.9
Cervix	83	0.5
All cancers combined	20,928	134.8

also greater than those from unstratified analyses (Supplementary Table S3).

Discussion

The present study showed that obesity is an important risk factor for many cancers, including all cancers combined among US postmenopausal women, as represented by the WHI participants, even after controlling for potential confounding factors including height, which a few recent studies demonstrated is a risk factor for many cancers.^{30–32} Sites of those cancers include breast, colorectal, and colon in particular, lung among ever smokers, endometrial, non-Hodgkin lymphoma, kidney, and pancreatic among HT never users. Unlike all the other positive associations between paired risk categories, the finding of an inverse association between obesity and lung cancer among ever smokers is in accordance with the results of other studies.^{33,34}

Obesity is shown to be a stronger risk factor for breast, endometrial, and pancreatic cancers for those who never used hormone therapy than for those who used HT. This finding is in agreement with the results of previous studies^{16–19} and may be explained by the fact that the increase in risk associated with hormone therapy is easier to detect in non-obese women compared to in obese women who have higher circulating estrogen levels due to the conversion of testosterone to estrogen in adipose tissue.^{35,36} In addition to obesity, all other factors such as endogenous level of hormone levels,³⁷ histological types,³⁸ and types of therapy (e.g., estrogen-only or estrogen-progestin combination)³⁹ have been linked to risk of endometrial and breast cancer. Therefore, the inter-relationships among hormone therapy, obesity, and carcinogenesis remain complex.

Some cancer sites, nevertheless, are not associated with obesity among postmenopausal women, and the non-significant

associations do not appear to be due to low statistical power due to lower incidence rates. For example, melanoma had a higher incidence rate than endometrial and kidney cancers but was not associated with any anthropometric body fat measure. Likewise, cancer sites such as ovary, bladder, and leukemia were not associated with obesity, while kidney with a lower incidence rate than those sites was associated with all measures.

Our study also showed that subjects with BMI higher than 27–36 kg/m², depending on the cancer site (with the exception of lung cancer among ever smokers), would be at greater risk. This range of BMI cutoffs approximately coincides with obesity class 1 (BMI 30–35 kg/m²) classified by the NHLBI guidelines¹⁴ although colon cancer is associated with somewhat lower cutoff of BMI 27 kg/m² within the overweight classification range (BMI 25–30 kg/m²). Therefore, subjects with BMI 25–27, even if categorized as overweight, may be less vulnerable to cancer risks. From the unstratified analysis, while the BMI cutoffs for endometrial and kidney cancers were 34 and 36 kg/m², respectively, the BMI cutoffs for the other cancers were close to 30. Collectively, since obesity is associated with delaying cancer screening among women,^{40,41} overweight or obese postmenopausal women should be encouraged to have regular cancer screenings, perhaps especially for endometrial cancer among HT never users whose HR was greater than 3.0.

The discrimination abilities of all the anthropometric measures for both 5- and 10-year cancer incidences were comparable to each other and low in terms of both Youden index and AUC of the time-dependent ROC analysis likely due to the modest HR's. Both AUC and Youden indices were especially low for breast cancer, lung cancer among ever smokers, and all cancers combined. While low discrimination abilities can be associated with even sizable HRs,⁴² both AUC and Youden indices are relatively higher for HT never users who have greater HR's for the cutoffs. Furthermore, the discrimination ability did not depend on the time frames (i.e., 5 versus 10 years). In general, the specificity of the cutoffs for the obesity-related cancers is greater than the corresponding sensitivity. However, cutoffs with high sensitivity may deserve more attention for further screening purposes. The cutoffs with sensitivity greater than 0.70, if this is a reasonable criterion for more attention, are: WC cutoff for colon cancer, WC/Ht cutoffs for colon and colorectal cancers, weight cutoff for lung cancer among ever smokers, and WHR cutoffs for colon, colorectal cancers and all cancers combined for HT never users. In sum, central adiposity measures tend to have high sensitivities for colon or colorectal cancers.

The inverse association of the anthropometric measures with lung cancer among ever smokers could be a product of confounding by outcome indication. For example, lung cancer among never smokers is not significantly associated with any anthropometric measure. Therefore, the lung cancer among ever smokers could be an effect of smoking, and both the lung cancer and smoking might have had effects on weight loss. It follows that ever smokers with higher body weight might not necessarily have a lower risk for lung cancer. However, the present study was not able to tease out such a hypothetical pathway among smoking, weight, and lung cancer.

There were only small differences in discrimination ability between the optimal cutoffs of whole and central body fat measures for each cancer site. Nevertheless, more accurate measures of whole or regional body fat through dual-energy x-ray absorptiometry (DXA) scanners may not necessarily

TABLE 4. OPTIMAL CUTOFFS OF ANTHROPOMETRIC MEASURES AND ADJUSTED HAZARD RATIOS, 95% CONFIDENCE INTERVALS, AND *P*-VALUES OF HIGH- VS. LOW-RISK GROUPS DETERMINED BASED ON THE CUTOFFS

<i>Measures</i>	<i>Cancer site</i>	<i>Cutoff</i>	<i>% ≥ Cutoff^a</i>	<i>HR</i>	<i>95% CI</i>	<i>p-value</i>
Weight (kg)	Breast	76	36.0%	1.22	(1.15–1.28)	0.000
	HT ever	69	50.7%	1.12	(1.05–1.20)	0.001
	HT never	77	38.3%	1.34	(1.24–1.46)	0.000
	Colorectum	82	24.5%	1.17	(1.03–1.32)	0.014
	Lung (ES)	76	36.0%	0.76	(0.68–0.84)	0.000
	Colon	75	38.3%	1.21	(1.07–1.37)	0.002
	Endometrium	86	18.5%	2.38	(2.06–2.75)	0.000
	HT ever	78	28.5%	1.29	(1.05–1.58)	0.015
	HT never	89	17.8%	3.77	(3.11–4.56)	0.000
	Kidney	79	29.9%	1.35	(1.05–1.74)	0.018
	All cancers	89	14.8%	1.18	(1.14–1.23)	0.000
	HT ever	89	12.5%	1.15	(1.09–1.22)	0.000
	HT never	82	28.4%	1.25	(1.19–1.31)	0.000
BMI (kg/m ²)	Breast	30	30.2%	1.25	(1.18–1.32)	0.000
	HT ever	33	14.3%	1.19	(1.10–1.29)	0.000
	HT never	28	47.9%	1.34	(1.23–1.45)	0.000
	Colorectum	31	25.3%	1.12	(1.02–1.24)	0.024
	Lung (ES)	21	93.1%	0.71	(0.62–0.81)	0.000
	Colon	27	49.3%	1.18	(1.05–1.33)	0.006
	Endometrium	34	14.3%	2.37	(2.06–2.73)	0.000
	HT ever	31	21.5%	1.46	(1.16–1.83)	0.001
	HT never	33	21.4%	3.45	(2.85–4.17)	0.000
	Kidney	36	9.4%	1.38	(1.10–1.72)	0.005
	All cancers	31	25.3%	1.16	(1.12–1.20)	0.000
	HT ever	34	11.6%	1.09	(1.02–1.16)	0.007
	HT never	30	35.6%	1.25	(1.19–1.30)	0.000
Wt/Ht (kg/m)	Breast	47	35.6%	1.24	(1.17–1.31)	0.000
	HT ever	53	15.2%	1.16	(1.07–1.25)	0.000
	HT never	46	44.6%	1.37	(1.26–1.48)	0.000
	Colorectum	48	32.0%	1.12	(1.01–1.24)	0.025
	Lung (ES)	46	39.3%	0.80	(0.71–0.89)	0.000
	Colon	44	47.8%	1.21	(1.08–1.36)	0.001
	Endometrium	54	16.2%	2.30	(2.00–2.63)	0.000
	HT ever	51	19.7%	1.31	(1.07–1.60)	0.008
	HT never	54	19.8%	3.46	(2.87–4.17)	0.000
	Kidney	58	9.8%	1.33	(1.08–1.65)	0.008
	All cancers	53	18.2%	1.19	(1.15–1.24)	0.000
	HT ever	53	15.2%	1.10	(1.04–1.17)	0.002
	HT never	51	27.5%	1.24	(1.19–1.30)	0.000
WC (cm)	Breast	87	42.2%	1.17	(1.12–1.23)	0.000
	HT ever	93	23.9%	1.16	(1.07–1.25)	0.000
	HT never	82	62.2%	1.30	(1.19–1.41)	0.000
	Colorectum	87	42.2%	1.20	(1.08–1.32)	0.000
	Lung (ES)	86	45.1%	0.80	(0.72–0.89)	0.000
	Colon	76	74.8%	1.27	(1.13–1.43)	0.000
	Endometrium	104	10.8%	2.00	(1.74–2.30)	0.000
	HT ever	110	4.3%	1.07	(0.87–1.31)	0.534
	HT never	94	31.1%	2.90	(2.41–3.48)	0.000
	Kidney	91	32.3%	1.58	(1.27–1.96)	0.000
	All cancers	94	25.9%	1.16	(1.12–1.20)	0.000
	HT ever	94	21.9%	1.11	(1.06–1.17)	0.000
	HT never	88	45.8%	1.12	(1.07–1.17)	0.000
WC/Ht (cm/cm)	Breast	0.56	34.4%	1.20	(1.13–1.27)	0.000
	HT ever	0.56	29.4%	1.18	(1.09–1.27)	0.000
	HT never	0.51	62.4%	1.31	(1.20–1.42)	0.000
	Colorectal	0.49	66.0%	1.17	(1.05–1.29)	0.004
	Lung (ES)	0.51	56.1%	0.83	(0.75–0.93)	0.001
	Colon	0.49	66.0%	1.31	(1.16–1.47)	0.000

(continued)

TABLE 4. (CONTINUED)

<i>Measures</i>	<i>Cancer site</i>	<i>Cutoff</i>	<i>% ≥ Cutoff^a</i>	<i>HR</i>	<i>95% CI</i>	<i>p-value</i>
WHR (cm/cm)	Endometrium	0.60	21.1%	1.75	(1.54–2.00)	0.000
	HT ever	0.68	4.5%	1.03	(0.84–1.26)	0.802
	HT never	0.55	45.0%	2.68	(2.23–3.23)	0.000
	Kidney	0.55	38.4%	1.46	(1.17–1.83)	0.001
	All cancers	0.61	18.5%	1.17	(1.13–1.21)	0.000
	HT ever	0.56	29.4%	1.10	(1.05–1.16)	0.000
	HT never	0.60	26.3%	1.22	(1.16–1.28)	0.000
	Breast	0.79	57.8%	1.09	(1.03–1.15)	0.004
	Colorectum	0.75	78.4%	1.18	(1.07–1.30)	0.001
	Colon	0.76	73.8%	1.24	(1.11–1.39)	0.000
	Endometrium	0.89	14.0%	1.16	(1.02–1.31)	0.019
	HT never	0.81	52.3%	1.79	(1.48–2.16)	0.000
	Pancreas					
	HT never	0.86	27.7%	1.63	(1.21–2.21)	0.001
	NHL	0.94	4.9%	1.07	(0.94–1.22)	0.324
	Kidney	0.80	52.0%	1.49	(1.18–1.88)	0.001
	All cancers	0.80	52.0%	1.09	(1.06–1.12)	0.000
	HT ever	0.80	47.8%	1.04	(1.00–1.08)	0.063
	HT never	0.77	73.5%	1.20	(1.14–1.08)	0.000

The selected paired risk categories between the cancer sites and the anthropometric measures had significant associations based on the analysis results on Table 3.

^aProportions of subjects whose corresponding measures are greater than equal to the cutoffs; the subjects represent the high risk groups except for the lung cancer among ever smokers.

improve cutoffs or their discrimination ability, since recent work has shown that performances of DXA-measured body fat measures for predicting cancer incidence differed little from those of the anthropometric measures considered in this paper^{43,44}. Likewise, the performance of Wt/Ht is close to that of BMI despite the fact that Wt/Ht was more strongly associated with DXA-measured whole body fat in the National Health and Nutrition Examination Survey (NHANES) 1999–2004 adult sample regardless of age, sex, and race/ethnicity.⁸

Several limitations should be kept in mind in interpreting the present findings. First, the anthropometric measures are not true measures of body fat per se or its distribution. Second, the number of cutoffs on a continuous scale is limited to only one, yielding two groups of high- and low-risk subjects. It might be possible to improve discrimination ability and provide a more accurate grouping in terms of within-group outcome homogeneity if one could develop methods for determining an optimal number of cutoffs. Third, the findings may not be generalizable to other populations with different premenopausal age ranges, to males, or to those in other countries. To this end, replication of the findings analyzing other cohort data is needed. Fourth, the results may have been influenced by unmeasured or inadequately controlled potential confounders specific to each cancer. For example, neither time outdoors nor sun protection by clothing was measured, and these variables may confound the association between obesity and melanoma. Finally, identification and examination of other potential effect modifiers than the HT use may also prove fruitful.

In conclusion, obesity is a risk factor for several cancers in postmenopausal women, and the obesity–cancer association is stronger in HT never users, in whom obesity has greater discrimination ability than for HT ever users. Although all the discrimination abilities are very modest, the developed anthropometric cutoffs might serve as indicators for more careful monitoring of body weight, especially among HT

never users. However, these findings require confirmation in other cohort studies. In sum, the results of this study could serve as a valuable starting point from which to determine adiposity cutoffs for inclusion in risk prediction models for specific cancers.

Acknowledgments

MH, GCK, and TER conceived and designed the study; MH and JL acquired the data and conducted statistical analysis; MH, GCK, HDS, and TER analyzed and interpreted data; MH drafted the manuscript; MH had primary responsibility for the final content. All authors read, provided critical revisions to, and approved the final manuscript. The present study was in part supported by the Einstein-Montefiore Institute for Clinical and Translational Research Center (Clinical and Translational Science Award UL1 RR025750). The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

The authors acknowledge the following WHI Investigators:

Program office. National Heart, Lung, and Blood Institute, Bethesda, Maryland: Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, Nancy Geller.

Clinical coordinating center. Fred Hutchinson Cancer Research Center, Seattle, WA: Garnet Anderson, Ross Prentice, Andrea LaCroix, Charles Kooperberg, Barbara Cochrane, Julie Hunt, Marian Neuhouser, Lesley Tinker, Susan Heckbert, Alex Reiner.

Regional centers. Brigham and Women's Hospital, Harvard Medical School, Boston, MA: JoAnn E. Manson,

Kathryn M. Rexrode, Brian Walsh, J. Michael Gaziano, Maria Bueche; MedStar Health Research Institute/Howard University, Washington, DC: Barbara V. Howard, Lucile Adams-Campbell, Lawrence Lessin, Cheryl Iglesia, Brian Walitt, Amy Park; The Ohio State University, Columbus, OH: Rebecca Jackson, Randall Harris, Electra Paskett, W. Jerry Mysiw, Michael Blumenfeld; Stanford Prevention Research Center, Stanford, CA: Marcia L. Stefanick, Mark A. Hlatky, Manisha Desai, Jean Tang, Stacy T. Sims; University of Arizona, Tucson/Phoenix, AZ: Cynthia A. Thomson, Tamsen Bassford, Cheryl Ritenbaugh, Zhao Chen, Marcia Ko; University at Buffalo, Buffalo, NY: Jean Wactawski-Wende, Maurizio Trevisan, Ellen Smit, Amy Millen, Michael LaMonte; University of Florida, Gainesville/Jacksonville, FL: Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson; University of Iowa, Iowa City/Davenport, IA: Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar, Jennifer Robinson; University of Pittsburgh, Pittsburgh, PA: Lewis Kuller, Jane Cauley, N. Carole Milas; University of Tennessee Health Science Center, Memphis, TN: Karen C. Johnson, Suzanne Satterfield, Rongling Li, Stephanie Connelly, Fran Tylavsky; and Wake Forest University School of Medicine, Winston-Salem, NC: Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker, Michelle Naughton.

Women's Health Initiative Memory Study. Wake Forest University School of Medicine, Winston-Salem, NC: Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker, Michelle Naughton.

Former principal investigators and project officers. Albert Einstein College of Medicine, Bronx, NY: Sylvia Wassertheil-Smolter, Baylor College of Medicine, Houston, TX: Haleh Sangi-Haghpeykar, Aleksandar Rajkovic, Jennifer Hays, John Foreyt; Brown University, Providence, RI: Charles B. Eaton, Annlouise R. Assaf; Emory University, Atlanta, GA: Lawrence S. Phillips, Nelson Watts, Sally McNagny, Dallas Hall; Fred Hutchinson Cancer Research Center, Seattle, WA: Shirley A.A. Beresford, Maureen Henderson; George Washington University, Washington, DC: Lisa Martin, Judith Hsia, Valery Miller; Harbor-UCLA Research and Education Institute, Torrance, CA: Rowan Chlebowski, Kaiser Permanente Center for Health Research, Portland, OR: Erin LeBlanc, Yvonne Michael, Evelyn Whitlock, Cheryl Ritenbaugh, Barbara Valanis; Kaiser Permanente Division of Research, Oakland, CA: Bette Caan, Robert Hiatt; National Cancer Institute, Bethesda, MD: Carolyn Clifford¹; Medical College of Wisconsin, Milwaukee, WI: Jane Morley Kotchen, National Heart, Lung, and Blood Institute, Bethesda, Maryland: Linda Pottern; Northwestern University, Chicago/Evanston, IL: Linda Van Horn, Philip Greenland; Rush University Medical Center, Chicago, IL: Lynda Powell, William Elliott, Henry Black; State University of New York at Stony Brook, Stony Brook, NY: Dorothy Lane, Iris Granek; University at Buffalo, Buffalo, NY: Maurizio Trevisan; University of Alabama at Birmingham, Birmingham, AL: Cora E. Lewis, Albert Oberman; University of Arizona, Tucson/Phoenix, AZ: Tamsen Bassford, Cheryl Ritenbaugh, Tom Moon; University of California at Davis, Sacramento, CA: John Robbins; University of California at Irvine, CA: F. Allan Hubbell, Frank Meyskens, Jr.; University of California at Los Angeles, CA: Lauren Nathan, Howard Judd (deceased); University of Ca-

ifornia at San Diego, LaJolla/Chula Vista, CA: Robert D. Langer; University of Cincinnati, Cincinnati, OH: Michael Thomas, Margery Gass, James Liu; University of Hawaii, Honolulu, HI: J. David Curb¹; University of Massachusetts/Fallon Clinic, Worcester, MA: Judith Ockene; University of Medicine and Dentistry of New Jersey, Newark, NJ: Norman Lasser; University of Miami, Miami, FL: Mary Jo O'Sullivan, Marianna Baum; University of Minnesota, Minneapolis, MN: Karen L. Margolis, Richard Grimm; University of Nevada, Reno, NV: Robert Brunner, Sandra Daugherty (deceased); University of North Carolina, Chapel Hill, NC: Gerardo Heiss, Barbara Hulka, David Sheps; University of Tennessee Health Science Center, Memphis, TN: Karen Johnson, William Applegate; University of Texas Health Science Center, San Antonio, TX: Robert Brzyski, Robert Schenken; University of Wisconsin, Madison, WI: Gloria E. Sarto, Catherine Allen (deceased); Wake Forest University School of Medicine, Winston-Salem, NC: Mara Vitolins, Denise Bonds, Electra Paskett, Greg Burke; Wayne State University School of Medicine/Karmanos Cancer Institute, Detroit, MI: Michael S. Simon, Susan Hendrix.

Author Disclosure Statement

No competing financial interests exist.

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