Racial Differences in Measures of Obesity and Risk of Colon Adenoma

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Obesity is an established risk factor for several malignancies. However, the specific measurement of obesity most relevant to colon neoplasia is still debated, and evidence has suggested gender and racial differences in this measurement. In this study, we sought to compare which measurement—BMI, waist circumference (WC), waist-to-hip ratio (WHR) or waist-to-height ratio (WHtR)—is most strongly associated with development of colon adenomas, a precursor of colon cancer, and to investigate differences in this association between racial groups. We confirmed the strong association between WHR, as a measure of central obesity, and development of colon neoplasia. In our overall analysis, patients in the highest WHR quartile showed a substantial increase in risk of colon adenomas compared to patients in the lowest WHR quartile (odds ratio (OR) = 1.82, 95% confidence interval (CI): 1.12–2.71, $P_{\text{trend}} = 0.0017$). In stratified analyses, we noted that strongly associated obesity measures in European Americans were WC (OR = 2.38, 95% CI = 1.45–3.92, $P_{\text{trend}} = 0.0004$) and BMI (OR = 2.18, 95% CI = 1.37–3.49, $P_{\text{trend}} = 0.0015$), whereas in African Americans, WHR was the strongest and the only obesity measure statistically significantly associated with adenoma risk (OR = 2.12, 95% CI = 1.05–4.30, $P_{\text{trend}} = 0.025$). Our data highlight the importance of obesity in the development of early colon neoplasia and suggest substantial racial differences in the measures of obesity most strongly associated with risk of colon adenomas.

Obesity (2012) **20**, 673–677. doi:10.1038/oby.2011.295

INTRODUCTION

Obesity, central obesity in particular, has consistently been associated with numerous types of malignancies, including colon cancer and adenomas (1–7). A large meta-analysis suggested that individuals with the largest waist circumference (WC) have a 45% increased risk of colorectal cancer compared to those at the lowest level of central obesity (2). They also noted an increase in risk of colorectal cancer of 7% with every 2 kg/m² increase in BMI (2).

A number of biological mechanisms are thought to underlie the link between obesity with cancer. These include insulin resistance and hyper-insulinemia, chronic inflammation associated with obesity, and increased steroid hormone production from adipose tissue (reviewed in ref. 8). The increasing incidence of obesity in the United States and elsewhere makes it pressing to understand the role of obesity in the pathogenesis of cancer in order to develop interventions to disrupt obesity-related carcinogenesis.

While percent fat mass via full body scans is considered the gold standard to assess obesity, it is common practice in epidemiological and clinical research to use proxies such as WC, BMI, or waist-to-hip ratio (WHR). However, which of these

measures is most relevant to carcinogenesis is not clear. Waist-to-height ratio (WHtR) has recently been proposed to be a better measure to capture central obesity, and has been shown to be the best predictor of cardiovascular events as well as mortality in large population-based cohort studies (6). However, the predictive value of WHtR on cancer and cancer-related endpoints has not been studied.

Previous studies have demonstrated differences in the association of obesity measures by gender. It is well documented that the BMI-colon cancer risk association is stronger in men than in women (1,2). More recently, several large cohort studies have shown that WHR or WC is equally strongly associated with risk of colon cancer in both men and women (7,9). Other studies of body size and risk of colorectal cancer suggested that the strength of the association between obesity and colorectal cancer risk varied by which measure of obesity was used, as well as by sex (4,5).

Furthermore, while it is well known that there exist ethnic differences in the incidence of cancer as well as the prevalence of obesity, no study has investigated if there are differences in the measure of obesity most predictive of cancer-related outcomes by racial group. A vast majority of studies on obesity and

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Received 3 May 2011; accepted 23 August 2011; published online 13 October 2011. doi:10.1038/oby.2011.295

cancer utilize European or predominantly European-American samples, limiting our understanding of these measures in relation to outcome in other racial groups and restricting our successful utilization of these measurements in practice. In order to fully understand the role of obesity in cancer development in different populations, it is critical that the most relevant measure of obesity is utilized in the specific populations under study. Given the paucity of data in minority racial groups, more studies on the role of obesity and cancer in these populations, as well as studies to identify which measure of obesity is most important, are necessary.

In this study, we aim to expand our understanding of the relationship between obesity and colon neoplasia, in particular in African Americans. Here, we present comprehensive analyses that investigate the associations of various measures of obesity, including WHR, BMI, WC, and WHtR, with colon adenomas, a well established precursor to colon cancer, and we further examine racial differences in the effect of these measures.

METHODS AND PROCEDURES

Study population

The study population used here was described earlier (10). We recruited 1,591 outpatients scheduled for an elective routine colonoscopy at University Hospitals Case Medical Center. Patients were ineligible for study participation if they had a prior colorectal adenoma diagnosis, or had previously been diagnosed with inflammatory bowel disease. Of eligible patients, ~65% agreed to participate. The participants were not statistically significantly different from those patients who declined to participate with regards to age, gender, and/or race. Pathology reports were obtained after colonoscopy and patients with histologically confirmed colon adenomas were classified as cases and all others were classified as controls. Patients with rectal adenomas only were excluded as obesity seems to be more strongly correlated with colon cancer compared to rectal cancer (4). All patients provided written informed consent. This study was approved by the University Hospitals Case Medical Center Institutional Review Board.

Data collection and obesity measures

All participants were surveyed over the phone for potential colorectal cancer risk factors prior to their colonoscopy as described in detail earlier (10). In brief, patients were surveyed for demographic information (including race), lifestyle factors (such as smoking and alcohol consumption), medical history, and family history of cancer. In addition, all patients completed the Arizona Food Frequency and Physical Activity Questionnaires (<http://www.azcc.arizona.edu/research/shared-services/bmss/questionnaires>) for overall dietary and physical activity assessment, and were asked to report on the year prior to recruitment. Self-reported race was classified as African American, European American, or Other. Subject weight (in pounds) and height (in feet and inches) were obtained on a leveled platform scale by a trained nurse just prior to their colonoscopy. WC (in inches) was measured at the narrowest part of the torso to the nearest ¼ inch. In markedly obese subjects where it was difficult to observe waist narrowing, we accepted the smallest horizontal circumference between the ribs and the iliac crest as the correct measurement. Hip circumference (in inches) was measured to the nearest ¼ inch at the level of the greatest lateral extension of the hips, using the greater trochanter as an anatomic landmark. BMI was calculated as weight, converted to kilograms, divided by height (in meters) squared. WHR was calculated as their waist measurement divided by their hip measurement and WHtR was calculated as their waist measurement divided by their height.

Statistical analyses

Quartiles of BMI, WHR, and WHtR were defined by the quartile distribution in the control patients. Univariate differences in each variable between cases and controls were assessed via a *t*-test (for continuous variables such as age, BMI, WHR, and WHtR) or a χ^2 test (for categorical variables such as gender and race) in the entire sample. For continuous variables, a pooled *t*-test was used unless there was evidence for differences in variances between the cases and controls, in which case the Satterthwaite *t*-tests was used. Adjusted multivariate associations of BMI, WHR, and WHtR with colon adenomas were assessed via a logistic regression adjusting for age, gender, and race. To further control for potential confounding, we performed logistic regression additionally adjusting for family history of colorectal cancer (first or second degree relative with colorectal cancer), average daily physical activity (in metabolic equivalents, as calculated from physical activity questionnaire), and total caloric intake (as derived from food frequency questionnaire). The statistical significance of interactions between race or gender and each obesity measure was assessed by adding a multiplicative term of race or gender and obesity into the logistic regression. Further logistic regressions were performed on each obesity measure adjusting for age and gender when stratified by race. For the stratified analyses, due to small numbers, those reporting a race other than European Americans or African Americans were excluded. All statistical analyses were completed using SAS 9.2 and *P* values <0.05 were considered statistically significant.

RESULTS

Of the 1,591 patients, 402 were diagnosed with colon adenomas at the time of their colonoscopy. We excluded 32 patients with rectal adenomas alone, leaving 1,559 patients in the final analyses. On average, these adenoma cases were older, more likely to be male and more likely to be African American (Table 1). By any measure (BMI, WC, WHR, or WHtR), cases were more obese than controls (Table 1). Interestingly, when stratified by race, WHR was the most statistically significant measure of obesity associated with colon adenomas among the African Americans whereas BMI, WC, and WHtR were highly statistically significantly associated obesity measure in European Americans and WHR was not (Table 1). Interaction analyses showed a borderline statistically significant interaction between race and BMI ($P_{\text{int}} = 0.063$). There was no evidence for potential interactions with WHR ($P_{\text{int}} = 0.18$), WC ($P_{\text{int}} = 0.41$), and WHtR ($P_{\text{int}} = 0.12$).

Quartile analysis (Table 2) suggests an 82% increase in risk of colon adenomas (95% confidence interval (CI) = 23–171%) among patients in the highest quartile of WHR, compared with those in the lowest quartile ($P_{\text{trend}} = 0.0007$), a similar association of WC with adenomas (odds ratio (OR) = 1.70, 91% CI = 1.17–2.46), and a weaker, but still statistically significant, association with BMI, with an OR of 1.47 for the highest quartile of BMI (95% CI = 1.04–2.07, $P_{\text{trend}} = 0.020$). WHtR was not statistically significantly associated with development of colon adenomas in the entire sample.

Among European Americans, WC showed evidence of the strongest effect on risk of colon adenomas (for the highest quartile vs. lowest quartile: OR = 2.38, 95% CI = 1.45–3.92), although BMI showed almost as large of an effect on risk of colon adenomas (for the highest quartile vs. lowest quartile: OR = 2.18, 95% CI = 1.37–3.49). In contrast, among African Americans, the only measure with evidence of association is

Table 1 Descriptive statistics on study population

	Cases (N = 402)	Controls (N = 1,157)	<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c	<i>P</i> ^d
Gender			<0.0001	—	—	—
Male	203 (46.8%)	392 (33.9%)				
Female	231 (53.2%)	765 (66.1%)				
Race			0.025	—	—	—
African American	188 (43.4)	416 (36.0)				
European American	234 (54.0)	709 (61.4)				
Other	11 (2.5)	30 (2.6)				
Age (years), mean (s.d.)	57.5 (9.2)	54.6 (8.8)	<0.0001	—	—	—
Waist circumference (WC), inches, mean (s.d.)	40.0 (7.0)	38.4 (6.7)	<0.0001	0.017	0.0043	0.33
Waist-to-hip ratio (WHR), mean (s.d.)	0.94 (0.093)	0.91 (0.091)	<0.0001	0.0022	0.10	0.0096
Waist-to-height ratio (WHtR), mean (s.d.)	0.60 (0.11)	0.58 (0.10)	0.0021	0.0096	0.0029	0.18
BMI (kg/m ²), mean (s.d.)	30.2 (7.2)	29.3 (6.9)	0.018	0.035	0.0029	0.61

^a*P* value for univariate differences between cases and controls. ^b*P* value from logistic regression model accounting for age, gender, and race. ^c*P* value from logistic regression model accounting for age and gender in self-reporting European Americans. ^d*P* value from logistic regression model accounting for age and gender in self-reporting African Americans.

Table 2 Odds ratios from logistic regression for colon adenomas by race

	Entire population			European Americans			African Americans		
	N (cases/ controls)	OR (95% CI)	<i>P</i> ^a	N (cases/ controls)	OR (95% CI)	<i>P</i> ^a	N (cases/ controls)	OR (95% CI)	<i>P</i> ^a <i>P</i> _{int} ^b
WC, quartiles			0.012			0.0004			0.75 0.41
1	58/288	1.0 (referent)		35/220	1.0 (referent)		19/58	1.0 (referent)	
2	105/288	1.54 (1.06–2.23)		55/193	1.64 (1.01–2.65)		46/86	1.60 (0.84–3.05)	
3	111/288	1.55 (1.07–2.26)		62/162	2.08 (1.28–3.37)		49/119	1.29 (0.68–2.42)	
4	128/288	1.70 (1.17–2.46)		62/133	2.38 (1.45–3.92)		64/152	1.34 (0.73–2.46)	
WHR, quartiles			0.0007			0.015			0.025 0.18
1	62/287	1.0 (referent)		48/216	1.0 (referent)		13/61	1.0 (referent)	
2	69/288	1.04 (0.71–1.54)		39/185	0.93 (0.58–1.49)		29/97	1.45 (0.69–3.06)	
3	112/288	1.45 (0.99–2.13)		54/166	1.26 (0.76–2.09)		54/115	2.01 (0.99–4.06)	
4	159/288	1.82 (1.23–2.71)		73/140	1.85 (1.09–3.15)		82/142	2.12 (1.05–4.30)	
WHtR, quartiles			0.056			0.0074			0.57 0.12
1	83/288	1.0 (referent)		48/228	1.0 (referent)		28/53	1.0 (referent)	
2	77/288	0.81 (0.57–1.17)		48/196	1.02 (0.66–1.61)		28/83	0.66 (0.34–1.26)	
3	129/288	1.37 (0.99–1.91)		72/165	1.80 (1.18–2.76)		57/115	1.11 (0.62–1.98)	
4	113/288	1.20 (0.85–1.69)		46/119	1.56 (0.97–2.50)		65/164	0.97 (0.55–1.72)	
BMI, quartiles			0.020			0.0015			0.64 0.063
1	75/289	1.0 (referent)		43/230	1.0 (referent)		26/53	1.0 (referent)	
2	94/289	1.11 (0.78–1.58)		57/184	1.51 (0.97–2.37)		36/93	0.80 (0.43–1.60)	
3	114/290	1.33 (0.94–1.87)		63/178	1.70 (1.09–2.64)		50/106	1.03 (0.57–1.87)	
4	120/289	1.47 (1.04–2.07)		52/117	2.18 (1.37–3.49)		66/166	1.02 (0.58–1.81)	

^aOdds ratios (OR), 95% confidence interval (CI) and *P* for trend of quartile in logistic regression adjusting for age and gender (and race, in entire population). ^b*P* value of interaction of race and measurement (as continuous variable) in logistic regression also adjusting for age, gender and race.

Table 3 Odds ratios from logistic regression for colon adenomas by gender

	Entire population			Females			Males			
	<i>N</i> (cases/ controls)	OR (95% CI)	<i>P</i> ^a	<i>N</i> (cases/ controls)	OR (95% CI)	<i>P</i> ^a	<i>N</i> (cases/ controls)	OR (95% CI)	<i>P</i> ^a	<i>P</i> _{int} ^b
WC, quartiles			0.012			0.14			0.017	0.99
1	58/288	1.0 (referent)		46/243	1.0 (referent)		12/45	1.0 (referent)		
2	105/288	1.54 (1.06–2.23)		54/180	1.50 (0.96–2.35)		51/108	1.93 (0.93–4.02)		
3	111/288	1.55 (1.07–2.26)		56/160	1.69 (1.07–2.66)		55/128	1.77 (0.86–3.65)		
4	128/288	1.70 (1.17–2.46)		54/179	1.41 (0.88–2.25)		74/109	2.57 (1.26–5.26)		
WHR, quartiles			0.0007			0.0059			0.029	0.96
1	62/287	1.0 (referent)		59/273	1.0 (referent)		3/14	1.0 (referent)		
2	69/288	1.04 (0.71–1.54)		50/237	0.99 (0.65–1.51)		19/51	1.76 (0.44–7.07)		
3	112/288	1.45 (0.99–2.13)		59/149	1.68 (1.09–2.60)		53/139	1.80 (0.48–6.73)		
4	159/288	1.82 (1.23–2.71)		42/103	1.72 (1.05–2.80)		117/185	2.60 (0.70–9.61)		
WHtR, quartiles			0.056			0.24			0.076	0.75
1	83/288	1.0 (referent)		42/195	1.0 (referent)		41/93	1.0 (referent)		
2	77/288	0.81 (0.57–1.17)		35/165	0.92 (0.56–1.53)		42/123	0.74 (0.44–1.24)		
3	129/288	1.37 (0.99–1.91)		67/184	1.48 (0.94–2.33)		62/104	1.30 (0.79–2.14)		
4	113/288	1.20 (0.85–1.69)		66/218	1.18 (0.74–1.88)		47/70	1.33 (0.78–2.28)		
BMI, quartiles			0.020			0.37			0.0060	0.24
1	75/289	1.0 (referent)		45/203	1.0 (referent)		30/86	1.0 (referent)		
2	94/289	1.11 (0.78–1.58)		46/175	1.09 (0.69–1.74)		48/114	1.19 (0.69–2.05)		
3	114/290	1.33 (0.94–1.87)		54/175	1.23 (0.78–1.95)		60/115	1.54 (0.91–2.62)		
4	120/289	1.47 (1.04–2.07)		66/212	1.23 (0.78–1.94)		77/54	2.02 (1.16–3.52)		

^aOdds ratios (OR), 95% confidence interval (CI) and *P* for trend of quartile in logistic regression adjusting for age and race (and gender, in entire population). ^b*P* value of interaction of race and measurement (as continuous variable) in logistic regression also adjusting for age gender and race.

WHR, with more than double the risk of adenomas for patients with the highest quartile of WHR, compared to those in the lowest quartile (OR = 2.12, 95% CI = 1.05–4.30).

Gender stratified analyses suggest that WHR is the strongest, and only statistically significant, measure associated with colon adenomas in women (OR = 1.72, 95% CI:1.05–2.80) (Table 3). Among men, WHR (OR = 2.60, 95% CI:0.70–9.61) and WC (OR = 2.57, 95% CI:1.26–5.26) showed the strongest effects, although BMI was most statistically significant among males (OR = 2.02, 95% CI = 1.16–3.52, *P*_{trend} = 0.006) (Table 3).

We assessed the association of these measures of obesity by adjusting for age, gender, and race, as we suspect these covariates may influence the association of obesity with carcinogenesis. Further adjustment for additional covariates, potentially associated with adenoma risk, including family history of colorectal cancer, total caloric intake, and average physical activity did not substantially alter the associations and conclusions observed here. In our sample, neither family history, total caloric intake, nor average daily physical activity was statistically significantly associated with colon adenomas (*P* > 0.4). Total caloric intake and average daily physical activity did not differ between African Americans and whites (*P* > 0.5), and family history was only borderline statistically significantly different by race (*P* = 0.045).

DISCUSSION

Here we present further evidence for a strong association between obesity and colon adenomas, adding support for a significant role of obesity in early colon carcinogenesis. We also provide new evidence that the most relevant measure of obesity may differ among racial groups. BMI is a measure of overall obesity, whereas WC, WHR, or WHtR account for the circumference of the waist and thus better capture central adiposity. We found that BMI is only predictive of colon neoplasia risk in males, whereas WHR is associated with risk of colon adenomas in both men and women. These results are in line with other studies of colon cancer (4,5). Interestingly, our data show that while WHR is fairly equally predictive of colon adenoma risk in both European and African Americans, BMI is only predictive of risk among European Americans, but not among African Americans. This suggests that assessment of central obesity, rather than overall obesity, may be most relevant in assessing risk of colon neoplasia in African Americans compared to European Americans. Evidence suggests racial differences in fat distribution, specifically, when compared to European Americans, African Americans has relatively more subcutaneous fat in their trunk and back, and less subcutaneous fat in their extremities and front of their bodies (reviewed

in ref. 11), and the difference in BMI-risk association observed here may be reflective of racial differences in body composition and fat mass distribution given a specific BMI, although future studies will need to be done to better understand this.

Our data suggest a strong effect of obesity on the development of colon adenomas, which is at least as strong as the previously reported associations of obesity with colon cancer (6,7). This suggests that the effect of obesity on colon cancer is important early in the carcinogenesis process.

A major strength of this study is the prospective design and recruitment of patients undergoing screening colonoscopy, that is, all anthropometric measures, as well as data on other risk factors, were obtained prior to the pathological diagnosis of colon adenomas. Furthermore, the measurement of height, weight, waist, and hip by a trained nurse minimizes biases and underreporting by patients, which may differ by race or gender, as well as increases measurement consistency. A limitation of this study is the use of self-reported race. However, we believe that while patients may classify themselves into a racial category based more on cultural factors than biological factors, we would not expect any differential reporting by case/control status and thus this would only tend to bias the results toward the null. A further limitation is the modest and reduced sample size available for the subset analysis, which might have limited our ability to detect smaller associations, especially among African Americans. However, the OR we observed in this subgroup, specifically for the highest quartiles of WHtR and BMI were quite close to 1 (Table 2) and thus not suggestive of the lack of association due only to small sample size.

The data presented here highlight the importance of considering population ethnicity background and potentially utilizing multiple measures of obesity when investigating the role of obesity in cancer, although these must be interpreted with caution due to the fact that the *P* values for interaction of race with the individual measurements were not statistically significant. Since a vast majority of the research in the obesity and cancer-related outcomes has been done in European or predominantly European-American populations, our understanding of the relationship of obesity to carcinogenesis in minority populations is less developed. Our results suggest that obesity is an important factor for colon adenoma risk in both African American and European-American populations.

However, not surprisingly, since the distribution of subcutaneous fat in individuals of different racial groups differs, our data suggest the necessity of utilizing different measures in different populations to characterize the increased risk of adenoma associated with obesity. Further work is warranted to confirm our observations and to assess the relevance of various obesity measures on cancer and cancer-related outcomes in other ethnic populations.

ACKNOWLEDGMENTS

We would like to thank Jeffrey Negrey, Kassandra Auker, Anuprit Kaur, Salma Shaikhouni, Laurie Logan, RN, Laura Veri, RN, Wendy Brock, RN and Beth Bednarchik, RN for their help in the recruitment and data collection for this study. This work was supported by the National Cancer Institute (grant numbers U54 CA116867 to NAB, K07 CA136758 to CLT, K22 CA120545 and R01 CA136726 to LL) and the Case Comprehensive Cancer Center (P30 CA043703).

DISCLOSURE

The authors declared no conflict of interest.

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