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Metabolic obesity phenotypes and risk of colorectal cancer in postmenopausal women

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Abstract

Obesity has been postulated to increase the risk of colorectal cancer by mechanisms involving insulin resistance and the metabolic syndrome. We examined the associations of body mass index (BMI), waist circumference, the metabolic syndrome, metabolic obesity phenotypes and homeostasis model-insulin resistance (HOMA-IR—a marker of insulin resistance) with risk of colorectal cancer.
colorectal cancer in over 21,000 women in the Women’s Health Initiative CVD Biomarkers subcohort. Women were cross-classified by BMI (18.5–<25.0, 25.0–<30.0 and ≥30.0 kg/m²) and presence of the metabolic syndrome into 6 phenotypes: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight (MHOW), metabolically unhealthy overweight (MUOW), metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO). Neither BMI nor presence of the metabolic syndrome was associated with risk of colorectal cancer, whereas waist circumference showed a robust positive association. Relative to the MHNW phenotype, the MUNW phenotype was associated with increased risk, whereas no other phenotype showed an association. Furthermore, HOMA-IR was not associated with increased risk. Overall, our results do not support a direct role of metabolic dysregulation in the development of colorectal cancer; however, they do suggest that higher waist circumference is a risk factor, possibly reflecting the effects of increased levels of cytokines and hormones in visceral abdominal fat on colorectal carcinogenesis.

**Keywords**

body mass index; waist circumference; metabolic status; HOMA-IR; colorectal cancer risk; postmenopausal women

Obesity is associated with increased risk of colorectal cancer.\textsuperscript{1–6} Both higher levels of body mass index (BMI, kg/m²) and other measures of adiposity, such as waist circumference, are risk factors for the disease,\textsuperscript{1–6} although both obesity measures show weaker associations in women compared to men.\textsuperscript{5,6} Insulin resistance and hyperinsulinemia are frequently present in obese individuals and have been posited to play a role in colorectal cancer.\textsuperscript{7} In this regard, relatively high circulating insulin and glucose levels have been associated with increased colorectal cancer risk.\textsuperscript{8–10} Insulin resistance is one component of the metabolic syndrome, which includes hyperlipidemia and hypertension as well.\textsuperscript{11} In an analysis conducted in a subcohort of the Women’s Health Initiative,\textsuperscript{12} presence of the metabolic syndrome was associated with increased risk of colorectal cancer in postmenopausal women (HR 2.15, 95% CI 1.30–3.53) and colon cancer (HR 2.28, 95% CI 1.31–3.98). A meta-analysis\textsuperscript{13} reported that presence of the metabolic syndrome was associated with increased risk colorectal cancer in both men and women.

To date, few studies have examined the association of metabolically defined body size phenotypes with risk of colorectal cancer.\textsuperscript{14,15} In a nested case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC),\textsuperscript{14} compared to normal weight individuals without hyperinsulinemia (indicated by C-peptide level), both normal weight individuals (BMI < 25 kg/m²) and overweight individuals (BMI ≥25.0 kg/m²) with hyperinsulinemia were at increased risk of colorectal cancer. In contrast, among those without hyperinsulinemia, overweight individuals were not at increased risk compared to normal weight individuals. Generally similar results were seen when waist circumference was used to assess adiposity instead of BMI. In an analysis restricted to normal weight women in the Women’s Health Initiative,\textsuperscript{15} metabolically unhealthy normal weight women were at increased risk of colorectal cancer compared to metabolically healthy normal weight women.
Here we examine the association of 6 obesity phenotypes, defined at baseline by combinations of body weight and metabolic health, as well as homeostasis model assessment-insulin resistance (HOMA-IR), a marker of insulin resistance, with risk of colorectal cancer in the CVD biomarkers cohort of 24,210 participants in the Women’s Health Initiative study.

**Methods**

The Women’s Health Initiative is a large, multicenter study designed to improve our understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component (CT, \( n = 68,132 \)) and an observational study component (OS, \( n = 93,676 \)).\(^{16}\) The CT component included four randomized controlled intervention studies: hormone therapy (two trials), low-fat dietary modification and calcium + vitamin D supplementation. Women between the ages of 50 and 79 and representing the major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998. Details of the study design and reliability of the baseline measures have been published.\(^{16,17}\)

**The CVD biomarkers subsample**

Individuals who had baseline measurements of fasting serum glucose and insulin and other clinical parameters that were made in various sub-studies within WHI were assembled into the CVD biomarkers subsample (\( n = 25,446 \)). Some sub-studies entailed selecting a random sample; others selected participants based on specific age and ethnicity/race criteria within the hormone therapy trials; another sub-study was a nested case–control study within the hormone therapy trials with random sampling of controls (Fig. 1).

**Follow-up and ascertainment of outcomes**

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed or telephone questionnaires. Self-reports of malignancy were verified by central review of medical records and pathology reports by trained physician adjudicators.\(^{18}\)

**Covariates**

At study entry, self-administered questionnaires were used to collect information on demographics, medical and reproductive history, family history of cancer, and lifestyle factors, including smoking history, alcohol consumption, dietary habits, and recreational physical activity. All participants had their weight, height, waist and hip circumference measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Waist circumference was measured with a tape measure at the narrowest part of the torso between the participant’s ribs and iliac crest. Hip circumference was measured at the site of maximum extension of the buttocks. BMI was computed as weight in kilograms divided by the square of height in meters. Two blood pressure measurements were obtained ≥30 sec apart, and the average of the 2 measurements was used in the analysis. Questions about physical activity at baseline referred to a woman’s usual pattern of activity, including walking and recreational physical activity. A variable “current
Assays for glucose, HDL-C and triglycerides

Blood was obtained after at least 8 hr of fasting for 99.8% of participants in the subsample. The specimens were centrifuged, and serum and plasma were frozen at −70°C and shipped on dry ice to a central processing facility, where they were stored at −80°C. HDL-C was measured in serum using the HDLC Plus 3rd Generation Direct Method (Roche) on the Roche Modular P Chemistry Analyzer. Triglycerides were measured in serum using Triglyceride GB reagent (Roche) on the Roche Modular P Chemistry Analyzer. In the vast majority of women \( n = 22,314, \) 88%), glucose was measured in serum using the Glucoquant Glucose/hexokinase reagent (Roche Diagnostics, Indianapolis, IN 46250) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation); in the remainder, serum glucose was determined by the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, IN). Insulin was determined using the Sandwich Immunoassay (Roche Diagnostics) on Roche Elecsys 2010 Analyzer.

Definition of the metabolic syndrome

We used the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition of the metabolic syndrome: having ≥3 of the 5 following criteria: waist circumference ≥88 cm, triglycerides ≥150 mg/dl, HDL-C <50 mg/dl, glucose ≥100 mg/dl and systolic/diastolic blood pressure ≥130/85 mmHg or treatment for hypertension. To assess the relative contributions of adiposity and metabolic factors to the risk of colorectal cancer, we also examined the metabolic obesity phenotypes using an alternative definition which excluded waist circumference from the ATP III definition (presence of the metabolic syndrome defined as ≥2 of the 4 remaining components). Furthermore, because the metabolic syndrome is a constellation of heterogeneous factors, we additionally computed homeostasis model assessment-insulin resistance (HOMA-IR), a measure of insulin resistance, using the formula \((\text{fasting glucose (mg/dl) \times fasting insulin (mg/dl)/405})\).

Exclusions

For the purposes of the present analysis, baseline BMI and components of the metabolic syndrome were available for 23,900 (99%) of the 24,210 women in the subsample. We excluded women with diabetes reported at baseline \((n = 2,346, 9.7\%)\), women with BMI <18.5 \((n = 310, 1.3\%)\), women missing waist circumference measurements \((n = 59, 0.2\%)\) and women with a history of colorectal cancer \((n = 387, 1.6\%)\). Women with diabetes reported at enrollment were excluded for two reasons: (i) our focus is on the influence of the metabolic syndrome, which is a precursor of diabetes and (ii) treatment of diabetes may influence the clinical factors (i.e., components of the metabolic syndrome). After exclusions (some of which were overlapping), 21,170 women were available for analysis (88% of women with information on the metabolic syndrome and BMI), among whom, as of September 30, 2016, 474 incident invasive colorectal cancer cases had been ascertained. Of these, 397 were classified as colon cancer, 47 as rectal cancer and 5 as both colon and rectal cancer. For 25 cases, information on subsite was not available. We compared the distribution
of sociodemographic and lifestyle variables in excluded women to the distribution in the study population. Most factors, including age, BMI, WC, smoking, caloric intake, education and hormone therapy did not differ between excluded and included subjects. However, alcohol intake, physical activity and the proportion of whites were lower in the excluded subjects.

**Statistical analysis**

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the associations of interest. The outcome was time to diagnosis of colorectal cancer. Participants who had not developed the disease by the end of follow-up, who had died or who withdrew from the study before the end of follow-up were censored. Cases contributed person-time to the study from their date of enrollment until the date of diagnosis, and noncases (participants who were censored) contributed person-time from their date of enrollment until the date of withdrawal from the study, the date of death, or the end of follow-up (September 30, 2016), whichever came first. We examined both age-adjusted and fully-adjusted models, which included colorectal cancer risk factors as well as other potential confounding variables. As the results differed little, we present the fully adjusted results. We also adjusted for red meat intake; however, this made no difference, and meat was not included in the final model.

We examined the association of categories of BMI (18.5– <25.0, normal weight; 25.0–<30.0, overweight; ≥30.0 kg/m\(^2\), obese) and waist circumference (<83.0, 83.0–<95.0 and ≥95.0 cm) and of presence of the metabolic syndrome, separately and with mutual adjustment, with risk of colorectal cancer. We then estimated risk after cross-classifying women by categories of BMI and presence of the metabolic syndrome simultaneously, yielding six groups: metabolically healthy/normal weight (MHNW); metabolically unhealthy/normal weight (MUNW); metabolically healthy/overweight (MHOW); metabolically unhealthy/overweight (MUOW); metabolically healthy/obese (MHO); metabolically unhealthy/obese (MUO).

Because the metabolic syndrome is a composite, which additionally includes components other than those related to hyperglycemia/hyperinsulinemia (i.e., lipids and hypertension), we also examined the associations of other components of the metabolic syndrome (hypertension, HDL-C and triglycerides) and quartiles of HOMA-IR with risk of colorectal cancer, with and without adjustment for BMI and waist circumference.

Tests for linear trend were performed by assigning the median value to each category, modeling the variable as a continuous variable, and using the Wald test for linear trend ($p < 0.05$).

We conducted four sensitivity analyses: (i) we excluded the first 3 years of follow-up to address the possibility of reverse causation (effects of subclinical cancer on body weight and metabolic status). (ii) Because waist circumference is strongly correlated with BMI, we repeated the analyses after excluding waist circumference from the definition of the metabolic syndrome and defining presence of the syndrome as ≥2 of the four remaining components. (iii) Because participation in the intervention arm of the dietary clinical trials...
could affect the results, we repeated the main analyses excluding women who were in these interventions. (iv) Because the distribution of clinical variables (including glucose and insulin) differed in the 4 studies making up the subcohort, as an alternative to using cutpoints derived from the total study population, we reanalyzed the data for the association of glucose, HLD-C, triglycerides and HOMA-IR, with colorectal cancer using the original cutpoints from each study and “stacking” the different studies.

We tested the proportional hazards assumption using PROC LIFETEST (SAS Institute, Cary, NC). Formal tests for nonproportional hazards and the log–log survival plots did not indicate any marked deviation from the proportional hazards assumption. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). All p values are two-sided.

Results

The metabolic obesity phenotypes showed differences by demographic and behavioral characteristics (Table 1). Within BMI categories, compared to metabolically healthy women, metabolically unhealthy women tended to be older and to have fewer years of education, and were more likely to be white and to be current smokers. Both alcohol intake and MET-hr/week of physical activity showed decreasing trends from MHNW to MUO.

Neither body mass index nor presence of the metabolic syndrome was associated with colorectal cancer risk—in age-adjusted models, when considered separately with adjustment for other covariates, or when mutually adjusted (Table 2). The results were similar in women who had never used hormone therapy (data not shown).

In the age-adjusted model and the model adjusted for covariates other than the metabolic syndrome, waist circumference was positively associated with colorectal cancer risk (HR for highest tertile 1.34, 95% CI 1.04–1.72), whereas the metabolic syndrome was not associated with altered risk (Table 3). When waist circumference and presence of the metabolic syndrome were mutually adjusted, the HR for waist circumference was slightly attenuated, and that for the metabolic syndrome was further weakened. Similar results were seen when the analysis was restricted to never users of hormone therapy (data not shown).

When waist circumference and BMI were entered in the same model with metabolic syndrome, HRs for the 2nd and 3rd tertile of waist circumference were 1.40, 95% CI 1.03–1.89 and 2.29, 95% CI 1.57–3.35, respectively, p for trend <0.0001, and HRs for BMI 25.0–30.0 and for BMI ≥30.0 kg/m² were 0.69, 95% CI 0.51–0.93 and 0.48, 95% CI 0.33–0.70, respectively, p for trend = 0.01. Presence of the metabolic syndrome continued to show no association (data not shown).

Compared to metabolically healthy normal weight women (reference group), only metabolically unhealthy normal weight women had an elevated HR (1.65, 95% CI 0.99–2.74) (Table 4). No other group showed any suggestion of an elevated risk (in spite of the larger numbers compared to the MUNW group). When the first 3 years of follow-up were excluded to address the possibility of reverse causation, the results were similar, although the confidence intervals were wider due to the decreased sample size. When examined individually, with the exception of waist circumference, none of the components of the

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metabolic syndrome (glucose, HDL-C, triglycerides or hypertension) showed any
association with colorectal cancer (data not shown). In the sensitivity analysis excluding
women in the intervention arms of the 2 dietary clinical trials, the association of BMI and
WC with CRC were unchanged, whereas the association of MUNW with CRC was
strengthened (HR 1.83, 95% CI 1.04–3.21).

HOMA-IR, a measure of insulin resistance, showed no association with colorectal cancer;
however, in the same model, waist circumference showed a robust positive association
(Table 5). The pattern of associations was unchanged when the analysis was restricted to
women who had never used hormone therapy (data not shown).

In the analyses restricted to colon cancer, the HR for presence of the metabolic syndrome
was 1.22, 95% CI 0.98–1.52 and the HRs for colon cancer associated with the different
phenotypes, relative to the MHNW phenotype, were MUNW 1.79, 95% CI 1.02–3.12;
MHO 0.87, 95% CI 0.63–1.21; MUOW 1.26, 95% CI 0.87–1.83; MHO 0.93, 95% CI
0.64–1.36; MUO 1.12, 95% CI 0.80–1.56. The association of waist circumference with
colon cancer was strengthened (HR for highest vs. lowest tertile 1.45, 95% CI 1.10–1.91).

In the sensitivity analysis in which waist circumference was not included as a component
of the metabolic syndrome, the HR for MUNW relative to MHNW was attenuated (1.35, 95%
CI 0.91–2.02). None of the other metabolic phenotypes was associated with risk (Supporting
Information, Table). In the sensitivity analysis using the original study-specific cutpoints, the
results were unchanged.

Discussion

In this prospective study of postmenopausal women, BMI was not associated with risk of
colorectal cancer, whereas waist circumference was positively associated with risk. Of 5
metabolic obesity phenotypes, relative to metabolically healthy normal weight women, only
metabolically unhealthy normal weight women showed a borderline increased risk.
Individual components of the metabolic syndrome showed no association. Furthermore,
HOMA-IR was not associated with risk. Overall, our results suggest that that abdominal
adiposity is a robust risk factor for colorectal cancer in women, whereas both presence of the
metabolic syndrome and insulin resistance showed no overall association and only a possible
association in normal weight women.

Two previous studies suggest that metabolically unhealthy normal weight individuals are at
elevated risk of colorectal cancer compared to metabolically healthy normal weight
individuals,14,15 and one of these14 indicated that metabolically unhealthy overweight
individuals were at increased risk compared to metabolically healthy normal weight and to
metabolically healthy overweight individuals. Metabolically healthy overweight individuals
were not at increased risk compared to metabolically healthy normal weight individuals.14

In contrast to the EPIC study,14 our analysis was not limited by comparing normal weight
versus overweight/obese, but included 3 levels of BMI: normal weight, overweight and
obese, thereby permitting us to examine the full range of adiposity. Our results are consistent
with those of Murphy et al.14 regarding MUNW versus MHNW; however, we found little
indication that either the MUOW or MUO phenotypes were at increased risk relative to MHNW women.

Differences between our results and those of Liang et al., which also made use of the CVD biomarkers subcohort of the Women’s Health Initiative, can be explained by the different analytic approaches taken in the two analyses. Liang et al. restricted attention to normal weight women in WHI, whereas we included normal weight, overweight and obese women. Further, Liang et al. excluded women with a history of any cancer (except nonmelanoma skin cancer), whereas we only excluded women with a history of colorectal cancer. On the other hand, we excluded women with a history of diabetes, whereas Liang et al. did not. The number of cases among normal weight women in the two analyses were 114 (Liang et al.) and 134 (this study). Our approach permitted us to examine waist circumference, BMI and HOMA-IR in the total study population (474 cases and 20,696 noncases). Thus, our finding of a positive association of waist circumference with risk is not in conflict with Liang et al.’s finding of no association of waist circumference with risk in normal weight women. As the number of cases among normal weight women is not large (n = 114), it is possible that differences in the selection of subjects and covariates included in the multivariable analyses in the two analyses may account for differences in which factors showed significant associations. For example, Liang et al. reported a positive association of fasting glucose (no/yes) with colorectal cancer: HR 1.70, 95% CI 1.12–2.58. The corresponding HR in our study was 1.48, 95% CI 0.92–2.37. Liang et al. found no association of waist circumference with risk. In our analysis of normal weight women, tertiles of waist circumference were also not significantly associated with risk, due to any differences in the study populations of the two analyses; HOMA-IR was also not associated with risk. HOMA-IR was also not associated with risk; and, of the metabolic phenotypes, the hypothesis that obesity and related metabolic alterations are associated with risk of colorectal cancer has gained widespread support in recent years. A meta-analysis summarizing the evidence from cohort studies indicated that the metabolic syndrome was associated with an elevated risk of colorectal cancer both in men (RR 1.33, 95% CI 1.18–1.50) and in women (RR 1.41, 95% CI 1.18–1.70). The risk associated with dysglycemia was similar to that of the full metabolic syndrome, suggesting that elevated glucose may account for the association with the syndrome. And an analysis of the EPIC cohort showed that the association of the metabolic syndrome with colon cancer was largely accounted for by abdominal obesity and abnormal glucose metabolism, suggesting that excess fat storage and consequent hyperglycemia and hyperinsulinemia are important factors.

Our findings provide little support for the hypothesis that metabolic dysregulation is directly associated with increased risk of colorectal cancer. Presence of the metabolic syndrome showed only a modest and imprecise association with colorectal cancer, and, except for waist circumference, the individual components of metabolic syndrome were not associated with risk. HOMA-IR was also not associated with risk; and, of the metabolic phenotypes,
only metabolically unhealthy normal weight women were at increased risk compared to metabolically healthy normal weight women. However, in view of the small number of colorectal cancer cases in this category, this association could be due to chance. On the other hand, waist circumference was significantly associated with increased risk. Our results suggest that that centrally located adipose tissue may be an important risk factor for colorectal cancer in women. This association could be driven by visceral (or intraabdominal) fat, as visceral fat is metabolically more active than subcutaneous abdominal fat and secretes larger amounts of cytokines and hormones compared to subcutaneous fat.\textsuperscript{24} However, we did not have a direct measure of different abdominal adipose tissue depots.

Strengths of this study include its large sample size, the central adjudication of all colorectal cancer diagnoses, the availability of fasting blood samples on virtually all participants, measurements of all components of the metabolic syndrome, as well as insulin and HOMA-IR, and anthropometric measures. Additionally, we carried out sensitivity analyses, first, excluding the first 3 years of follow-up to address the possibility of reverse causality, second, excluding waist circumference from the definition of the metabolic syndrome, since waist circumference is strongly correlated with BMI, which is used to define the metabolic obesity phenotypes. An additional sensitivity analysis excluded women in the intervention arms of the dietary clinical trials, which did not affect the results. Limitations include the small numbers of cases in the MUNW phenotype group and the lack of information on change in metabolic phenotype and adiposity over time. Also, misclassification of the study factors would likely attenuate the observed associations, whereas misclassification of covariates, such as physical activity, could weaken the correction for confounding. However, the main finding, regarding waist, was robust and was consistent in different analyses. Finally, the Women’s Health Initiative is not a representative sample and, therefore, our results are not generalizable to all postmenopausal women. Nevertheless, analyses within the cohort should have validity.

In conclusion, in this study, waist circumference was positively associated with risk of colorectal cancer, whereas BMI was not. Compared to metabolically healthy normal weight women, only metabolically unhealthy normal weight women had a borderline elevated risk; no other phenotypes showed any indication of increased risk. Overall, presence of the metabolic syndrome showed little association with risk, and HOMA-IR was not associated with risk. Our results provide little support for a direct association of metabolic dysregulation with risk of colorectal cancer. The association of waist circumference with increased risk, may be mediated by the effects of increased production of cytokines and hormones in visceral adipose tissue.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgements

References


What’s new?

Obesity is associated with increased risk of colorectal cancer, as is a high level of insulin in the bloodstream. To tease out the relationship between body weight, metabolic health, and colorectal cancer risk, these authors examined data on six different body profiles. Neither BMI nor metabolic syndrome appeared to impact colorectal cancer risk. Waist circumference, however, significantly boosted the risk, possibly due to the increased cytokines and hormones present in fat that accumulates around the waist.
Figure 1.
Make-up of WHI CVD biomarker sample.
Table 1.
Baseline characteristics by metabolic obesity phenotypes \(^1\) (n = 21,170)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MHNW N=4,612</th>
<th>MUNW N = 563</th>
<th>MHOW N = 5,224</th>
<th>MUOW N=2,456</th>
<th>MHO N=3,419</th>
<th>MUO N=4,941</th>
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<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>64.8 (7.5)</td>
<td>66.8 (6.6)</td>
<td>63.8 (7.4)</td>
<td>65.5 (6.9)</td>
<td>62.3 (7.2)</td>
<td>63.4 (7.0)</td>
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<tr>
<td>BMI (kg/m(^2))</td>
<td>22.7 (1.6)</td>
<td>23.3 (1.4)</td>
<td>27.3 (1.4)</td>
<td>27.9 (1.4)</td>
<td>34.7 (4.9)</td>
<td>35.6 (4.9)</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>75.0 (6.7)</td>
<td>81.0 (10.4)</td>
<td>83.7 (6.7)</td>
<td>90.2 (7.0)</td>
<td>96.5 (11.2)</td>
<td>103.1 (10.4)</td>
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<td>Alcohol intake (drinks/week)</td>
<td>2.7 (5.4)</td>
<td>2.4 (5.1)</td>
<td>2.1 (4.8)</td>
<td>2.0 (4.7)</td>
<td>1.5 (4.5)</td>
<td>1.4 (4.7)</td>
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<td>Pack-years of smoking</td>
<td>8.6 (16.5)</td>
<td>12.3 (21.3)</td>
<td>7.6 (15.7)</td>
<td>10.9 (19.1)</td>
<td>7.6 (15.5)</td>
<td>9.8 (18.7)</td>
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<td>MET (hr/week)</td>
<td>13.9 (15.3)</td>
<td>11.0 (13.0)</td>
<td>11.7 (13.7)</td>
<td>9.2 (11.6)</td>
<td>8.8 (12.3)</td>
<td>7.1 (10.4)</td>
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<tr>
<td>Aspirin intake</td>
<td>0.20 (0.40)</td>
<td>0.26 (0.44)</td>
<td>0.20 (0.40)</td>
<td>0.23 (0.42)</td>
<td>0.16 (0.38)</td>
<td>0.21 (0.41)</td>
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<tr>
<td>Red meat intake (med. serving/day)</td>
<td>0.58 (0.53)</td>
<td>0.62 (0.54)</td>
<td>0.67 (0.62)</td>
<td>0.72 (0.62)</td>
<td>0.84 (0.82)</td>
<td>0.93 (0.83)</td>
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<tr>
<td>Calcium intake (mg/day)</td>
<td>743 (459)</td>
<td>739 (451)</td>
<td>739 (484)</td>
<td>746 (473)</td>
<td>746 (505)</td>
<td>783 (510)</td>
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<td>Folate intake (mcg/day)</td>
<td>247 (120)</td>
<td>240 (121)</td>
<td>247 (128)</td>
<td>244 (125)</td>
<td>254 (139)</td>
<td>255 (145)</td>
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<td>Caloric intake (kcal/day)</td>
<td>1,499 (676)</td>
<td>1,504 (685)</td>
<td>1,569 (796)</td>
<td>1,584 (725)</td>
<td>1,722 (962)</td>
<td>1,775 (948)</td>
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<td>Parity</td>
<td>2.5 (1.7)</td>
<td>2.9 (1.7)</td>
<td>2.7 (1.7)</td>
<td>2.9 (1.7)</td>
<td>2.7 (1.8)</td>
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<td>Proportions</td>
<td></td>
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<td></td>
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<tr>
<td>Education (% postgraduate)</td>
<td>29.3</td>
<td>19.9</td>
<td>27.2</td>
<td>19.4</td>
<td>24.6</td>
<td>18.4</td>
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<tr>
<td>Ethnicity (% white)</td>
<td>56.4</td>
<td>65.7</td>
<td>44.8</td>
<td>56.3</td>
<td>32.4</td>
<td>50.1</td>
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<tr>
<td>% current smokers</td>
<td>12.1</td>
<td>16.6</td>
<td>7.4</td>
<td>12.0</td>
<td>6.1</td>
<td>8.5</td>
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<tr>
<td>Oral contraceptives (% ever used)</td>
<td>37.0</td>
<td>32.8</td>
<td>38.1</td>
<td>34.3</td>
<td>38.2</td>
<td>37.4</td>
</tr>
<tr>
<td>Hormone therapy (% ever used)</td>
<td>43.5</td>
<td>40.3</td>
<td>43.3</td>
<td>39.8</td>
<td>40.7</td>
<td>35.1</td>
</tr>
<tr>
<td>Family history of colorectal cancer (% yes)</td>
<td>15.5</td>
<td>15.2</td>
<td>15.4</td>
<td>16.4</td>
<td>16.7</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

\(^1\) Phenotypes based on definition of metabolic syndrome based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), which includes waist circumference.
Table 2.
Separate and mutually adjusted associations of body mass index and presence of the metabolic syndrome with colorectal cancer, Women’s Health Initiative CVD biomarkers subcohort

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Cases</th>
<th>Noncases</th>
<th>HR¹</th>
<th>95% CI</th>
<th>HR²</th>
<th>95% CI</th>
<th>HR³</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–&lt;25.0</td>
<td>131</td>
<td>5,033</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>25.0–&lt;30.0</td>
<td>163</td>
<td>7,504</td>
<td>0.85</td>
<td>0.68–1.07</td>
<td>0.84</td>
<td>0.65–1.09</td>
<td>0.81</td>
<td>0.63–1.06</td>
</tr>
<tr>
<td>≥30.0</td>
<td>180</td>
<td>8,159</td>
<td>0.94</td>
<td>0.75–1.18</td>
<td>0.86</td>
<td>0.66–1.12</td>
<td>0.81</td>
<td>0.61–1.06</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td>0.76</td>
<td></td>
<td>0.33</td>
<td></td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

| MetS       |        |          |     |        |     |        |     |        |
| No         | 230    | 10,758   | 1.19| 0.99–1.44 | 1.16| 0.95–1.41 | 1.19| 0.97–1.47 |
| Yes        | 244    | 9,938    |     |        |     |        |     |        |

¹ Age-adjusted HR.
² HRs for waist circumference and MetS are from separate models, adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week—continuous), physical activity (MET-hr/week), aspirin intake, dietary calcium intake, dietary folate intake, caloric intake, oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of colorectal cancer in first-degree relative (no, yes), education (less than high school grad, high school grad/some college, college grad, postcollege), ethnicity (white, black, other) and allocation to the OS or specific arm of clinical trials.

³ In addition to the above covariates, waist circumference and MetS are mutually adjusted.
Table 3.
Separate and mutually adjusted associations of waist circumference and presence of the metabolic syndrome with colorectal cancer, Women’s Health Initiative CVD biomarkers subcohort

<table>
<thead>
<tr>
<th>Waist circumference (cm)</th>
<th>Cases (n = 474)</th>
<th>Noncases (n = 20,028)</th>
<th>HR(^1)</th>
<th>95% CI</th>
<th>HR(^2)</th>
<th>95% CI</th>
<th>HR(^3)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;83.0</td>
<td>154</td>
<td>7,369</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>83.0–&lt;95.0</td>
<td>151</td>
<td>7,038</td>
<td>1.04</td>
<td>0.83–1.30</td>
<td>1.02</td>
<td>0.79–1.31</td>
<td>1.00</td>
<td>0.77–1.29</td>
</tr>
<tr>
<td>≥95.0</td>
<td>171</td>
<td>6,407</td>
<td>1.39</td>
<td>1.12–1.73</td>
<td>1.34</td>
<td>1.04–1.72</td>
<td>1.29</td>
<td>0.99–1.68</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td>0.003</td>
<td>0.05</td>
<td></td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>MetS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>230</td>
<td>10,758</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>Yes</td>
<td>244</td>
<td>9,938</td>
<td>1.09</td>
<td>0.90–1.31</td>
<td>1.16</td>
<td>0.95–1.41</td>
<td>1.09</td>
<td>0.88–1.35</td>
</tr>
</tbody>
</table>

\(^1\)Age-adjusted HR.

\(^2\)HRs for waist circumference and MetS are from separate models, adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week—continuous), physical activity (MET-hr/week), aspirin intake, dietary calcium intake, dietary folate intake, caloric intake, oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of colorectal cancer in first-degree relative (no, yes), education (less than high school grad, high school grad/some college, college grad, postcollege), ethnicity (white, black, other) and allocation to the OS or specific arm of clinical trials.

\(^3\)In addition to the above covariates, waist circumference and MetS are mutually adjusted.
Table 4.
Metabolic obesity phenotypes defined by presence of the metabolic syndrome\(^1\) and body mass index in relation to risk of colorectal cancer, in the Women’s Health Initiative CVD biomarkers subcohort.

<table>
<thead>
<tr>
<th>Metabolic phenotypes</th>
<th>N cases</th>
<th>N noncases</th>
<th>HR(^2)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population (n cases 474; n noncases 20,696)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHNW</td>
<td>111</td>
<td>4,491</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>MUNW</td>
<td>20</td>
<td>542</td>
<td>1.65</td>
<td>0.99–2.74</td>
</tr>
<tr>
<td>MHOW</td>
<td>99</td>
<td>5,116</td>
<td>0.80</td>
<td>0.59–1.08</td>
</tr>
<tr>
<td>MUOW</td>
<td>64</td>
<td>2,388</td>
<td>1.11</td>
<td>0.79–1.57</td>
</tr>
<tr>
<td>MHO</td>
<td>70</td>
<td>3,338</td>
<td>0.85</td>
<td>0.60–1.20</td>
</tr>
<tr>
<td>MUO</td>
<td>110</td>
<td>4,821</td>
<td>0.97</td>
<td>0.72–1.32</td>
</tr>
<tr>
<td><strong>First 3 years of follow-up excluded (n cases 378; n noncases 20,280)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHNW</td>
<td>91</td>
<td>4,404</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>MUNW</td>
<td>16</td>
<td>518</td>
<td>1.63</td>
<td>0.92–2.89</td>
</tr>
<tr>
<td>MHOW</td>
<td>80</td>
<td>5,042</td>
<td>0.79</td>
<td>0.56–1.10</td>
</tr>
<tr>
<td>MUOW</td>
<td>51</td>
<td>2,324</td>
<td>1.11</td>
<td>0.76–1.63</td>
</tr>
<tr>
<td>MHO</td>
<td>55</td>
<td>3,281</td>
<td>0.85</td>
<td>0.57–1.25</td>
</tr>
<tr>
<td>MUO</td>
<td>85</td>
<td>4,711</td>
<td>0.94</td>
<td>0.67–1.33</td>
</tr>
</tbody>
</table>

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

\(^1\) Definition includes waist circumference.

\(^2\) Adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week – continuous), physical activity (MET-hrs/wk), aspirin intake, dietary calcium intake, dietary folate intake, caloric intake, oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of colorectal cancer in first-degree relative (no, yes), education (less than high school grad, high school grad/some college, college grad, post-college), ethnicity (white, black, other), allocation to the OS or specific arm of clinical trials.
### Table 5.
Association of quartiles of HOMA-IR and anthropometric measures with colorectal cancer, Women’s Health Initiative CVD biomarkers subcohort

<table>
<thead>
<tr>
<th></th>
<th>(N) cases</th>
<th>(N) noncases</th>
<th>(HR)^1</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMA-IR</strong>(^2,3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>125</td>
<td>5,517</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>5,436</td>
<td>1.02</td>
<td>0.77–1.34</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>5,192</td>
<td>0.84</td>
<td>0.62–1.14</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>3,992</td>
<td>0.88</td>
<td>0.63–1.24</td>
</tr>
<tr>
<td>(p) trend</td>
<td></td>
<td></td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td><strong>Waist circumference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC &lt;83.0 cm</td>
<td>145</td>
<td>7,121</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>WC 83.0–&lt;95.0 cm</td>
<td>143</td>
<td>6,805</td>
<td>1.09</td>
<td>0.84–1.40</td>
</tr>
<tr>
<td>WC &gt;95.0 cm</td>
<td>167</td>
<td>6,211</td>
<td>1.52</td>
<td>1.15–2.01</td>
</tr>
<tr>
<td>(p) trend</td>
<td></td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

^1 Adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week - continuous), physical activity (MET-hr/week), aspirin intake, dietary calcium intake, dietary folate intake, caloric intake, oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of colorectal cancer in first-degree relative (no, yes), education (less than high school grad, high school grad/some college, college grad, postcollege), ethnicity (white, black, other), allocation to the OS or specific arm of clinical trials and mutually adjusted (HOMA-IR and WC).

^2 Quartiles: <7.3, 7.3–<11.4, 11.4–<18.7, ≥18.7.

^3 Twenty-one cases and 682 noncases missing HOMA-IR measurement.