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A Longitudinal Study of the Metabolic Syndrome and Risk of Colorectal Cancer in Postmenopausal Women

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Abstract

The metabolic syndrome is associated with increased risk of diabetes and coronary heart disease. Although higher BMI and other related factors have been frequently associated with colorectal cancer (CRC), whether the metabolic syndrome is associated with the risk of colorectal cancer is unclear. We therefore assessed the association of the metabolic syndrome with the risk of CRC in a subsample of participants of the Women's Health Initiative who had repeated measurements of the components of the syndrome at baseline and during follow-up. Women with diabetes at baseline enrollment were excluded. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) at baseline and in time-dependent analyses. Among 4,862 eligible women, 81 incident cases of colorectal cancer were identified over a median follow-up of 12 years. Presence of the metabolic syndrome at baseline was associated with increased risk of colorectal cancer (HR 2.15, 95% CI 1.30-3.53) and colon cancer (HR 2.28, 95% CI 1.31-3.98). These associations were largely explained by positive associations of serum glucose and systolic blood pressure with both outcomes. Time-dependent covariate analyses supported the baseline findings. Our results suggest that the positive association of the metabolic syndrome with risk of colorectal cancer is largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.

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Keywords

Metabolic syndrome; diabetes; insulin resistance; hyperinsulinemia; hypertension; lipids; obesity; abdominal adiposity; colorectal cancer; postmenopausal women; time-dependent covariates

Introduction

Obesity, visceral adiposity, and physical inactivity show consistent positive associations with risk of colorectal cancer (Huxley *et al.*, 2009; Moghaddam *et al.*, 2007; Ning *et al.*, 2010). These factors are the major modifiable determinants of insulin resistance, hyperinsulinemia, hyperglycemia, and the metabolic syndrome, (Giovannucci, 1995; Giovannucci, 2007; McKeown-Eyssen, 1994) a cluster of anthropometric and clinical factors (elevated abdominal adiposity, blood glucose, triglycerides, and blood pressure, and low levels of HDL-cholesterol). The metabolic syndrome has been demonstrated to predict risk of developing type 2 diabetes and cardiovascular disease (Ford *et al.*, 2002; Meigs, 2003). In the United States, both obesity and the metabolic syndrome have increased in prevalence in recent years, and it is estimated that currently, 50 million Americans have the metabolic syndrome (Alexander *et al.*, 2003; Sathyaprakash & Henry, 2002).

Hyperinsulinemia and hyperglycemia result from a dysregulation of the balance between insulin secretion and insulin action and are precursors of type-2 diabetes. Insulin has long been regarded as a possible mediator of the effects of obesity and physical activity on colorectal cancer risk (Giovannucci, 1995; McKeown-Eyssen, 1994). Insulin is a regulator of energy metabolism and a potent mitogenic agent (Bruce & Corpet, 1996). High insulin levels may increase the risk of colorectal cancer by stimulating cell proliferation and/or inhibiting apoptosis (Bjork *et al.*, 1993; Koenuma *et al.*, 1989; Wu *et al.*, 1995). In addition, insulin can increase the bioactivity of insulin-like growth factor-1 (IGF-1) by inhibiting the production of IGF-binding proteins (Werner & LeRoith, 1996). High glucose levels, in theory, could additionally increase the risk of postmenopausal colorectal cancer by exacerbating insulin resistance (Marshall *et al.*, 1991) and conferring a selective growth advantage to malignant cells (Dang & Semenza, 1999; Warburg, 1956).

To date, a number of studies have examined the association of the metabolic syndrome with risk of colorectal cancer (Ahmed *et al.*, 2006; Bowers *et al.*, 2006; Colangelo *et al.*, 2002; Inoue *et al.*, 2009; Jaggers *et al.*, 2009; Pelucchi *et al.*, 2010; Stocks *et al.*, 2010; Stocks *et al.*, 2008; Sturmer *et al.*, 2006; Trevisan *et al.*, 2001). These studies differed in their definition of the syndrome and the cut-off values for the individual components, and for the most part have used only baseline measurements to assess the metabolic syndrome. One study (Sturmer *et al.*, 2006) used repeated questionnaire data to assess the metabolic syndrome, and another (Stocks *et al.*, 2010) used repeated measurements on a subset of participants to correct measurements of all subjects for random measurement error. Because a single measurement is subject to considerable random error due to imprecision in measurement and short-term and long-term intra-individual variation (Stocks *et al.*, 2010), use of repeated measurements may improve the characterization of an individual's habitual levels.

We therefore evaluated the association of the metabolic syndrome with risk of postmenopausal colorectal cancer in a subsample of women in the Women's Health Initiative who had repeated measurements of the components of the syndrome during follow-up, thereby permitting assessment of the association longitudinally.

Materials and Methods

Study Subjects

The Women's Health Initiative is a large, multicenter, prospective study of factors affecting the health of postmenopausal women. It includes an observational study (OS, n = 93,676) and three clinical trials (CT, n= 68,132) of hormone therapy, dietary modification, and calcium plus vitamin D supplementation (The Women's Health Initiative Study Group, 1998). Women were recruited at 40 clinical centers throughout the United States, largely via direct mailings, and were eligible to participate if they were postmenopausal, aged 50 to 79, likely to reside in their current residence for at least 3 years, and had provided written informed consent. Enrollment took place from October 1, 1993 to December 31, 1998.

The present analysis is based on a 6% random sample of women in the CT (N = 4,544) and a 1% sample of women in the OS (N = 1,062). All WHI participants had provided a fasting blood sample at baseline. Women in the 6% subsample additionally provided fasting blood samples at years 1, 3, and 6 of follow-up, and women in the 1% sample of women in the OS additionally provided fasting blood samples in year 3 (Howard *et al.*, 2004). Blood samples were analyzed for glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) (Howard *et al.*, 2004). In addition, waist circumference, and systolic and diastolic blood pressure were measured by study staff using a standardized protocol at clinical visits. The 6% random sample was stratified by age, clinical center, and hysterectomy status, with oversampling of minority groups to increase the numbers of Black, Hispanic, and Asian-Pacific women.

Case Ascertainment—In the CT cancer outcomes were ascertained through self-administered questionnaires completed every 6 months, and then confirmed by a centralized review of pathology reports, discharge summaries, operative and radiology reports, and tumor registry abstracts. In the OS, outcomes were ascertained annually, and confirmed by the same procedures. After the end of CT period (2005), outcomes in all women were identified on an annual basis by mailed questionnaires.

Median follow-up was 11.9 years (range: 0.05 to 15.4).

Laboratory Methods—Fasting blood samples were collected with minimal stasis and maintained at 4° C until plasma/serum was separated. Plasma/serum aliquots were then frozen at −80° C and sent on dry ice to the central repository (Fisher Bioservices), where storage at −80° C was maintained. Glucose was measured using the hexokinase method on the Hitachi 747 analyzer (Boehringer Mannheim Diagnostics) (Bergmeyer, 1974; Peterson & Young, 1968). An ongoing monthly quality assurance program was maintained with the Diabetes Diagnostic Laboratory at the University of Missouri. Monthly interassay coefficients of variation (CV) were <2% for mean concentrations of 84 and 301 mg/dL.

Total cholesterol and triglycerides were analyzed by enzymatic methods on the Hitachi 747 analyzer (Steiner *et al.*, 1981). HDL-C was isolated using heparin manganese chloride (Warnick & Albers, 1978). CVs for total cholesterol, triglycerides, and HDL-C were all ≤2%.

Anthropometric Measures and Blood Pressure—Waist circumference at the natural waist or narrowest part of the torso was measured to the nearest 0.1 cm. On each visit, two blood pressure measurements were obtained ≥30 seconds apart, and the average of the two measurements was used in the analysis. Values for waist circumference and blood pressure in the years corresponding to the blood analytes were used in the analysis.

Definition of the Metabolic Syndrome—We used the definition of the metabolic syndrome proposed by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (Grundy *et al.*, 2005; National Heart, Lung, and Blood Institute, 2002). An indicator variable was created for the presence of the metabolic syndrome (yes/no), defined as having ≥3 of the following characteristics: waist circumference >88 cm, fasting glucose ≥100 mg/dL, fasting HDL-C <50 mg/dL, fasting triglycerides ≥150 mg/dL, and blood pressure ≥130/85 mmHg.

Exclusion of Women with Diabetes—Women who reported taking diabetes medication at baseline or having a baseline fasting serum glucose of ≥126 mg/dL were excluded from the analysis (8 cases and 554 non-cases). However, the results were essentially unchanged when women with diabetes were included in the analysis.

After exclusion of women with diabetes and those missing measurements of components of the metabolic syndrome, 81 colorectal cancer cases and 4,821 non-cases were available for analysis. Of the 81 cases, 65 were in the colon, 6 in the rectosigmoid junction, and 10 in the rectum.

Statistical Analysis—Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between presence of the metabolic syndrome and its components and risk of colorectal cancer, with duration of follow-up (days) as the time scale. For these analyses, study participants were considered to be at risk from their date of enrollment until the date of diagnosis of colorectal cancer, termination of follow-up (March 31, 2011), loss to follow-up, withdrawal from the study, or death, whichever occurred first. Event times of participants who had not developed colorectal cancer by the end of follow-up, who had died, or who withdrew from the study before the end of follow-up, were censored.

In the first stage of the analysis, we estimated the risk of colorectal cancer in association with presence of the metabolic syndrome or its individual components at baseline. As indicated above, presence of the metabolic syndrome was defined as having ≥3 of the individual components and this category was compared with those subjects having ≤2 of the individual components. In addition, the individual components of the metabolic syndrome were divided into three categories, using the ATP III cutoffs for the highest category (lowest for HDL-C), and the median for the remainder of the distribution. Tests for trend were

obtained by assigning the median value to each category and modeling this variable as a continuous variable. We also examined the association of “degree of metabolic syndrome” with risk, using each individual’s score, ranging from 0 (reference group) to 5 and obtained by summing scores (1 = present, 0 = absent) for each of the individual components.

We compared the results of a model with age and ethnicity as covariates and a fuller multivariable model. Variables were included in the latter if their addition to the model changed the parameter estimate of the study factors by >10%. Variables included in the final model were: age (continuous), ethnicity (white, black, other), body mass index (kg/m^2 - continuous), alcohol intake (drinks per week - continuous), physical activity (MET-hrs/wk - continuous), family history of colorectal cancer (no, yes), and participation in the OS vs. CT, and treatment arm in each CT. Results of the two models differed little, and we present the fuller multivariable results. All p-values are 2-sided.

We also repeated the main analysis after excluding cases who were diagnosed with colorectal cancer during the first year of follow-up, in order to reduce the possibility that the presence of preclinical disease affected components of the metabolic syndrome.

In the second stage of the analysis, repeated measurements of the components of the metabolic syndrome were analyzed by modeling them as time-dependent covariates in the Cox proportionate hazards model (Gail, 1981). With this approach, we evaluated the predictive value of the average of all measurements and measurements obtained in the intervals 1 to 3 years, 2 to 4 years, and 3 to 5 years prior to diagnosis. In all time-dependent analyses, measurements that were obtained within 1 year of diagnosis were excluded, because these values may have been affected by the presence of subclinical disease.

Results

Cases and non-cases were generally similar in terms of background characteristics. However, compared to non-cases, cases were older (64.4 vs. 62.5 y, respectively), were more likely to be non-Hispanic white, and had lower levels of physical activity [see (Kabat *et al.*, submitted) for comparison of background characteristics].

The presence of the metabolic syndrome at baseline was associated with increased risk of both colorectal cancer and colon cancer: multivariable-adjusted HRs 2.15, 95% CI 1.30-3.53, and 2.28, 95% CI 1.31-3.98, respectively (Table 1). (There were too few rectosigmoid or rectal cancer cases for separate analysis of these subsites). Of the individual components of the metabolic syndrome at baseline, only serum glucose and systolic blood pressure were associated with increased risk. The HR for colorectal cancer among women with a fasting glucose level ≥100 mg/dL, relative to <90, was 1.79, 95% CI 0.99-3.24, p = 0.05, and that for colon cancer was 2.22, 95% CI 1.12-4.42, p for trend 0.02. Elevated systolic blood pressure was associated with increased risk of colorectal colon cancer (HRs 1.82, 95% CI 0.98-3.38, p for trend 0.07), but not colon cancer (HR 1.65, 95% CI 0.86-3.19, for trend 0.12). These associations were unchanged when mutually adjusted. When the number of components of the syndrome was treated as an ordinal variable (relative to the reference group), women with ≥4 components compared with women with 0 components

had a HR for colorectal cancer of 1.65, 95% CI 0.74-3.66, p for trend 0.06 and for colon cancer of 2.05, 95% CI 0.83-5.07, p for trend 0.03.

When cases diagnosed within the first year of follow-up were excluded (17 colorectal cancer cases and 13 colon cancer cases), the HRs for the association of the metabolic syndrome (yes, no) with colorectal and colon cancer were: 2.07, 95% CI 1.18-3.63 and 2.25, 95% CI 1.21-4.19, respectively.

In time-dependent covariates analyses, presence of the metabolic syndrome was associated with increased risk of colorectal and colon cancer (Table 2). Hazard ratios were statistically significant for colorectal cancer for the period 2-4 years prior to diagnosis and were elevated for other time periods. When the averages of all measurements of each component were considered, none of the components showed a significant association, although there was a borderline significant trend for average serum glucose with colorectal and colon cancer (p = 0.11 and 0.09, respectively) (data not shown).

Discussion

Our results suggest that presence of the metabolic syndrome in non-diabetic postmenopausal women is associated with increased risk of colorectal cancer. The majority of the cases included in the study were in the colon, and there were insufficient rectosigmoid or rectal cancer cases to allow separate analyses in these subgroups. The association was largely accounted for by elevated serum glucose and elevated systolic blood pressure, which made independent contributions to risk, whereas waist circumference, serum triglycerides, serum HDL-C, and diastolic blood pressure were not associated with risk. Time dependent analyses were supportive of results of the baseline analysis.

Previous studies that have examined the association of the metabolic syndrome with risk of colorectal cancer (Ahmed *et al.*, 2006; Bowers *et al.*, 2006; Colangelo *et al.*, 2002; Inoue *et al.*, 2009; Jaggers *et al.*, 2009; Pelucchi *et al.*, 2010; Stocks *et al.*, 2010; Stocks *et al.*, 2008; Sturmer *et al.*, 2006; Trevisan *et al.*, 2001) have reported conflicting results. A number of them reported a positive association of the metabolic syndrome with risk of colorectal cancer (Jaggers *et al.*, 2009; Pelucchi *et al.*, 2010; Stocks *et al.*, 2010); whereas others did not. Most studies have found associations with only one or two components of the metabolic syndrome with colorectal cancer risk. The most common associations were for serum glucose (Ahmed *et al.*, 2006; Colangelo *et al.*, 2002; Trevisan *et al.*, 2001) and obesity (Bowers *et al.*, 2006; Stocks *et al.*, 2010; Sturmer *et al.*, 2006).

In addition to studies that examined the association of the metabolic syndrome per se with risk of colorectal cancer (Ahmed *et al.*, 2006; Bowers *et al.*, 2006; Colangelo *et al.*, 2002; Inoue *et al.*, 2009; Jaggers *et al.*, 2009; Pelucchi *et al.*, 2010; Stocks *et al.*, 2010; Stocks *et al.*, 2008; Sturmer *et al.*, 2006; Trevisan *et al.*, 2001), other studies have focused on the association of individual components of the syndrome with risk of colorectal cancer, some of which have received more study than others. Increased central adiposity (as measured by waist circumference and/or waist-hip-ratio) has been associated with increased risk of colorectal cancer in most cohort studies and meta-analyses (Larsson & Wolk, 2007;

Moghaddam *et al.*, 2007; Ning *et al.*, 2010; Oxentenko *et al.*, 2010; Park *et al.*, 2011; Schoen *et al.*, 1999; Wang *et al.*, 2008). Findings regarding dyslipidemia, including total cholesterol (Jarvinen *et al.*, 2001; Schatzkin *et al.*, 1988; Tornberg *et al.*, 1986) and triglycerides (Tsushima *et al.*, 2005; van Duijnhoven *et al.*, 2011) have been inconsistent or null. Few studies have examined HDL cholesterol in relation to colorectal cancer risk, but a recent study showed an inverse association (van Duijnhoven *et al.*, 2011). In several studies, hypertension has been linked to higher colorectal cancer risk (Ahmed *et al.*, 2006; Palmqvist *et al.*, 2003; Stocks *et al.*, 2008), but no association was found in other studies (Bowers *et al.*, 2006; Sturmer *et al.*, 2006). Of 5 studies that examined insulin levels (Gunter *et al.*, 2008; Limburg *et al.*, 2006; Schoen *et al.*, 1999; Tsushima *et al.*, 2005; van Duijnhoven *et al.*, 2011), only one reported evidence of a positive association (Schoen *et al.*, 1999) after adjustment for covariates. Of eight studies that examined blood glucose levels in relation to colorectal cancer risk (Gunter *et al.*, 2008; Jee *et al.*, 2005; Limburg *et al.*, 2006; Nilsen & Vatten, 2001; Schoen *et al.*, 1999; Trevisan *et al.*, 2001; Tsushima *et al.*, 2005; Yamada *et al.*, 1998), one found a weak positive association (with in situ carcinoma) (Yamada *et al.*, 1998), two reported significant positive associations with colorectal cancer (Schoen *et al.*, 1999; Trevisan *et al.*, 2001), two reported a significant association in one sex but not in the other (Jee *et al.*, 2005; Nilsen & Vatten, 2001), and three studies found no association (Gunter *et al.*, 2008; Limburg *et al.*, 2006; Tsushima *et al.*, 2005).

The literature on the metabolic syndrome and colorectal cancer suffers from the difficulty of teasing apart a large number of highly correlated behavioral (elevated BMI, abdominal adiposity, low physical activity, and an energy-rich diet) and metabolic factors (diabetes, hyperinsulinemia, hyperglycemia, hypertrigyceridemia, high blood pressure, and dyslipidemia). In the present study, the HRs for the full multivariable model presented in Table 1 did not differ from those adjusted for age and ethnicity, indicating that our results were not confounded by such factors as BMI or physical activity. Furthermore, the associations of baseline glucose level and systolic blood pressure were unchanged when mutually adjusted, suggesting that they make independent contributions to risk. Other components of the metabolic syndrome, including waist circumference, serum HDL-cholesterol, serum triglycerides, and diastolic blood pressure showed no association with colorectal cancer. In an earlier analysis of the associations of insulin and glucose levels in this dataset (Kabat *et al.*, submitted), we reported the positive association of glucose with colorectal cancer, whereas insulin levels showed no association with risk. Most previous studies examining the metabolic syndrome in relation to colorectal cancer risk included subjects with diabetes (Ahmed *et al.*, 2006; Pelucchi *et al.*, 2010; Stocks *et al.*, 2008; Sturmer *et al.*, 2006; Trevisan *et al.*, 2001), whereas we excluded women with confirmed diabetes at baseline. However, their inclusion in alternative analyses did not alter the results.

Our results and those of a number of other studies suggest that the association of the metabolic syndrome with colorectal cancer may be driven by several of the individual rather than by the syndrome per se. Furthermore, it is unclear what mechanism underlies the associations of specific components with risk, such as serum glucose and obesity. Our results regarding glucose are consistent with those of a number of other studies (Ahmed *et al.*, 2006; Colangelo *et al.*, 2002; Schoen *et al.*, 1999; Stocks *et al.*, 2008; Trevisan *et al.*,

2001) and suggest that hyperglycemia and resulting hyperinsulinemia in particular may play a causative role in colorectal carcinogenesis.

The present study benefited from the availability of clinical measurement data collected at baseline and at scheduled intervals throughout follow-up on a subset of the Women's Health Initiative cohort. Additional strengths include the centralized adjudication of colorectal cancer, the high degree of completeness of follow-up, and the availability of information on risk factors for colorectal cancer. Moreover, we excluded diabetics from the analysis, because we were interested in whether insulin resistance is associated with increased risk of colorectal cancer.

The major limitation of this study is the small number of cases which limited our ability to assess the metabolic syndrome in subgroups (particularly rectal cancer) and among women who were not in any intervention group in the clinical trial. Nevertheless, the observed associations of serum glucose and systolic blood pressure with risk of colon and colorectal cancer appeared to be robust and to be unaffected when treatment arm of the clinical trials and other potential confounding variables were included in the Cox models. Regarding the time-dependent covariates analysis, except for the average of measurements of the individual components, the number of cases was reduced by approximately 50%, and for this reason, the analyses should be considered exploratory. Nevertheless, presence of the metabolic syndrome per se at various intervals preceding diagnosis was associated with increased risk.

In summary, we found a positive association of the metabolic syndrome with risk of colorectal and colon cancer, which was largely accounted for by serum glucose levels and systolic blood pressure. The biological mechanism underlying these associations remains to be clarified.

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Table 1

Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of presence at baseline of the metabolic syndrome, and of individual components of the metabolic syndrome, with risk of colorectal and colon cancer in the Women's Health Initiative

Variables	**$N_{CRC\ cases}$**	**Colorectal Cancer (N = 81) MV-adjusted* HR (95% CI)**	**Colon Cancer (N = 65) MV-adjusted* HR (95% CI)**
Metabolic syndrome			
No	45	1.00 (ref.)	1.00 (ref.)
Yes	35	2.15 (1.30-3.53)	2.28 (1.31-3.98)
No. of components:			
0	17	1.00 (ref.)	1.00 (ref.)
1	16	0.63 (0.31-1.26)	0.71 (0.31-1.61)
2	12	0.57 (0.26-1.26)	0.79 (0.33-1.90)
3	18	1.31 (0.62-2.78)	1.68 (0.71-3.96)
4-5	17	1.65 (0.74-3.66)	2.05 (0.83-5.07)
Ptrend		*0.06*	*0.03*
Individual components of the metabolic syndrome			
Waist circumference (cm)			
<79	23	1.00 (ref.)	1.00 (ref.)
79 –<88	23	1.09 (0.59-2.03)	1.05 (0.52-2.10)
≥88	34	1.08 (0.50-2.34)	1.01 (0.43-2.37)
P_{trend}		*0.84*	*0.99*
Continuous (per cm)		1.00 (0.97-1.04)	1.00 (0.97-1.03)
Ptrend		*0.81*	*0.94*
Glucose (mg/dL)			
<90	22	1.00 (ref.)	1.00 (ref.)
90-<100	32	1.25 (0.72-2.16)	1.64 (0.86-3.09)
>100	27	1.79 (0.99-3.24)	2.22 (1.12-4.42)
P_{trend}		*0.05*	*0.02*
Continuous (per mg/dL)		1.03 (1.01-1.05)	1.03 (1.01-1.06)
Ptrend		*0.007*	*0.007*
HDL-cholesterol (mg/dL)			

Variables	$N_{CRC\ cases}$	Colorectal Cancer (N = 81) MV-adjusted* HR (95% CI)	Colon Cancer (N = 65) MV-adjusted* HR (95% CI)
>63	33	1.00 (ref.)	1.00 (ref.)
50-<=63	22	0.67 (0.39-1.17)	0.69 (0.37-1.30)
<50	26	1.03 (0.59-1.78)	1.22 (0.67-2.25)
P_{trend}		*0.99*	*0.74*
Continuous (per mg/dL)		1.00 (0.98-1.01)	0.99 (0.97-1.01)
Ptrend		*0.69*	*0.49*
Triglycerides (mg/dL)			
<104		1.00 (ref.)	1.00 (ref.)
104-<150	23	1.01 (0.56-1.85)	0.91 (0.44-1.90)
>150	22	1.33 (0.76-2.32)	1.24 (0.63-2.42)
P_{trend}	36	*0.29*	*0.54*
Continuous		1.00 (1.00-1.00)	0.99 (0.97-1.01)
Ptrend		*0.12*	*0.51*
Systolic blood pressure (mm Hg)			
<118	15	1.00 (ref.)	1.00 (ref.)
118-<130	23	1.59 (0.88-3.09)	1.24 (0.60-2.57)
>130	43	1.82 (0.98-3.38)	1.65 (0.86-3.18)
Ptrend		*0.07*	*0.12*
Continuous (per mm Hg)		1.01 (1.00-1.02)	1.01 (0.99-1.02)
Ptrend		*0.13*	*0.25*
Diastolic blood pressure (mm Hg)			
<74		1.00 (ref.)	1.00 (ref.)
74-<85	32	1.25 (0.77-2.04)	1.20 (0.69-2.06)
>85	36	1.09 (0.57-2.11)	1.12 (0.55-2.31)
P_{trend}	13	*0.61*	*0.64*
Continuous (per mm Hg)		1.00 (0.98-1.03)	1.00 (0.97-1.03)
Ptrend		*0.91*	*0.86*

*Multivariable adjusted HR – adjusted for the following variables: age (continuous), ethnicity (white, black, other), body mass index (continuous), alcohol (servings per week – continuous), family history of colorectal cancer (yes/no), physical activity (METs per week - continuous), participation in the OS or CT, and treatment arm in the clinical trials.

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Table 2

Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of the metabolic syndrome (MS) and its individual components with colorectal cancer in time-dependent covariates analyses in the Women's Health Initiative

Metabolic Syndrome	Colorectal cancer HR (95% CI)*	Colon cancer HR (95% CI)*
1–3 years**	(N_{cases} = 32)	(N_{cases} = 22)
No	1.00 (ref.)	1.00 (ref.)
Yes	2.06 (0.93–4.54)	1.76 (0.66–4.69)
2–4 years**	(N_{cases} = 32)	(N_{cases} = 25)
No	1.00 (ref.)	1.00 (ref.)
Yes	2.68 (1.23–5.83)	2.30 (0.94–5.59)
3–5 years**	(N_{cases} = 35)	(N_{cases} = 29)
No	1.00 (ref.)	1.00 (ref.)
Yes	1.88 (0.89–3.99)	2.02 (0.88–4.64)

*Adjusted for the following variables: age (continuous), ethnicity (white, black, other), body mass index (continuous), alcohol (servings per week – continuous), family history of colorectal cancer (yes/no), physical activity (METs per week - continuous), and participation in the OS vs. CT, and treatment arm in the clinical trials.

**Most recent measurement within the time interval was used to predict presence of the metabolic syndrome.

†Mutually adjusted for all other components of the metabolic syndrome in addition to covariates listed above.