Metabolic phenotype and risk of colorectal cancer in normal-weight postmenopausal women

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Abstract

Background: The prevalence of metabolically unhealthy phenotype in normal-weight adults is 30%, and few studies have explored the association between metabolic phenotype and colorectal cancer incidence in normal-weight individuals. Our aim was to compare the risk of colorectal cancer in normal-weight postmenopausal women who were characterized by either the metabolically healthy phenotype or the metabolically unhealthy phenotype.

Methods: A large prospective cohort, the Women's Health Initiative (WHI), was used. The analytical sample included 5,068 postmenopausal women with BMI 18.5-<25 kg/m^2. Metabolic phenotype was defined using the Adult Treatment Panel-III (ATP-III) definition, excluding waist circumference; therefore, women with one or none of the four components (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) were classified as metabolically healthy. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for the association between metabolic phenotype and risk of colorectal cancer.

Results: Among normal-weight women, those who were metabolically unhealthy had higher risks of colorectal cancer (HR: 1.49, 95% CI: 1.02-2.18) compared to those who were metabolically healthy.

Conclusions: A metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight women.

Impact: Normal-weight women should still be evaluated for metabolic health and appropriate steps taken to reduce their risk of colorectal cancer.

Introduction

According to estimates by the International Agency for Research on Cancer (IARC), in 2012, colorectal cancer accounted for 9.2% of all incident cancers among women in the world, which made it the second most common cancer in women (1). In 2016 in the United States, it is estimated that 63,670 women will be diagnosed with colorectal cancer and 23,170 will die from it (2).

The risk of developing colorectal cancer is associated with genetic, environmental, socio-economic, and lifestyle factors. These include age, sex, race, and family history, as well as modifiable risk factors including smoking, alcohol consumption, diet (intake of high percent calories from fat, low consumption of dietary fiber), physical inactivity and obesity. Of particular interest for the current study, overweight and obesity are already well-established risk factors for colorectal cancer (3, 4). Protective factors include current or past regular use of non-steroidal anti-inflammatory drugs (NSAIDs), and prior screening examinations (5, 6).

Obesity often co-occurs with metabolic disorders, but normal weight with a metabolically unhealthy phenotype has been recognized since the 1980s (7) and yet has been understudied. The definition of metabolic health varies among studies, but most researchers use the Adult Treatment Panel-III (ATP-III), which includes five components: elevated waist circumference, elevated triglyceride, low HDL-C, elevated blood pressure, and elevated glucose (8). The metabolically unhealthy phenotype is defined by two or more of four of these components except for waist circumference, and the

metabolic syndrome is identified by the presence of three or more of five components (9-11). A recent world-wide meta-analysis shows that 30.0% (95% CI: 25.6-35.6%) of normal-weight adults were metabolically unhealthy (12). Using criteria of two or more metabolic abnormalities, Wildman et al. found that 23.5% of normal-weight US adults were metabolically unhealthy (13).

Two meta-analyses of studies that evaluated the association of metabolic syndrome with colorectal cancer found a 30-40% higher risk in both men and women (3, 14). It is unclear whether the higher risk is independent of overweight and obesity, since waist circumference is a component of the metabolic syndrome and is highly correlated with BMI. Few studies have assessed the association between metabolically-defined unhealthy phenotype and risk of colorectal cancer, particularly in normal-weight people.

To build upon and contribute to the evidence relating metabolic phenotype to colorectal cancer risk, we used the rich WHI dataset to compare the risk of colorectal cancer between normal-weight postmenopausal women who were characterized by either metabolically healthy phenotype or metabolically unhealthy phenotype.

Materials and Methods

Population

We used data from the WHI Observational Study (OS) and Clinical Trial (CT), a prospective cohort study enrolled through 40 clinical centers throughout the United States. A total of 161,808 postmenopausal women between 50 and 79 years of age were

recruited from 1993 to 1998. Three CTs (n=68,132) included hormone therapy, dietary modification, and calcium plus vitamin D supplementation. All of the OS and CT women completed screening and enrollment questionnaires by self-report, interview, physical examination, and fasting blood sample collection. Written informed consent and appropriate institutional review board approval were obtained by each participating WHI site.

The WHI dataset includes metabolic biomarker data from several subsets of women. These data were collected prospectively 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) at baseline (15). Stored samples were used in WHI ancillary studies, including the SNP Health Association Resource cohort, and the European American Hormone Trial subcohort to provide additional metabolic biomarker results that were applied in the current analysis. The SNP Health Association Resource cohort includes 12,007 OS and CT participants (8,405 African Americans and 3,602 Hispanics), and the European American Hormone Trial includes 10,306 participants. Blood samples collected at baseline and included in this analysis were analyzed for glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C). In addition, baseline height, weight, waist circumference, and systolic and diastolic blood pressure were measured by study staff using a standardized protocols at clinical visits.

In this study, women were excluded if they had any prior diagnosis of cancer other than non-melanoma skin cancer before the date of the baseline questionnaire administration. Women with missing data on BMI (*n*=164), triglycerides (*n*=8), HDL cholesterol

(*n*=1,599), blood pressure (*n*=187), or fasting glucose (*n*=39) were excluded. As the exposure of interest for this analysis focused on normal-weight women with metabolic phenotype, those who were overweight, obese or underweight (BMI>=25 kg/m^2 or BMI<18.5 kg/m^2) (n=16,612) were excluded. Women with missing covariate data, i.e. age, ethnicity, smoking, alcohol consumption, were also excluded. For those missing data on family history of colorectal cancer, we created an indicator variable and included it in the multivariable model. A flowchart showing derivation of the included study population is presented as Figure 1.

Exposure measurements

We defined the metabolical phenotype using the Adult Treatment Panel-III (ATP-III) metabolic syndrome definition excluding the waist circumference ≥80 cm component due to its significant collinearity with BMI. Women were classified as metabolically healthy if they had less than two of the following four ATP-III components, and women with two or more of the four components were classified as metabolically unhealthy: (1) elevated triglycerides (≥150 mg/dL), (2) low HDL-C (<50 mg/dL or use of medication for reduced HDL-C), (3) elevated blood pressure (systolic/diastolic blood pressure ≥130/85 mmHg or use of antihypertensive medication), and (4) elevated fasting glucose (≥100 mg/dL or use of diabetes medication) (8, 16).

Metabolic syndrome was defined as having 3 or more of 5 components (elevated waist circumference, elevated triglyceride, low HDL-C, elevated blood pressure, and elevated

glucose). Seventeen additional women were excluded because of missing waist circumference.

HOMA-IR is a standard measure of insulin resistance and is defined by a formula that incorporates both insulin and glucose levels [(fasting insulin (mU/L)×fasting glucose (mmol/L))/22.5](17). We used the same method to define HOMA-IR as another WHI study (18), categorized HOMA-IR into quartiles (q1-q4), and used the 75th percentile value as the cut-off point to define metabolic phenotype: metabolically healthy (HOMA-IR–q1q2q3), metabolically unhealthy (HOMA-IR–q4) (19). One hundred and eighty-two additional women were excluded from the models because of missing insulin level.

Outcome measurements

The primary outcome of interest was incident colorectal cancer. In the WHI, incident colorectal cancer was documented and coded for primary site, anatomic subsite, diagnosis date, stage, tumor size, and grade. The diagnosis of colorectal cancer was ascertained through self-administered questionnaires, then confirmed by a centralized review of pathology reports from diagnostic aspirations, biopsies, surgeries, and discharge summaries, and subsequently adjudicated by trained, central adjudicators (20). For the present study, the end of follow-up time was September 30, 2015.

Laboratory methods (21)

Fasting blood samples collected at baseline were maintained at 4°C for up to one hour until plasma or serum was separated from cells. Plasma/serum aliquots were then frozen at -70°C and sent on dry ice to the central repository (Rockville, Maryland, USA), where they were stored at – 80°C. Glucose was measured using the hexokinase method on a Hitachi 747. Monthly inter-assay coefficients of variation were less than 2%. Total cholesterol and triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana, USA). HDL-C was isolated using heparin manganese chloride. Coefficients of variation for total cholesterol, triglycerides, and HDL-C were all 2% or less. Serum insulin was measured in a step-wise sandwich ELISA procedure on an ES 300 (Boehringer Mannheim Diagnostics, Indianapolis, Indiana, USA). An ongoing monthly quality assurance program was maintained with the Diabetes Diagnostic Laboratory at the University of Missouri.

Anthropometric measures and blood pressure (21)

Participants were asked to remove their shoes for anthropomorphic measures. Height (cm) was measured using a wall-mounted stadiometer to the nearest 0.1 cm. Weight (kg) was measured using a balance beam scale to the nearest 0.1 kg. Waist circumference at the natural waist or narrowest part of the torso was measured to the nearest 0.1 cm. Blood pressure was measured twice in the right arm with the participant in the seated position and rested for 5 minutes using a conventional mercury sphygmomanometer and appropriately sized cuffs. Two blood pressure measurements were obtained at least 30s

apart, and the average of the two measurements was used in the analysis.

Statistical Analysis

Characteristics of women with the metabolically healthy phenotype were compared with those of women with the metabolically unhealthy phenotype. Means (± standard deviations) were used to summarize continuous characteristics at baseline, while proportions were used for categorical variables. T-tests were used to compare continuous variables, and Chi-square tests were used to compare the distributions of categorical variables.

Survival time was measured as the date from enrollment to colorectal or colon cancer diagnosis, death or end of follow-up, whichever came first. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios for colorectal and colon cancer incidence. Each model was adjusted for age, and we also ran additional models that included age, race/ethnicity, smoking, alcohol consumption, physical activity, total energy intake, dietary fiber, percent calories from fat, family history of colorectal cancer, NSAIDs use, and treatment arm in each CT. Proportional hazards assumptions were tested based on the Schoenfeld residuals, and no violation was observed.

We also evaluated the associations between each of the four components of metabolic phenotype (elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) and cancer incidence.

Sensitivity analyses were carried out in all models, including (1) metabolic unhealthy phenotype was replaced with metabolic syndrome, (2) using HOMA-IR to define metabolic phenotype, (3) excluding women with diabetes at baseline enrollment, and (4) limiting analysis to non-users of NSAIDs.

Results

Of 5,068 normal-weight women in the analysis, women with metabolically healthy and metabolically unhealthy phenotypes accounted for 66.3% and 33.7%, respectively (Table 1). There were significant differences between the two groups with respect to age, race/ethnicity, smoking status, alcohol intake, total energy intake, and physical activity. Metabolically unhealthy women were older, were more likely to be non-Hispanic white, were more likely to currently smoke, had lower alcohol consumption, total energy intake and dietary fiber, and reported less physical activity. There were 114 cases of colorectal cancer that occurred during mean follow-up time of 14.3 years, and average follow-up time from study entry to diagnosis of colorectal cancer was 5.3 years (0.2-18.0 years).

In both age-adjusted and fully adjusted models, compared with women with metabolically healthy normal weight, metabolically unhealthy normal weight was associated with a higher risk of colorectal cancer. The hazard ratio for colorectal cancer in the fully adjusted model was 1.49 (95% CI: 1.02-2.18) (Table 2).

Among the individual components of metabolic syndrome, elevated fasting glucose was associated with a higher risk of colorectal and colon cancer (HR: 1.71, 95% CI: 1.12-

2.58; HR: 1.68, 95% CI: 1.04-2.71, respectively). Elevated triglycerides, low HDL-C, and elevated blood pressure were not associated with colorectal or colon cancer (Table 3).

A sensitivity analysis showed that when metabolic syndrome was used instead of metabolic phenotype, women with metabolic syndrome had a higher risk for both colorectal and colon cancer than those in the main results (HR: 2.14, 95% CI: 1.38-3.32; HR: 2.42, 95% CI: 1.48-3.95, respectively) (Table S1). When HOMA-IR was used to define metabolic phenotype, the results were similar to the main results. In addition, when women with diabetes (*n*=205) were excluded from the analysis, the results were similar to the main results (Table S2). Among non-users of NSAIDs, metabolically unhealthy women had a higher risk for both colorectal and colon cancer than those in the main results (HR: 1.56, 95% CI: 1.04-2.35; HR: 1.61, 95% CI: 1.01-2.56, respectively) (Table S3).

Discussion

The results of this long-term prospective study of normal-weight postmenopausal women suggest that metabolically unhealthy women have a higher risk of colorectal cancer than metabolically healthy women.

Using WHI data, Gunter et al. found that, compared with metabolically healthy normal weight women, metabolically unhealthy normal weight women were at higher risk of breast cancer (18). We observed a similar positive association for the metabolically

unhealthy normal-weight phenotype and colorectal cancer. With younger participants (around 57 years old on average), a recently published nested case-control study in Europe by Murphy et al. observed that, compared with metabolically healthy normal-weight individuals, a higher colorectal cancer risk was observed among metabolically unhealthy normal-weight participants (OR: 1.59, 95% CI: 1.10-2.28) (22), findings consistent with our study (HR: 1.49, 95% CI: 1.02-2.18), despite the fact that they classified individuals as metabolically healthy or unhealthy based on the C-peptide level, which is not a generally accepted clinical definition. In addition, use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that were associated with reduced risk of colorectal cancer were not included in the Murphy et al study.

Colorectal cancer includes colon cancer, rectosigmoid cancer, and rectal cancer. In our study, the association between metabolic phenotype and risk of colon cancer was not significant. These results are similar with those of Murphy et al. who did not find a statistically significant association between metabolic unhealthy phenotype and risk of colon cancer among normal-weight individuals (OR: 1.49, 95% CI: 0.92-2.43) (22).

Kabat et al. used WHI data to identify 81 incident cases of colorectal cancer among 4862 eligible women with median follow-up of 12 years, and found that among the individual components of metabolic syndrome, only elevated fasting glucose was associated with higher risk of colorectal and colon cancer (23), which is consistent with our findings. In other studies, elevated fasting glucose or diabetes has been repeatedly shown to be associated with the risk of colorectal and colon cancer (24, 25).

The reason why colorectal cancer risk is higher in normal-weight women with metabolic abnormalities is not entirely clear, but mechanistically these results may suggest that the phenotype represents a pro-inflammatory state. In fact, anti-inflammatory medications such as aspirin are among the strongest preventive agents for primary prevention of colorectal cancer (4). The current study shows that the association between metabolic phenotype and colorectal cancer risk was strengthened among non-users of NSAIDs, which indicates that there is some residual confounding after the basic adjustment for NSAIDs use. Additionally, pro-inflammatory and anti-inflammatory cytokine concentrations have been associated with colorectal cancer risk (26, 27). Further, compared with metabolically healthy normal-weight individuals, metabolically unhealthy normal-weight individuals may have less physical activity (28), and consume more saturated fat and less fiber (27); however, physical activity, saturated fat and dietary fiber were included as covariates in this study, and it is unlikely that the differences in these lifestyle factors would account for the observed association between metabolic abnormality and risk of colorectal cancer.

The present results indicate that among normal-weight women, a metabolically unhealthy phenotype is a relevant risk factor for colorectal cancer. Current guidelines recommend commencing colorectal cancer screening based primarily on age. Earlier identification of individuals at higher risk based on obesity or high-risk metabolic phenotype could result not only in appropriate preventive interventions, but also earlier screening thus increased likelihood of early stage diagnosis and improved survival. Consideration of this possibility would require analyses of the potential benefits of

alternative screening recommendations relative to costs.

The strengths of this study lie in the prospective long-term follow-up among several subcohorts of the WHI. In addition, multiple important confounding factors were included in the analysis such as NSAIDs use and dietary information, which have been linked with the risk of colorectal cancer. However, two limitations should be taken into account. First, BMI and metabolic factors were measured at baseline, and we were not able to evaluate possible changes during follow-up. Therefore, there might be misclassification bias due to changes in these risk factors over time. As a consequence of aging, we would expect metabolically healthy women at baseline to be more likely to become metabolically unhealthy at follow-up, rather than the reverse. Thus, this type of misclassification bias would likely make our estimates conservative. Second, the study population consisted of four WHI subsets of women, which could be generalized to postmenopausal women, but not men or younger women.

In summary, a metabolically unhealthy phenotype was associated with higher risk of colorectal cancer among normal-weight postmenopausal women. These data suggest that normal-weight postmenopausal women should be evaluated for metabolic health and appropriate steps taken to reduce their risk of diseases including colorectal cancer.

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Table 1. Baseline characteristics of the WHI normal-weight participants by metabolic phenotype (*n*=5,068)

	Metabolically healthy	**Metabolically unhealthy**	***P* value**
Total number of women	3,358	1,710	
Age at cohort entry (mean±SD, yrs)	63.8±7.7	66.7±6.9	<0.001
Race/Ethnicity (%)			
Black or African-American	23.8	20.5	0.014
Hispanic/Latino	15.9	15.4	
Non-Hispanic white	56.1	58.7	
Others	4.2	5.4	
Smoking status (%)			<0.001
Never smokers	52.5	52.8	
Former smokers	37.0	32.4	
Current smokers	10.5	14.8	
Alcohol intake (7+ drinks/wk, %)	41.1	33.9	<0.001
Total energy intake (mean±SD), med serv/day)	1515.0±678.4	1472.3±670.7	0.033
Dietary fiber (mean±SD), med serv/day)	15.3±7.2	14.9±7.3	0.031
Percent calories from fat (mean±SD), med serv/day)	32.0±8.6	31.9±8.7	0.532
Physical activity (%)			
0-1.5 METs/wk	18.0	19.8	<0.001
>1.5-8 METs/wk	24.5	29.2	
>8-19 METs/wk	29.5	28.3	
>19 METs/wk	28.0	22.8	
Family history of colorectal cancer (%)			0.807
No	75.8	75.0	
Yes	14.1	14.7	
Missing	10.1	10.3	
NSAIDs use (%)	13.5	13.4	0.899
Systolic blood pressure (mean±SD, mmHg)	122.2±17.1	134.6±18.2	<0.001
Diastolic blood pressure (mean±SD,	73.0±8.9	75.8±9.6	<0.001
Total cholesterol (mean±SD, mg/dL)	221.6±36.0	236.2±46.5	<0.001
HDL cholesterol (mean±SD, mg/dL)	66.0±13.9	52.4±14.2	<0.001

Triglycerides (mean±SD, mg/dL)	95.7±39.3	165.2±104.5	<0.001
Glucose (mean±SD, mg/dL)	88.9±12.2	102.9±32.1	<0.001
C-reactive protein (mean±SD, mg/mL)	2.3±4.3	3.7±11.0	<0.001
HOMA-IR (mean±SD, mmol/L*mu/L)	1.4±1.1	2.6±7.1	<0.001
Waist circumference (mean±SD, cm)	74.5±7.0	77.8±7.9	<0.001
Hypertension (%)	25.0	61.1	<0.001
Diabetes (%)	1.0	13.0	<0.001
Metabolic syndrome (%)	0	40.0	<0.001

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Table 2. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between metabolic phenotype and colorectal/colon cancer among WHI normal-weight women

	Cases	Age-adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
Colorectal cancer			
Metabolically healthy	64	1	1
Metabolically unhealthy	50	1.51 (1.03-2.19)	1.49 (1.02-2.18)
Colon cancer			
Metabolically healthy	50	1	1
Metabolically unhealthy	38	1.48 (0.96-2.27)	1.51 (0.98-2.33)

[a]HR and 95% CI adjusted for age. [b]HR and 95% CI adjusted for age, ethnicity, smoking, alcohol consumption, physical activity, total energy intake, dietary fiber, percent calories from fat, family history of colorectal cancer, NSAIDs use, and treatment arm in each CT.

Table 3. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between individual components of metabolic phenotype and colorectal/colon cancer among normal-weight women

	Colorectal cancer		Colon cancer	
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**
Elevated triglycerides [a]				
No	76	1	55	1
Yes	38	0.99 (0.65-1.52)	33	1.32 (0.82-2.12)
Low HDL-C [b]				
No	82	1	65	1
Yes	32	1.33 (0.84-2.09)	23	1.13 (0.67-1.91)
Elevated blood pressure [c]				
No	51	1	40	1
Yes	63	1.09 (0.74-1.60)	48	1.04 (0.67-1.62)
Elevated fasting glucose [d]				
No	81	1	63	1
Yes	33	1.70 (1.12-2.58)	25	1.68 (1.04-2.71)

HR and 95% CI adjusted for age, ethnicity, smoking, alcohol consumption, physical activity, total energy intake, dietary fiber, percent calories from fat, family history of colorectal cancer, NSAIDs use, and treatment arm in each CT.

[a] Elevated triglycerides: ≥150 mg/dL

[b] Low HDL-C: <50 mg/dL or use of medication for reduced HDL-C

[c] Elevated blood pressure: systolic/diastolic blood pressure ≥130/85 mmHg or use of antihypertensive medication

[d] Elevated fasting glucose: ≥100 mg/dL or use of diabetes medication