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Association Between Plasma Adiponectin Levels and Colorectal Cancer Risk in Women

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Abstract

Background—Adiponectin, an adipocyte-secreted hormone, has insulin-sensitizing characteristics. It remains unclear whether adiponectin may influence colorectal cancer development.

Methods—To determine whether prediagnostic levels of adiponectin were associated with risk of incident colorectal cancer in the Women's Health Study (WHS), we conducted a nested case-control study of 275 colorectal cancer cases and 275 matched controls. Each case was matched to a control by age, ethnicity, fasting status at the time of blood collection, time of day when blood was drawn, and month of blood draw. Multivariable logistic regression with adjustment for colorectal cancer risk factors was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for risk of colorectal cancer incidence and mortality by adiponectin quartiles based on the control distribution.

Results—Median plasma adiponectin level was similar in cases versus controls (6.00 ug/mL vs. 6.24 ug/mL). In multivariable-adjusted logistic regression models, high plasma adiponectin levels were not significantly associated with risk for colorectal cancer (quartile 4 [Q4] versus quartile 1 [Q1]: OR (95% CI): 0.86(0.48–1.56), ptrend 0.63).

Conclusions—These results suggest no appreciable association between plasma adiponectin and risk of colorectal cancer in women. Confirmation of these observations in larger studies is needed.

Keywords

adiponectin; colorectal cancer; women

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Clinical Trial Registration Women's Health Study URL http://clinicaltrials.gov/ct/show/NCT0000047

Conflicts of Interest: Drs. Zhang and Lin are currently employees of Takeda.

Introduction

Obesity is an important risk factor for colorectal cancer (CRC)[1] the third leading cause of cancer incidence and death in women.[2] The physiological mechanisms underlying this association are not well understood. It is hypothesized that insulin[3] and adipokines[4] are important regulators for the possible link between obesity and CRC.[5] Multiple biological mechanisms have been suggested to explain this association, including insulin resistance and subsequent hyperinsulinemia[6], circulating insulin-like growth factors[3], and sex hormone influenced production of adipokines.[7]

Adiponectin, an adipocyte-secreted hormone[8], plays an important role in insulin sensitivity. Circulating adiponectin has been inversely associated with obesity[9] and diabetes.[10] Animal studies have revealed that adiponectin increases insulin sensitivity and improves insulin resistance. Human studies have shown that adiponectin is inversely associated with plasma insulin and is reduced in individuals with insulin-resistant states such as obesity and type 2 diabetes.[11] Given its crucial role in mediating insulin sensitivity, adiponectin may be essential in the biological pathway of the development of obesity-associated cancers such as colorectal cancer. It has also been shown that rapid tumor growth is inversely associated with serum adiponectin levels.[12] The increase in expression of adiponectin receptors AdipoR1 and AdipoR2 is greater in cancerous than normal colonic tissue.[13] To date, three meta-analysis reviews have revealed a weak association between higher adiponectin levels and lower colorectal cancer risk.[14, 15,16] Nevertheless, two among the three reviews have suggested substantial heterogeneity among studies.[14, 15] Accordingly, we prospectively examined the association between plasma adiponectin and colorectal cancer risk in a large cohort of initially healthy women where plasma samples were collected prior to cancer diagnosis. We hypothesized that higher adiponectin levels would be associated with reduced risk of incident colorectal cancer and colorectal cancer mortality in women.

Methods

Study Participants

The Women's Health Study (WHS) is a completed randomized, placebo-controlled double-blinded trial originally designed to examine the role of aspirin (100mg every other day) and vitamin E (600 IU every other day) in the prevention of cancer and cardiovascular disease (CVD) among 39, 876 women free of cancer and CVD since 1992. Every 6 months for the first year and every year thereafter, participants received questionnaires that assessed their compliance with study drug, potential side effects, and clinical outcomes of interest. When the trial ended in 2004, 33,682 women (88.6% of those alive) consented to continue with observational follow-up, reporting on their health habits and medical history annually on questionnaires. Morbidity follow-up rates were complete for 97.2% and mortality follow-up rates for 99.4%.

For cases of colorectal cancer reported during the trial or post-trial period, subjects granted written consent for medical record review. Medical records were then obtained and reviewed by a committee comprising physicians who were blinded to the treatment assignment. With mean follow-up time of 16 years, a total of 275 confirmed invasive colorectal cancer cases

were identified. Cases were individually matched to controls by age (+/− 1 year), ethnicity, fasting status at time of blood collection (>8 hours versus not), time of day when blood was drawn (+/− 4 hours), and month of blood draw.

Baseline blood collection—Prior to randomization in the WHS, blood was collected by mail using a blood-collection kit containing instructions, tubes, blood draw supplies, a gel-filled freezer pack, and a completed overnight courier air bill. Women were asked to freeze the gel-filled freezer pack overnight to serve as a coolant and to return the completed blood kit to us via overnight courier. Of the 39,876 randomized women in the trial, 28,345 (71%) provided a baseline blood sample. Women who did and did not donate blood were similar for a wide range of variables related to cancer.[17]

Plasma Adiponectin Assay—Total circulating plasma adiponectin was assayed in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA) and was measured using an enzyme-linked immunosorbent assay from ALPCO Diagnostics (Salem, NH). All samples for plasma adiponectin were shipped in a single batch to the reference laboratory, with laboratory personnel blinded to case, control, or quality control status. The mean intra-assay coefficient of variance for blinded, replicate quality control samples was 11.8%.

Statistical analysis—Using a nested case-control design with 1:1 matching (by age, ethnicity, month of blood draw, fasting more than 8 hours status) we evaluated whether the risk of colorectal cancer is associated with baseline plasma levels of adiponectin. The distributions of baseline characteristics by cancer and control groups were compared using McNemar test for continuous variables and chi-square test for categorical variables. Adiponectin was categorized by quartiles based on the distribution in control subjects. A conditional logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Tests for trend were calculated by using the median values for the quartiles of adiponectin based on the control distribution. The simple model included the following covariates: season of blood draw and randomized treatment assignment to aspirin or vitamin E. For multivariable-adjusted models, we additionally adjusted for established risk factors for colorectal cancer assessed at baseline including family history of colon cancer, red meat intake, dietary calcium intake, alcohol intake, postmenopausal hormone use, body mass index (BMI), physical activity, smoking status, and multivitamin use. Missing values for each covariate, if applicable, were coded as an indicator variable to indicate missing.

When analyzing risk for rectal cancer and colorectal cancer mortality, we utilized unconditional logistic regression with adjustment for matching factors, season of blood draw and randomized treatment assignment to aspirin or vitamin E (simple model), as well as with adjustment for additional established risk factors for colorectal cancer as described earlier (multivariable model). The multivariable unconditional logistic regression was also utilized to perform stratified analysis by postmenopausal hormone use, BMI (BMI< 25, ≥ 25 kg/m^2), and physical activity (above median and below median of reported physical activity) with the Wald test of cross-product terms. We used SAS 9.2 for all analyses with a two-sided test.

Results

The median follow-up for this study population is 16.3 years. At baseline, characteristics were similar between colorectal cancer cases and controls with regards to BMI, current smoking, family history of colorectal cancer, physical activity, and intakes of alcohol, red meat, calcium and multivitamins (Table 1). There was no difference between cases and controls in baseline postmenopausal hormone use and colonoscopy screening exams. The baseline plasma adiponectin was similar between colorectal cancer cases and controls (cases:6.00 ug/mL; controls: 6.24 ug/mL; p=0.31).

According to the multivariable model shown in Table 2, women in the highest quartile had a nonsignificant lower risk for colorectal cancer compared with those in the lowest quartile, $OR_{Q1:Q4}$ (95% CI):0.86(0.48–1.56), ptrend=0.63. Additional adjustment for baseline colorectal cancer screening (colonoscopy or sigmoidoscopy) did not change the results. Comparing the highest versus the lowest quartile, $OR_{Q1:Q4}$ (95% CI):0.95(0.52–1.77), ptrend=0.88. The null association remained unchanged in the analysis according to cancer sites (ie, colon, rectum) (Table 2). A total of 67 colorectal cancer deaths were ascertained in this study population. We observed no association between plasma adiponectin level and risk for colorectal cancer death in both simple and multivariable models (simple:$OR_{Q1:Q4}$ (95% CI):0.98(0.44–2.22), ptrend0.87; multivariable: ($OR_{Q1:Q4}$(95% CI):1.04(0.43–2.51), ptrend0.77) (Table 2).

Subgroup analysis by tumor characteristics including location (proximal, distal, rectal), stage (A, B, C/D) and grade (well-, moderately-, poorly differentiated) did not reveal significant association with adiponectin levels (p-values for trend ≥0.10). No significant interaction was observed between postmenopausal hormone use (PMH), BMI or physical activity and plasma adiponectin in relation to colorectal cancer (PMH: p for interaction=0.51; BMI: p for interaction=0.33; physical activity: p for interaction =0.30).

Discussion

In this nested-case control study, we found no significant association between pre-diagnostic adiponectin levels and subsequent risk of colorectal cancer, after controlling for several established risk factors for colorectal cancer including BMI. In addition, there was no association between adiponectin and colorectal cancer mortality.

Several lines of evidence have suggested a potential association between plasma adiponectin levels and anti-tumorigenesis. Colon cancer patients tend to have lower adiponectin levels as compared with healthy controls.[4,18] Low levels of plasma adiponectin have been linked to increased colorectal cancer risk and tumor grade, but mainly in male patients.[19, 20] Furthermore, adiponectin messenger RNA (mRNA) was not detected in colonic tissues, but AdipoRs (receptor) mRNA was lower in CRC than in normal tissue.[18]

Experimental data also support a link between adiponectin and colorectal neoplasia prevention.[21] Adiponectin receptors, AdipoR1 and AdipoR2, are expressed in normal colonic mucosa and malignant cells.[22] High-molecular weight (HMW) and non-HMW adiponectin fractions have different biological activities. Furthermore the HMW form is

more closely related to insulin sensitivity, whereas complexes with lower molecular weight have stronger anti-inflammatory protein. Thus, it may be important to consider adiponectin fractions as separate factors.[23] Previously, Aleksandrova et al. investigated different adiponectin fractions within the large cohort European Prospective Investigation into Cancer and Nutrition Study (EPIC) and found stronger risk associations with CRC in both sexes for non-HMW than for total adiponectin (OR=0.39).[24]

Several studies have evaluated the genetic association of adiponectin gene[25, 26] or adiponetin receptors[27] with CRC and the results have been inconsistent. One study has shown that two single nucleotide polymorphisms (SNPs), rs2241766 and rs1501299, of the adiponectin (ADIPOQ) gene were associated with increased risk of colorectal cancer.[25] However, another study of over 7000 cases and 7000 controls drawn from 10 study populations in the Genetics and Epidemiology of Colorectal Cancer Consortium found no statistically significant association between 19 adiponectin-associated SNPs and CRC risk; odds ratios were from 0.89 to 1.05, all $p > 0.05$. In the same study, each SNP explained less than 2.50% of the variance of plasma adiponectin, and the genetic score collectively accounted for 2.95 and 1.42% of the variability of adiponectin in women and men, respectively.[27]

Epidemiological data regarding circulating adiponectin and colorectal cancer are limited and inconsistent.[4, 28, 14, 15,16] Age and BMI distributions in this study population are similar to past epidemiologic studies.[5, 24] The range of adiponectin reported in observational studies is comparable to the range in this study (5–6 ug/mL). A recent meta-analysis review of 6 prospective cohort studies performed by Joshi et al. revealed a weakly inverse association of adiponectin with CRC risk (OR = 0.90, 95%CI: 0.82–0.99, P = 0.03).[16] Of note, Joshi et al. recalculated risk estimates by combining quantiles by study; quartiles 1 and 2 were combined and became the reference category while quartiles 3 and 4 here combined and were tested against the reference category. Based on these new risk estimates among the 6 included studies, only the WHI-OS[5] study reported a significant association, which became insignificant after additional adjustment for waist circumference and/or insulin. In contrast, the original estimates from three[4,24, 26] of the studies were significantly associated with reduced risk of colorectal cancer with higher adiponectin values. No association was seen in the meta-analysis of 3 case-control studies (OR=1.00, 95% CI: 0.74–1.36, p=0.99).[29] Another meta-analysis showed that significant differences in adiponectin levels between patients with CRC and healthy controls was reported only in case-control studies or small sample size studies (n<100), but not in nested case-control studies or large sample size studies (n>/=100).[15] Similarly, metaregression analysis indicated that study design and sample size partly contributed to the significant heterogeneity (P=0.022 for study design and P=0.018 for sample size, respectively).[15]

A variety of reasons may have contributed to the null association with adiponectin seen in our study. First, our population included only women and adiponectin was only measured once, at baseline, and may not reflect long term plasma concentrations. Second, previous findings in men[3] have suggested an inverse association between circulating adiponectin and colorectal cancer risk in men. However, two[27, 30] of the three previous studies[27,30, 24] have suggested a null association in women. Our null findings are in line with the 2 female

studies. A possible mechanism underlying the different findings by sex may be attributable to body fat.[31, 32] Specifically, body fat percentage has been found to be negatively associated with adiponectin in men but not in women [32]suggesting an independent association between body fat and adiponectin in women.

Third, in the present study, we only measured total adiponectin, which may not reflect the real association with colorectal cancer risk. As discussed earlier, in the EPIC study[24], total adiponectin was not associated with colorectal cancer risk after multivariable adjustment. More studies of both overall and HMW-adiponectin data are warranted to resolve the potential different findings according to sex.

Strengths of the present study include the nested case-control design, rigorous collection of covariate data, and detailed information on metabolic parameters that may influence adiponectin levels such as alcohol use, diabetes, obesity, and smoking status. Limitations of the current study include having only a single measure of adiponectin. However, the present findings may be subject to chance due to the small number of cases and controls.

In conclusion, higher prediagnostic levels of circulating adiponectin were not significantly associated with risk of colorectal cancer. Future studies with larger sample size and race/ethnic diversity are warranted to evaluate the potential role of adiponectin in colorectal cancer development.

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Abbreviations

BMI	body mass index
CI	confidence interval
g	grams
hr	hours
MET	metabolic equivalent
mg	milligrams
OR	odds ratio

WHS Women's Health Study.

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Table 1

Baseline characteristics (mean or %) among cases of colorectal cancer and matched controls in the Women's Health Study

Characteristics	Cases (N=275)	Controls (N=275)	P_{value}
Age, year	58.8 (8.3)	58.8 (8.3)	matched
Race-Caucasian, %	96.4	96.4	matched
Body mass index, kg/m^2	26.8 (6.0)	26.3 (5.1)	0.31
Current smoking (%)	9.8	11.3	0.57
History of sigmoidoscopy/colonoscopy (%)	11.3	10.2	0.66
History of colorectal polyps (%)	3.6	4.0	0.83
Family history of colorectal cancer (%)	12.0	9.82	0.38
Postmenopause (%)	74.2	75.7	0.13
Postmenopausal hormone use (%)	59.8	54.6	0.16
Current use of multivitamins (%)	36.7	37.8	0.79
Physical activity (MET-hrs/week)	15.4 (21.3)	16.5 (18.6)	0.53
Calcium mg/d	1045.8 (535.6)	1060.6 (569.4)	0.70
Alcohol intake (g/day)	5.0 (9.4)	4.8 (11.0)	0.78
Plasma Hemoglobin A1C levels, %	5.1 (0.6)	5.2 (0.8)	0.36
Plasma adiponectin levels, ug/mL†	6.00(4.26–7.95)	6.24(4.40–8.56)	0.31

Abreviations: g, grams;hr hours; mg, milligrams; MET, metabolic equivalent;

*Information was obtained at the 12-month follow-up questionnaire. Mean is calculated for continuous variables

†Median value (25^{th} – 75^{th} range).

Table 2

Odds ratios and 95% confidence interval (CIs) of colorectal cancer incidence according to plasma levels of adiponectin in the Women's Health Study

	Quartiles of plasma adiponectin levels ug/ML*				
Range	**≤4.40**	**4.41–6.25**	**6.26–8.60**	**>8.60**	P_{trend}
Model			**Colorectal Cancer**		
No. cases/controls	71/68	75/70	69/69	60/68	
Simple OR†	1.00	0.98(0.61–1.57)	0.95 (0.58–1.55)	0.79 (0.46–1.35)	0.42
Multivariable OR†	1.00	1.03 (0.62–1.72)	0.98 (0.58–1.66)	0.86 (0.48–1.56)	0.63
			Colon Cancer		
No. cases/controls	55/53	55/49	52/51	43/52	
Simple RR†	1.0	1.02 (0.59–1.76)	0.97 (0.55–1.72)	0.74 (0.40–1.37)	0.38
Multivariable RR†	1.0	1.08 (0.60–1.97)	1.02 (0.55–1.91)	0.80 (0.40–1.60)	0.58
			Rectal Cancer††		
Range	≤4.40	4.41–6.25	6.26–8.52	>8.52	
No. cases/controls	16/71	20/65	17/69	17/70	
Simple OR	1.0	1.32 (0.62–2.81)	1.08 (0.49–2.35)	1.11 (0.50–2.46)	0.88
Multivariable OR	1.0	1.30(0.59–2.89)	1.03(0.45–2.33)	1.08(0.45–2.59)	0.98
			Colorectal Cancer Death††		
Range	≤4.40	4.41–6.31	6.32–8.43	>8.43	P_{trend}
No. cases/controls	17/69	15/70	19/65	16/70	
Simple OR	1.0	1.00(0.44–2.26)	1.30(0.59–2.86)	0.98(0.44–2.22)	0.87
Multivariable OR	1.0	0.98(0.42–2.29)	1.31(0.57–3.00)	1.04(0.43–2.51)	0.77

Abbreviations: OR, odds ratio

*The quartiles were defined based on distribution among all control participants. The log value of adiponectin was used for the analyses.

†Simple models were adjusted for randomized treatment assignment to aspirin and vitamin E (aspirin vs. placebo, vitamin E vs. placebo). Multivariable models were additionally adjusted for body mass index (BMI) (weight (kg)/height $(m)^2$, continuous), physical activity (MET-hour/week), family history of colorectal cancer, smoking status (current), alcohol consumption (g/day), menopausal status and hormone therapy use (never/ever), month of blood draw, multivitamin use.

††Rectal cancer incidence and colorectal cancer death were evaluated with an unconditional analysis because of the small number of cases. Simple models were adjusted for randomized treatment assignment to aspirin and vitamin E (aspirin vs. placebo, vitamin E vs. placebo), month of blood draw, age at randomization. race, and fasting status. Multivariable models were additionally adjusted for

body mass index (BMI) (weight (kg)/height (m)^2, continuous), physical activity (MET-hour/week), family history of colorectal cancer, smoking status (current), alcohol consumption (g/day), menopausal status and hormone therapy use (never/ever), multivitamin use.