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Serum adiponectin, leptin, C-peptide, homocysteine, and colorectal adenoma recurrence in the Polyp Prevention Trial

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Abstract

Background—Serum adiponectin, leptin, C-peptide, and homocysteine are indicators for obesity, hyperinsulinemia, and chronic inflammation, which have all been associated with colorectal cancer.

Aims—To determine whether serum adiponectin, leptin, C-peptide, and homocysteine are associated with fat, fiber, fruit & vegetable, flavonol, or dry bean intake, and colorectal adenoma recurrence.

Methods—Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for adenoma recurrence in 627 participants from the control arm of the Polyp Prevention Trial, a 4-year trial that examined the effectiveness of a low-fat, high-fiber, high-fruit & vegetable diet on adenoma recurrence.

Results—Serum concentrations of C-peptide and homocysteine were inversely related to fiber, fruits & vegetables, and flavonol intake and positively related to percentage of calories from fat (all $P_{trend} \leq 0.01$). High homocysteine concentrations were associated with any (4th versus 1st quartile, OR = 2.26, 95% CI: 1.30-3.94) and more than one adenoma recurrence (OR = 2.11, 95% CI: 1.01-4.40). Individuals in the highest, versus lowest, tertile of serum leptin concentration had a decreased risk of advanced adenoma recurrence (OR = 0.22, 95% CI: 0.06-0.79).

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Conclusion—Our results suggest that serum homocysteine may serve as an indicator of dietary exposure, including a low-fat and high-fiber, -fruit & vegetable, and -flavonol diet, as well as colorectal adenoma recurrence.

Impact—Discovering biomarkers that are both modifiable and can predict cancer risk is critical. We identified serum homocysteine as a novel indicator that is modified by diet and predicts risk of adenoma recurrence.

Keywords

colorectal adenoma; colorectal cancer; flavonols; adiponectin; leptin; C-peptide; homocysteine

Introduction

Epidemiologic studies have recognized obesity as a risk factor for colorectal adenomas (1) and cancer (2,3). Proteins that are secreted by adipocytes provide a plausible link between obesity and colorectal cancer. Two of those proteins, adiponectin and leptin, can alter the risk of cancer either directly through activating signal transduction pathways involved in carcinogenesis or indirectly through acting on insulin sensitivity and the inflammatory response (4-6). Hyperinsulinemia or insulin resistance is directly related to excess adipose tissue (7).

Serum concentrations of adiponectin have been inversely associated with colorectal adenoma (8-10) and cancer (11,12) but not all (13,14) studies. The data for leptin are inconsistent, with some studies finding a positive association for colorectal adenoma (15) and cancer (16-18) and others an inverse association for colorectal adenoma (8) and cancer (8,19-21). C-peptide is an inactive by-product and marker of insulin production (22) and has been positively associated with colorectal cancer (23-25); in contrast, the evidence for a positive association with colorectal adenoma is limited to one (26) of the three (27,28) studies conducted. Circulating homocysteine has been positively associated with hyperinsulinemia (29), and this highly reactive metabolite can promote inflammation, tissue damage, cardiovascular disease, and carcinogenesis (30,31). Some studies observed a positive association between circulating homocysteine and colorectal adenoma (32) and adenoma recurrence (33), while others found no association between homocysteine and risk of colorectal adenoma (34-36).

In the Polyp Prevention Trial (PPT), participants that consumed a low-fat, high-fiber, high-fruit & vegetable diet and more specifically a diet high in flavonols and dry beans had a decreased risk of advanced adenoma recurrence (40); however, participants in the intervention and control arm did not differ in adenoma recurrence (37-39). The aim of this study was to determine whether serum concentrations of adiponectin, leptin, C-peptide, and homocysteine were associated with diet and adenoma recurrence.

Subjects and Methods

Study Population

Participants were from the PPT, a large 4-year multi-center, randomized, controlled trial to evaluate the effects of promoting a low-fat, high-fiber, and high-fruit & vegetable diet on the recurrence of colorectal adenomas. The study was approved by the institutional review boards of the National Cancer Institute and those of the collaborating centers. All subjects provided written informed consent. A detailed description of the study has been published elsewhere (40,41). Briefly, men and women, aged 35 years or older, with at least one histologically confirmed colorectal adenoma removed in the prior 6 months, were randomized at baseline (T0) to the dietary intervention group or control group for 4 consecutive years of follow-up (T1, T2, T3 and T4). In order to be eligible, potential participants must not have had prior

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surgically resected adenomas or diagnoses of colorectal cancer, inflammatory bowel disease, or a polyposis syndrome and they had to be no more than 150% of their recommended body weight. In addition, participants could not be using lipid-lowering drugs or have medical conditions or dietary restrictions that would limit their compliance with the protocol.

A total of 2,079 participants were enrolled in the trial; 1,037 were randomized to the intervention arm and 1,042 to the control arm. At baseline and at each of the four annual follow-up visits, participants completed an interviewer-administered questionnaire about demographics, family history, and use of medication or supplements. In addition, participants completed a self-administered, validated, modified Block-National Cancer Institute food frequency questionnaire (FFQ) (41), which asked about the frequency of intake and portion size of 119 food and beverage items during the past year. Trained, certified nutritionists reviewed all FFQs with participants. Flavonol intake was estimated based on 55 food and beverage items using the 2007 U.S. Department of Agriculture (USDA) flavonoid database (42) and was calculated as the sum of isorhamnetin, kaempferol, myricetin, and quercetin (38). Dry bean intake was estimated based on a single question that asked about the intake of cooked dry beans such as pinto, navy beans, lentils, and bean soup (37). Compared with 24-hr dietary recall and four-day food record data, the FFQ slightly overestimated fat and underestimated fiber, fruit & vegetable intake and had acceptable correlations of fat ($r = 0.63$), fiber ($r = 0.63$), fruit & vegetable ($r = 0.72$), dry bean ($r = 0.76$), and other macro- and micronutrients (41,43).

Four years after randomization, 1,905 (91.6%) participants (958 in the intervention group and 947 in the control group) completed the study and underwent colonoscopy at T4. All lesions were examined for histological features and degree of atypia by two independent pathologists. Recurrence outcomes were defined as having any, multiple (≥2), advanced (≥ 1 adenoma of ≥ 1 cm in size, having ≥ 25% villous component, or exhibiting high-grade dysplasia), or high risk (≥ 1 advanced adenoma or ≥ 3 adenomas) adenoma recurrence, relative to no polyp recurrence. This study only included participants in the control arm of the PPT that had serum samples, dietary exposure data from T1, and a final colonoscopy (n=627). For the analysis of adenoma recurrence, data from 108 individuals with non-adenomatous polyps only were excluded, which left data from 519 participants.

Serum Assays

At the baseline visit and at each of the 4 subsequent annual visits, participants were weighed and provided a venous blood sample after an overnight fast. Serum samples were stored at -70 °C. Samples taken at T1 were used for adiponectin, leptin, C-peptide and homocysteine analysis; in addition, blood samples taken at T4 were used to measure serum concentrations of adiponectin and leptin. Since we were primarily interested in proteins secreted by adipocytes, we did not measure C-peptide and homocysteine at T4. Serum concentrations of adiponectin and leptin were determined at Pierce Biotechnology (Woburn, MA), using multiplex 96-well immune-chemiluminescent SearchLight Proteome Arrays and a SearchLight Imaging System. Bound adiponectin and leptin were detected with a biotinylated detection antibody, followed by the addition of streptavidin-horseradish peroxidase (SA-HRP) and lastly, a patented chemiluminescent substrate (Patent No.: 6,432,662).

Serum concentrations of C-peptide and homocysteine were measured at the Department of Laboratory Medicine, Harvard Medical School (Boston, MA). C-peptide was measured by a competitive electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN). The concentration of total homocysteine was determined using an enzymatic assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, using reagents and calibrators from Catch Inc. Seattle, WA). The assay measures the formation of NAD from NADH, which is proportional to the amount of homocysteine in the sample. Adiponectin, C-peptide and homocysteine were measured in duplicate and leptin in quadruplicate. Three standard assay controls that covered a range of concentrations and one pooled NIH serum sample were run on each plate as repeated duplicate measures and had interassay coefficients of variation (CV) of 39.9%, 13.2%, 5.0%, and 5.3% for adiponectin, leptin, C-peptide, and homocysteine, respectively. The high adiponectin CV was caused by day-to-day variation of the adiponectin values of the pooled NIH serum sample, as standard curves for adiponectin were consistent and CVs within-day and within-plates were below 20%.

Statistical Analysis

Baseline and T1 characteristics (T1 was the time of serum collection) by adenoma recurrence at T4 were evaluated using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables and are shown as medians and interquartile ranges (IQR). The associations between serum indicators (continuous) and dietary exposures (in energy-adjusted quartiles using the nutrient density method), as well as sex, age quartiles, body mass index (BMI; <25, 25.0-29.9, ≥30 kg/m^2), physical activity (hrs/wk moderate and vigorous exercise) quartiles, race, and regular non-steroidal anti-inflammatory drug (NSAID) use at T1, were evaluated using Spearman correlation coefficients, Kruskal-Wallis tests, and multiple linear regression models. We selected the five dietary exposure indicators (% fat from calories, fiber, fruits & vegetables, flavonols, and dry beans) proposed to decrease (alone or in combination) the risk of adenoma recurrence in the PPT (37-39).

The association between serum indicators at T1 and adenoma recurrence at T4 (no polyp vs. any, multiple, high risk, or advanced adenoma) was estimated by logistic regression calculation of odds ratios (ORs) and 95% confidence intervals (CIs), using the lowest quartile of serum analyte concentration as the referent category. Linear trend testing was carried out using median values from the quartiles of the serum biomarker concentrations. Tertiles of serum concentrations were used when investigating the association between each of the four analytes and advanced adenoma recurrence because of the small number of advanced cases.

For all logistic and multiple regression models, potential confounders (listed in Table 1) were added to the models in a stepwise fashion; if a variable changed the association by > 10%, was associated with both study variables, and had a χ^2 *p*-value ≤ 0.20, it remained in the model. Logistic regression models were adjusted for sex, age quartiles, BMI (<25, 25.0-29.9, ≥30 kg/m^2), and regular NSAID use, defined as at least once monthly usage on the baseline questionnaire. Analyses were stratified by sex, BMI (<25, 25.0-29.9, ≥30 kg/m^2 at T1), and physical activity tertiles (at T1). All *p* values correspond to two-sided tests. Statistical tests were considered to be statistically significant when $P \leq 0.05$.

Results

At the end of the 4-year trial, 44.2% of participants had no polyps, 38.6% had ≥ 1 adenoma, 16.3% had multiple adenomas, 10.8% had high risk adenoma, and 5.3% had ≥ 1 advanced adenoma (Table 1). Adenoma recurrence was more common in men, but less common in users of supplements and in women who used hormone therapy (Table 1). Furthermore, individuals with multiple, high risk, or advanced adenoma recurrence were older than those without polyps (Table 1).

Statistically significant, though weak, correlations were observed for serum concentrations of C-peptide with adiponectin ($r_{Spearman}$ = -0.16), homocysteine (r = 0.24), and leptin (r = 0.25), and between leptin and homocysteine (r = - 0.16). The serum concentrations of adiponectin and leptin at T1 were highly correlated with those at T4 (r = 0.68 and r = 0.82; respectively). On average, females had higher serum concentrations of adiponectin and leptin and lower concentrations of C-peptide and homocysteine (Table 2). With regard to race, Caucasians had higher concentrations of adiponectin. There was a curvilinear relationship between the four serum indicators and age with lower concentrations in the first quartile (36 to 56 years old) and similar concentrations in the other three quartiles (57 to 87 years old); the relationship was only statistically significant in males (data not shown). BMI was positively associated with serum leptin (r = 0.38), C-peptide (r = 0.39), and weakly correlated with homocysteine (r = 0.11); furthermore, physical activity was mildly inversely related to leptin (r = -0.25) and C-peptide (r = -0.15).

Those in the highest, versus the lowest, intake quartile of fiber, fruits & vegetables, and flavonols had lower serum concentrations of C-peptide (Table 2: 1.27 *vs.* 1.44 ng/mL for fiber, 1.23 *vs.* 1.45 ng/mL for fruits & vegetables; 1.21 *vs.* 1.47 ng/mL for flavonols) and homocysteine (12.6 *vs.* 13.9 μM/L for fiber, 12.0 *vs.* 13.9 μM/L for fruits & vegetables; 12.1 *vs.* 13.4 μM/L for flavonols), whereas % calories from fat were positively associated with C-peptide (1.44 *vs.* 1.26 ng/mL) and homocysteine (13.5 *vs.* 12.7 μM/L; Table 2). Serum homocysteine concentrations were weakly inversely correlated with folate consumption from foods (r = -0.14) and from supplements (r = -0.23). Multivariate regression models of serum indicators by dietary exposure were not mutually adjusted for all dietary variables (% calories from fat, fiber, fruits & vegetables, flavonols, and dry beans) because of the high correlations among them, especially between fiber and fruits & vegetables (r = 0.76), fiber and fat (r = -0.59), and flavonols and dry beans (r = 0.62).

Individuals without polyp recurrence after four years had the highest leptin and the lowest homocysteine concentrations in serum (Table 3). For homocysteine, higher concentrations were observed with increasing adenoma number and more advanced adenoma type, whereas no gradual differences were found for leptin.

Although there was no association for adiponectin or C-peptide and adenoma recurrence (Table 4), we observed a statistically significant inverse association between serum leptin concentrations and advanced adenoma recurrence (3^{rd} *vs.* 1^{st} tertile, OR = 0.22, 95% CI: 0.06-0.79). High homocysteine concentrations were positively associated with any (4^{th} *vs.* 1^{st} quartile, OR = 2.21, 95% CI: 1.27-3.86) and multiple adenoma recurrence (OR = 2.11, 95% CI: 1.01-4.40), and there was a suggestive positive association between high homocysteine concentrations and high risk adenoma recurrence (OR = 2.11, 95% CI: 0.89-4.97; Table 4).

Mutually adjusting multivariate regression models of adenoma recurrence by serum indicators or using the covariates reported at T1 (rather than baseline) did not substantially change the risk estimates (results not shown). The association between leptin and advanced adenoma recurrence (OR = 0.27, 95% CI: 0.07-0.98; P_{trend} = 0.04) and between homocysteine and any adenoma recurrence attenuated but remained statistically significant (OR = 1.67, 95% CI: 1.02-2.75; P_{trend} = 0.04) when the reference group was no adenoma recurrence, as opposed to the "no polyp" group was used for the main analyses.

There was no interaction between BMI or physical activity and serum adiponectin, leptin, C-peptide, or homocysteine concentrations and adenoma recurrence. Although there was no interaction between sex and adiponectin, C-peptide, or homocysteine, there was an interaction between sex and leptin ($P_{Interaction}$ for any adenoma = 0.01 and $P_{Interaction}$ for multiple adenoma = 0.06). In males, we observed a non-significant inverse association between serum leptin concentration and any (4^{th} *vs.* 1^{st} gender specific quartile, OR = 0.53, 95% CI: 0.25-1.12; *P* for trend = 0.03) and multiple adenoma recurrence (OR = 0.42, 95% CI: 0.17-1.08; *P* for trend = 0.08). In contrast, leptin concentrations in females had a non-significant positive association with any (OR = 1.44, 95% CI: 0.52-4.02; *P* for trend = 0.27) and multiple adenoma recurrence (OR = 3.16, 95% CI: 0.74-13.6; *P* for trend = 0.06), respectively.

An increase in serum leptin concentrations from T1 to T4 was associated with a statistically significantly increased risk of any (4^{th} *vs.* 1^{st} quartile, OR = 1.74, 95% CI: 1.04-2.93, P_{trend} = 0.03) and multiple adenoma recurrence (OR = 2.19, 95% CI: 1.08-4.44, P_{trend} = 0.04), which was not modified by sex (results not shown). In males, an increase in leptin concentration was positively significant associated with any (OR = 2.71, 95% CI: 1.41-5.22, P_{trend} = 0.008) and multiple adenoma recurrence (OR = 3.54, 95% CI: 1.36-9.22, P_{trend} = 0.03); the same trend was observed in women but did not reach statistical significance ($OR_{any\ recurrence}$ = 1.77, 95% CI: 0.72-4.31, P_{trend} = 0.26; $OR_{multiple\ recurrence}$ = 1.72, 95% CI: 0.55-5.37, P_{trend} = 0.48) (results not shown). We found no association for change in adiponectin concentration between T1 and T4.

Discussion

Our objective was to investigate whether adiponectin, leptin, C-peptide or homocysteine were associated with early stages of colorectal carcinogenesis or could be modified by diet. Elevated homocysteine concentrations were associated with approximately a two-fold increased risk of recurrence of any, multiple, and high risk adenoma at the end of the 4-year trial. A diet low in fat and rich in fiber, fruits & vegetables, and flavonols was associated with lower serum concentrations of C-peptide and homocysteine. The data suggest that elevated serum homocysteine concentrations may serve as an indicator for dietary exposure and early stages of colorectal carcinogenesis.

Similar to our observations, a positive association between circulating homocysteine and colorectal adenoma (32) or adenoma recurrence (33) as well as lower homocysteine concentrations in individuals with hyperplastic polyps than in individuals with adenomas (44) have been reported. The limited sample size (35 to 40 cases) of some previous studies may partly explain the inconsistency in the literature regarding the association between homocysteine and risk of colorectal adenoma (34-36). A plausible role for homocysteine in indicating early neoplastic changes has been reported in *in vitro* mechanistic studies. Elevated homocysteine may promote carcinogenesis by nuclear factor-kappa B activation, which induces the expression of pro-inflammatory cytokines and cancer-promoting genes, and by formation of reactive oxygen species from its highly reactive thiol group (31). Elevated homocysteine concentrations may also indicate altered DNA synthesis and methylation patterns because homocysteine concentrations are associated with cobalamin, riboflavin, and folate status and mutations in enzymes involved in one-carbon metabolism (30,31). In a previous analysis in the PPT, we found no association between total and dietary folate and adenoma recurrence (45). Given that homocysteine has been inversely associated with dietary folate and folate supplements (46-48) and positively associated with colorectal adenoma recurrence (33) in this and other studies, circulating homocysteine concentrations may predict or mediate a chemopreventive response to folate supplementation.

Previously published studies have reported both elevated serum leptin concentrations for colorectal adenoma (15) and cancer (16-18), particularly in men (15,18), as well as decreased concentrations for colorectal adenoma (8) and even lower concentrations for colorectal cancer (8,19-21). Our study found a decreased risk of any adenoma recurrence in men and advanced adenoma recurrence overall for those with higher leptin concentrations. The inconsistency in the literature may be a result of the small sample size used in some previous studies (all studies except for a Norwegian and a Swedish study had less than 80 cases), the tumor stage at blood draw, the proportion of males to females (15,18), or confounding by BMI [results were either not adjusted (8,19-21) or the effect attenuated after BMI adjustment (15)], although BMI did not confound the association between leptin and adenoma recurrence in our study. Studies in cell culture suggest that leptin may activate signal transduction pathways involved in carcinogenesis (6); although animal models using exogenous leptin do not confirm that leptin is a molecular target for early stages of colorectal carcinogenesis (49-51). In humans, increased expression of leptin in colorectal tumor tissue is positively associated with advanced tumor stage and increased disease free survival (52-55), suggesting that leptin does play a role in colorectal carcinogenesis. Serum leptin concentrations, however, have not been associated with expression of leptin and its receptor in colorectal tumor tissue (53). Our observation that the change in leptin concentrations from T1 to T4 is positively associated with adenoma recurrence is intriguing and consistent with the increase in leptin expression with tumor stage. In summary, our results for leptin as an indicator for the early stages of colorectal carcinogenesis are inconclusive. Further investigations are needed to evaluate whether changes in serum leptin concentrations over time rather than serum leptin concentrations at a single time point may be an indicator of adenoma recurrence.

We did not observe an association between serum adiponectin concentration and adenoma recurrence. Similarly, no association between adiponectin and colorectal adenoma was observed in the Japanese Self Defense Forces Health Study (13). However, three other studies revealed an inverse association between adiponectin and colorectal adenoma (8-10), which was even stronger between adiponectin and colorectal cancer (8,10). In addition, we observed lower adiponectin concentrations with advanced stage of colorectal adenoma. Both findings suggest that adiponectin concentrations may be a better risk indicator for more advanced stages of colorectal neoplasms. Reasons for the inconsistencies in the literature for adiponectin are not clear. Adiponectin receptors are expressed in normal and colorectal cancer tissue in humans (56). In cell culture, adiponectin inhibits colorectal carcinogenesis (57), but this has not been conclusively confirmed in transgenic animal models with elevated adiponectin concentrations (58,59).

Our study found that C-peptide was inversely associated with a healthy diet, low in fat and rich in fiber, flavonols, and fruits & vegetables, but not with colorectal adenoma recurrence. Most previous studies have failed to find an association between colorectal adenoma and C-peptide (27,28). In contrast, several studies have observed a positive association between C-peptide and colorectal cancer (23-25). Our observation of a marginal increase in C-peptide concentrations with advancing stage of colorectal adenoma may suggest that elevated C-peptide concentrations are a better indicator of risk for colorectal cancer than for colorectal adenoma.

A major strength of our study was the detailed adenoma data available from complete colonoscopies performed at baseline, year 1 and year 4, as well as histologic characteristics noted by two pathologists independently, decreasing the risk of misclassification. Other strengths of this study included the prospective collection of both serum and dietary data, as well as the use of a questionnaire that was developed specifically for this study to focus on fiber and fruit & vegetable consumption (41) and linked to the recently released and validated USDA flavonoid database (42). Furthermore, the dietary questionnaire was reviewed by registered dieticians, which further improved its accuracy (43).

There are, however, several limitations to our study. Our study findings may not apply to the general population because all participants had a history of adenomas, a relatively healthy diet, and most engaged in a health-promoting lifestyle. Because all analyzed samples were from participants in the control arm of an intervention study, potential conclusions about the effect of a low-fat, high-fiber, and high-fruit & vegetable dietary intervention on serum homocysteine and leptin concentrations are limited and warrant further investigation. Measurement error related to the dietary assessment techniques could be present and could lead to attenuated risk estimates. Furthermore, the serum analyses were associated with relatively high CVs, especially for adiponectin. Future studies are warranted to better understand and decrease the variation using the current adiponectin antibody.

In conclusion, our results suggest that high serum homocysteine concentrations may indicate both increased risk of colorectal adenoma recurrence and correlate with an "unhealthy" diet that is high in fat and low in fiber, fruits & vegetables, and flavonols. Verification of these results in prospective cohorts with high-quality dietary and serum homocysteine measures is needed to clarify the role of serum homocysteine concentrations for dietary cancer prevention.

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Abbreviations

BMI	body mass index
CI	confidence interval
CV	coefficient of variation
FFQ	food frequency questionnaire
IQR	interquartile range
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PPT	Polyp Prevention Trial

Table 1

Participant characteristics for the control arm of the Polyp Prevention Trial at T1, by adenoma recurrence* at T4

T1 Characteristics†	No Polyp	Any Adenoma		Multiple Adenoma		High Risk Adenoma		Advanced Adenoma	
			P value‡		*P value*‡		*P value*‡		*P value*‡
Sample size	277	242		102		68		33	
Sex (% male)	53	72	<.0001	73	0.0006	76	0.0005	73	0.04
Race (% Caucasian)	93	91	0.42	97	0.21	97	0.39	94	1.00
Education (% ≤ high school)	25	24	0.84	25	1.00	26	0.88	27	0.83
Family history of colorectal cancer ** **(% yes)**	29	29	0.92	28	1.00	29	0.88	33	0.55
Smoker (% current)	9	12	0.32	16	0.10	12	0.51	12	0.54
NSAID use ** **(% yes)**	41	35	0.15	36	0.48	35	0.49	27	0.19
Supplement use ** **(% yes)**	50	36	0.003	39	0.08	37	0.06	36	0.20
Hormone therapy ** **(% yes)**	17	9	0.007	9	0.05	7	0.04	3	0.04
Age (yr)	64.0 (56.0-70.0)	64.0 (57.0-71.0)	0.21	67.0 (61.0-73.0)	0.001	67.0 (62.0-73.0)	0.0006	67.0 (62.0-74.0)	0.02
Body Mass Index (kg/m^2)	27.1 (24.7-29.8)	26.9 (25.1-30.8)	0.41	26.9 (25.0-31.2)	0.37	26.7 (25.0-31.0)	0.73	26.0 (24.7-29.0)	0.34
Physical activity ** **(hr/wk)**	6.83 (3.32-11.7)	6.89 (3.65-12.9)	0.34	5.67 (2.85-11.3)	0.35	7.26 (4.44-14.8)	0.20	9.05 (5.48-16.0)	0.06
Alcohol intake (g/d)	0.61 (0.00-9.30)	1.63 (0.00-11.6)	0.13	1.16 (0.00-9.30)	0.43	0.61 (0.00-6.02)	0.51	0.61 (0.00-9.15)	0.84
Energy intake (1,000 kcal/d)	1.74 (1.39-2.10)	1.82 (1.48-2.17)	0.13	1.80 (1.45-2.14)	0.57	1.82 (1.44-2.11)	0.59	1.84 (1.35-2.09)	0.67
Fat intake (% kcal/d)	33.5 (28.3-39.8)	34.3 (28.0-38.2)	0.67	33.8 (28.3-38.2)	0.50	34.0 (28.2-39.2)	0.91	33.8 (26.4-38.7)	0.64
Fiber intake (g/1,000kcal/d)	9.72 (7.68-12.7)	9.55 (7.20-12.2)	0.49	10.1 (7.14-12.4)	0.99	10.3 (7.11-13.0)	0.89	9.40 (7.09-13.6)	0.82
Fruit & Vegetable intake (servings/1,000kcal/d)	2.14 (1.49-2.76)	2.02 (1.44-2.62)	0.35	2.14 (1.49-2.85)	0.63	2.06 (1.40-2.92)	0.92	2.04 (1.40-3.16)	0.90
Flavonol intake (mg/1,000kcal/d)	8.59 (6.15-12.7)	8.61 (5.78-12.3)	0.49	8.16 (5.67-12.0)	0.35	8.19 (5.55-11.0)	0.15	9.48 (7.42-12.6)	0.66
Dry bean intake (g/1,000kcal/d)	3.85 (1.55-7.72)	3.68 (1.50-7.41)	0.90	3.65 (1.30-7.90)	0.97	3.48 (1.18-6.19)	0.36	4.67 (2.51-9.34)	0.24

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[*] The 108 of the 627 participants with non-adenomatous polyps only were excluded from the analysis. Advanced adenoma is defined as ≥ 1 adenoma of ≥ 1 cm in size, having ≥ 25% villous component, or exhibiting high-grade dysplasia. High risk adenoma is defined as ≥ 1 advanced adenoma or ≥ 3 adenoma.

[†] Results presented as % for categorical variables and medians and interquartile ranges (IQR) for continuous variables.

[‡] All comparisons against the no polyp group. *P* values for differences in proportions were calculated using Fisher's exact test. *P* values for differences in medians were calculated using Wilcoxon rank-sum test.

[**] Family history of colorectal cancer was defined as having ≥ 1 first-degree relative with colorectal cancer at baseline. Physical activity was defined as self-reported time typically spent for any type of moderate or vigorous physical activity. Regular dietary supplement use was defined as taking supplement ≥ 1 weekly. Regular medication use, including NSAIDs, was defined as taking medication ≥ 1 monthly. Hormone replacement therapy included both unopposed estrogen and estrogen/progestin combinations.

Table 2

Medians (interquartile ranges) of serum adiponectin, leptin, C-peptide, and homocysteine concentrations at T1, by characteristics of participants at T1 in the control arm of the Polyp Prevention Trial (n = 627)

		Adiponectin (ng/mL)			Leptin (ng/mL)			C-peptide (ng/mL)			Homocysteine (μM/L)	
T1 Characteristics	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****
Total	627	3.16 (1.94-5.10)		627	9.31 (4.63-17.4)		623	1.37 (0.98-1.80)		625	13.0 (10.8-15.7)	
Sex												
Female	243	3.48 (2.19-6.03)		243	19.3 (10.4-21.2)		241	1.20 (0.90-1.64)		242	11.5 (9.86-14.0)	
Male	384	3.01 (1.80-4.67)	0.004	384	6.31 (3.40-10.5)	<.0001	382	1.45 (1.09-1.90)	<.0001	383	13.9 (11.8-16.4)	<.0001
Age quartiles (in yr)												
Q1 (36-56)	174	3.02(1.56-4.51)		174	7.41 (4.23-18.9)		174	1.20 (0.92-1.69)		174	11.9 (10.1-14.7)	
Q2 (57-64)	160	3.16 (1.77-5.09)		160	9.02 (5.04-17.1)		159	1.41 (0.98-1.89)		159	13.3 (10.9-15.8)	
Q3 (65-70)	139	2.99 (2.06-5.08)		139	9.91 (5.75-17.8)		138	1.42 (1.13-1.89)		138	14.1 (11.5-16.1)	
Q4 (71-87)	154	3.58 (2.29-5.82)	0.04	154	9.40 (4.04-17.2)	0.64	152	1.38 (1.04-1.78)	0.01	154	13.3 (11.2-16.0)	0.0004
BMI (in kg/m^2)												
<25	158	3.37 (2.15-6.33)		158	5.58 (2.45-10.4)		157	0.98 (0.78-1.25)		157	12.0 (10.3-15.1)	
25-29.9	320	3.10 (1.87-4.99)		320	8.15 (4.88-17.0)		318	1.41 (1.08-1.81)		319	13.3 (10.9-16.0)	
≥30	149	3.03 (1.80-4.84)	0.11	149	15.6 (9.91-28.4)	<.0001	148	1.69 (1.32-2.06)	<.0001	149	13.6 (11.5-15.4)	0.003
Physical activity quartiles (in hrs/wk)[†]												
Q1 (0-3.3)	156	3.16(1.93-4.75)		156	14.4 (6.82-25.6)		154	1.50 (1.14-2.01)		156	13.2 (11.0-16.1)	
Q2 (3.4-6.7)	156	3.19 (1.96-5.09)		156	9.26 (4.88-18.2)		155	1.37 (0.96-1.74)		155	12.8 (10.8-15.2)	
Q3 (6.8-12.0)	156	3.01 (1.75-4.77)		156	9.35 (4.38-15.7)		156	1.27 (0.96-1.68)		156	12.2 (10.3-15.5)	
Q4 (12.1-91.2)	156	3.39 (2.06-5.84)	0.18	156	6.60 (3.46-11.8)	<.0001	155	1.34 (0.89-1.74)	0.0005	155	13.6 (11.4-15.8)	0.12
Race												
Caucasian	576	3.21 (1.96-5.14)		576	9.14 (4.68-17.2)		572	1.37 (0.99-1.79)		574	13.0 (10.8-15.7)	
Other	51	2.68 (1.78-3.60)	0.04	51	10.7 (4.17-20.7)	0.45	51	1.41 (0.90-1.90)	0.94	51	12.9 (10.9-15.9)	0.91
NSAID use[‡]												
No	389	3.16 (1.86-5.08)		389	8.59 (4.70-17.0)		388	1.37 (0.98-1.83)		388	13.0 (10.9-15.7)	
Yes	235	3.21 (2.07-5.12)	0.75	235	9.76 (4.53-19.8)	0.34	232	1.38 (0.98-1.74)	0.73	234	13.0 (10.7-15.6)	0.73
Dietary Intake:												

		Adiponectin (ng/mL)			Leptin (ng/mL)			C-peptide (ng/mL)			Homocysteine (μM/L)	
T1 Characteristics	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****	***n***	**Median (IQR)**	***P-value****
Fat (% kcal)												
Q1 (15.2-28.3)	158	3.37 (2.10-5.83)		158	7.41 (3.88-15.8)		157	1.26 (0.98-1.67)		157	12.7 (10.4-15.4)	
Q2 (28.4-34.1)	155	2.84 (1.56-4.98)		155	10.5 (4.48-19.0)		153	1.29 (0.90-1.73)		154	12.6 (10.5-15.3)	
Q3 (34.3-39.3)	157	3.13 (1.85-4.84)		157	8.43 (5.18-17.8)		156	1.42 (1.09-1.81)		157	13.2 (11.2-15.6)	
Q4 (39.4-54.8)	156	3.12 (2.08-4.91)	0.14	156	10.0 (4.94-18.0)	0.05	156	1.44 (1.09-1.95)	0.0008	156	13.5 (11.2-16.1)	0.01
Fiber (g/1,000 kcal)												
Q1 (2.21-7.34)	157	3.02 (2.02-4.60)		157	9.06 (3.98-15.1)		157	1.44 (1.08-1.97)		157	13.9 (12.0-17.1)	
Q2 (7.35-9.55)	156	3.35 (2.26-4.95)		156	10.2 (5.32-21.9)		155	1.41 (1.01-1.77)		156	12.9 (10.9-15.2)	
Q3 (9.56-12.5)	157	3.00 (1.76-5.34)		157	9.05 (5.18-17.3)		157	1.28 (0.93-1.73)		157	12.5 (10.6-14.9)	
Q4 (12.6-28.5)	156	3.28 (1.77-5.98)	0.66	156	7.63 (4.18-15.9)	0.02	153	1.27 (0.94-1.70)	0.003	154	12.6 (10.3-15.4)	0.009
Fruits&Vegetables (servings/1,000 kcal)												
Q1 (0.33-1.45)	157	3.17 (1.99-4.68)		157	8.17 (4.02-14.7)		156	1.45 (1.12-1.96)		157	13.9 (11.8-16.4)	
Q2 (1.46-2.05)	156	3.08 (2.02-5.04)		156	7.61 (3.84-16.4)		156	1.38 (0.98-1.83)		156	13.5 (11.2-16.2)	
Q3 (2.06-2.72)	157	3.15 (1.92-4.74)		157	9.67 (5.75-19.6)		156	1.38 (0.96-1.76)		157	12.3 (10.4-15.0)	
Q4 (2.73-5.50)	156	3.30 (1.79-6.02)	0.84	156	10.4 (4.84-19.6)	0.24	154	1.23 (0.92-1.61)	0.002	154	12.0 (10.3-14.8)	0.002
Flavonols (mg/1,000 kcal)												
Q1 (1.11-7.68)	157	3.12 (2.01-4.68)		157	9.71 (4.70-16.3)		156	1.47 (1.12-1.96)		156	13.4 (9.81-19.5)	
Q2 (7.69-11.8)	156	3.22 (1.97-5.32)		156	8.83 (3.86-19.1)		155	1.35 (0.97-1.79)		156	13.3 (11.5-16.2)	
Q3 (11.9-17.7)	157	2.85 (1.57-4.60)		157	8.72 (4.29-19.0)		157	1.41 (1.04-1.78)		157	13.0 (10.9-15.7)	
Q4 (17.8-75.9)	156	3.32 (2.06-6.04)	0.36	156	9.01 (5.11-17.3)	0.11	154	1.21 (0.89-1.53)	0.0007	155	12.1 (10.2-14.6)	0.006
Dry Beans (g/1,000 kcal)												
Q1 (0-1.56)	157	2.99 (1.99-4.65)		157	9.38 (4.69-15.9)		156	1.40 (0.97-1.91)		157	13.7 (11.3-16.0)	
Q2 (1.57-3.77)	156	3.33 (1.96-5.22)		156	9.34 (4.43-18.6)		155	1.39 (0.96-1.82)		155	13.2 (11.0-16.2)	
Q3 (3.78-7.90)	157	3.24 (1.84-4.93)		157	9.38 (5.18-18.9)		156	1.37 (1.08-1.73)		157	12.5 (10.8-14.9)	
Q4 (7.91-58.5)	156	3.13 (2.03-5.82)	0.33	156	8.38 (4.11-15.3)	0.35	155	1.25 (0.97-1.76)	0.49	155	13.0 (10.3-15.3)	0.03

* *P* values for differences in medians were calculated using Wilcoxon rank sum test (2-group comparison) and Kruskal-Wallis test (comparison of > 2 groups). *P* values for trend of dietary intake characteristics were calculated using a multiple regression model adjusting for the baseline characteristics of age (in quartiles: <56, 56-63, 64-69, >69 yrs), sex, BMI (<25, 25.0-29.9, ≥30 kg/m^2), and regular NSAID use.

† Physical activity was defined as self-reported time typically spent for any type of moderate or vigorous physical activity in hrs/wk.

‡Regular NSAID use was defined as taking medication ≥ 1 monthly.

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Table 3

Medians (interquartile ranges) of serum adiponectin, leptin, C-peptide, and homocysteine concentrations at T1 in the control arm of the Polyp Prevention Trial by adenoma recurrence at T4[*]

		Adiponectin (ng/mL)			Leptin (ng/mL)			C-peptide (ng/mL)			Homocysteine (μM/L)	
Outcome	***n***	**Median (IQR)**	***P-value*[†]**	***n***	**Median (IQR)**	***P-value*[†]**	***n***	**Median (IQR)**	***P-value*[†]**	***n***	**Median (IQR)**	***P-value*[†]**
Total	627	3.16 (1.94-5.10)		627	9.31 (4.63-17.4)		623	1.37 (0.98-1.80)		625	13.0 (10.8-15.7)	
No polyp	277	3.29 (2.03-5.56)		277	10.5 (5.89-20.7)		274	1.34 (0.96-1.80)		276	12.5 (10.5-14.7)	
Non-adenomatous polyps only	108	2.97 (1.60-5.21)	0.29	108	7.22 (3.55-19.6)	0.06	107	1.32 (0.92-1.69)	0.80	107	13.4 (10.8-16.4)	0.02
Any adenoma	242	3.08 (1.82-4.74)	0.15	242	7.79 (4.30-13.9)	0.0008	242	1.42 (1.05-1.88)	0.06	242	13.7 (11.2-16.3)	0.0004
One adenoma	140	3.14 (1.88-4.60)	0.33	140	8.15 (4.35-14.1)	0.002	140	1.41 (1.00-1.85)	0.26	140	13.6 (11.1-16.3)	0.006
Multiple adenoma	102	2.98 (1.80-4.80)	0.17	102	8.16 (4.35-14.0)	0.03	102	1.45 (1.15-1.97)	0.05	102	13.8 (11.4-16.1)	0.03
Low risk adenoma	174	3.14 (1.78-4.84)	0.26	174	7.76 (4.49-14.2)	0.004	174	1.39 (1.03-1.80)	0.34	174	13.6 (11.1-16.3)	0.004
High risk adenoma	68	3.03 (1.98-4.60)	0.21	68	7.92 (3.86-13.3)	0.02	68	1.52 (1.16-2.00)	0.01	68	14.4 (11.6-16.2)	0.003
Non-advanced adenoma	209	3.10 (1.80-4.80)	0.22	209	8.15 (4.35-14.1)	0.002	209	1.41 (1.08-1.83)	0.09	209	13.7 (11.4-16.2)	0.0007
Advanced adenoma	33	3.03 (2.01-4.03)	0.25	33	7.34 (3.87-12.9)	0.04	33	1.46 (0.99-2.03)	0.24	33	14.2 (11.1-16.6)	0.07

[*] Advanced adenoma is defined as ≥ 1 adenoma of ≥ 1 cm in size, having ≥ 25% villous component, or exhibiting high-grade dysplasia. High risk adenoma is defined as ≥ 1 advanced adenoma or ≥ 3 adenoma; in contrast low risk adenoma is defined as 1 or 2 adenoma and no advanced adenoma.

[†] All comparisons against the no polyp group using the Wilcoxon rank sum test.

Table 4

Association between serum adiponectin, leptin, C-peptide, and homocysteine at T1 and adenoma recurrence at T4[*] (n = 519)

Metabolic Indicator Quartiles	*Control n (%)*	*Case n (%)*	Any Adenoma OR (95% CI)[†]	*Case n (%)*	Multiple Adenoma OR (95% CI)[†]	*Case n (%)*	High Risk Adenoma OR (95% CI)[†]	Metabolic Indicator Tertiles[§]	*Control n (%)*	*Case n (%)*	Advanced Adenoma OR (95% CI)[†]
Adiponectin (ng/mL)											
Q1 (0.08-1.94)	62 39.5	66 42.0	1[‡]	30 19.1	1[‡]	15 9.6	1[‡]	**Q1** (0.08-2.41)	82 39.2	11 5.3	1[‡]
Q2 (1.94-3.16)	69 43.9	59 37.6	0.87 (0.52-1.44)	24 15.3	0.73 (0.38-1.41)	22 14.0	1.38 (0.64-3.00)	**Q2** (2.43-4.04)	98 46.7	14 6.7	1.20 (0.50-2.89)
Q3 (3.1[?]-5.10)	67 42.7	68 43.3	1.05 (0.64-1.73)	26 16.6	0.88 (0.45-1.70)	21 13.4	1.46 (0.66-3.22)	**Q3** (4.05-17.4)	97 46.6	8 3.8	0.61 (0.22-1.70)
Q4 (5.11-17.4)	79 50.6	49 31.4	0.70 (0.41-1.18)	22 14.1	0.67 (0.34-1.33)	10 6.4	0.64 (0.25-1.61)				
***P*-trend**			0.24		0.34		0.30				0.30
Leptin (ng/mL)											
Q1 (0.63-4.64)	55 35.0	66 42.0	1[‡]	29 18.5	1[‡]	20 12.7	1[‡]	**Q1** (0.63-6.06)	72 34.4	14 6.7	1[‡]
Q2 (4.65-9.31)	66 42.0	68 43.3	0.86 (0.51-1.45)	24 15.3	0.79 (0.40-1.58)	16 10.2	0.78 (0.35-1.73)	**Q2** (6.07-13.9)	94 44.8	14 6.7	0.66 (0.27-1.61)
Q3 (9.3[?]-17.3)	73 46.5	63 40.1	0.78 (0.45-1.37)	28 17.8	0.78 (0.38-1.59)	21 13.4	0.92 (0.41-2.07)	**Q3** (14.0-185)	111 53.4	5 2.4	0.22 (0.06-0.79)
Q4 (17.4-185)	83 53.2	45 28.8	0.64 (0.32-1.28)	21 13.5	0.69 (0.29-1.67)	11 7.1	0.58 (0.20-1.64)				
***P*-trend**			0.22		0.50		0.34				0.02
C-peptide (ng/mL)											
Q1 (0.13-0.98)	74 47.4	52 33.3	1[‡]	18 11.5	1[‡]	11 7.1	1[‡]	**Q1** (0.13-1.13)	104 49.5	10 4.8	1[‡]
Q2 (0.99-1.37)	77 48.4	56 35.2	0.94 (0.56-1.57)	26 16.4	1.20 (0.59-2.44)	24 8.8	1.07 (0.44-2.62)	**Q2** (1.14-1.63)	81 39.3	9 4.4	0.98 (0.36-2.66)
Q3 (1.38-1.80)	57 37.0	67 43.5	1.49 (0.86-2.58)	28 18.2	1.65 (0.78-3.49)	19 12.3	1.91 (0.79-4.66)	**Q3** (1.64-4.50)	57 37.0	14 6.8	1.44 (0.53-3.88)
Q4 (1.81-4.50)	66 43.0	67 43.5	1.13 (0.65-1.97)	30 19.5	1.33 (0.62-2.85)	24 15.6	1.79 (0.74-4.34)				
***P*-trend**			0.49		0.46		0.14				0.45
Homocysteine (μM/L)											

Metabolic Indicator Quartiles	*Control n (%)*	*Case n (%)*	Any Adenoma OR (95% CI)[†]	*Case n (%)*	Multiple Adenoma OR (95% CI)[†]	*Case n (%)*	High Risk Adenoma OR (95% CI)[†]	Metabolic Indicator Tertiles[§]	*Control n (%)*	*Case n (%)*	Advanced Adenoma OR (95% CI)[†]
Q1 (4.78-10.8)	81 51.3	49 31.0	1[‡]	19 12.0	1[‡]	12 7.6	1[‡]	**Q1** (4.78-11.5)	103 49.3	11 5.3	1[‡]
Q2 (10.8-13.0)	78 49.7	58 36.9	1.04 (0.62-1.74)	25 15.9	1.06 (0.52-2.15)	18 11.5	1.16 (0.50-2.69)	**Q2** (11.6-14.7)	106 50.7	6 2.9	0.40 (0.14-1.16)
Q3 (13.1-15.6)	73 46.8	58 37.2	1.04 (0.61-1.78)	26 16.7	1.06 (0.51-2.18)	16 10.3	1.00 (0.42-2.40)	**Q3** (14.8-79.8)	67 32.4	16 7.7	1.66 (0.67-4.16)
Q4 (15.7-79.8)	44 28.6	77 50.0	2.26 (1.30-3.94)	32 20.8	2.11 (1.01-4.40)	22 14.3	2.11 (0.89-4.97)				
***P*-trend**			0.003		0.03		0.08				0.16

[*] The 108 of the 627 participants with non-adenomatous polyps only were excluded from the analysis. Advanced adenoma is defined as ≥ 1 adenoma of ≥ 1 cm in size, having ≥ 25% villous component, or exhibiting high-grade dysplasia. High risk adenoma is defined as ≥ 1 advanced adenoma or ≥ 3 adenoma.

[†] All comparisons against the no polyp group (control). Multivariate OR and 95% CI models were adjusted for the baseline characteristics of age (in quartiles: <56, 56-63, 64-69, >69 yrs), sex, BMI (<25, 25.0-29.9, ≥30 kg/m^2), and regular NSAID use. Regular NSAID use was defined as taking medication ≥ 1 monthly.

[‡] Reference category.

[§] Tertiles used for advanced adenoma due to small number