*Null Results in Brief*

# Serum Adiponectin is not Associated with Risk of Colorectal Cancer

**Annekatrin Lukanova,[1,2] Stefan Söderberg,[3] Rudolf Kaaks,[5] Egil Jellum,[6] and Pär Stattin[4]**

[1]Department of Obstetrics and Gynecology, New York University School of Medicine, New York; [2]Nutritional Research and [3]Medicine, Department of Public Health and Clinical Medicine; [4]Urology and Andrology, Department of Surgery and Perioperative Sciences, Umeå University Hospital, Umeå, Sweden; [5]Hormones and Cancer Unit, IARC, Lyon, France; and [6]Institute of Clinical Biochemistry, Rikshospitalet, Oslo, Norway

## Introduction

Obesity, an established risk factor for colorectal cancer, is characterized by the accumulation of excessive adipose tissue, which is the source of a variety of biologically active substances, collectively referred to as adipokines (1). Adipokines may mediate the effect of overweight and obesity on disease development, and we have previously shown that prediagnostic concentrations of the adipokine leptin are directly associated with the risk of colon cancer (2).

Adiponectin, an adipokine *decreased* in obesity, is inversely associated with the development of insulin resistance and has a strong anti-inflammatory function (3). Low levels of adiponectin may thus provide a link between obesity and risk of colorectal cancer. In support, a recent case-control study reported that patients with colorectal adenomas (established precursors of colorectal cancer) had lower adiponectin levels than healthy subjects (4).

We tested the hypothesis that prediagnostic adiponectin is inversely associated with the risk of colorectal cancer in a case-control study nested among men from the Janus Project in Norway.

## Materials and Methods

The Janus Project and the nested case-control study on colorectal cancer in men have been described in detail previously (2). In brief, prediagnostic (≥3 months) serum samples from 381 colorectal cancer cases, and 381 matched controls were available for the study. Specifically, there were 237 (62%) colon cancers and 144 (38%) rectal cancers. Controls were randomly selected from all male Janus Project participants alive and free of cancer at the time of diagnosis of the index case, and who matched the case on county of residence, age (±1 year), and date at blood sampling (±2 months). The study was approved by the research ethical committees of Rikshospitalet, Oslo, Norway and Umeå University Hospital, Umeå, Sweden.

**Laboratory Analyses.** Samples pertaining to matched cases and controls were always analyzed together in the same batch and laboratory personnel were unable to distinguish among cases and controls. Serum adiponectin was determined by double antibody RIA from Linco Research, Inc., St. Louis, MO. The mean intrabatch coefficient of variation, calculated from four quality control samples randomly inserted in each batch was 5.3%. Duplicate measurements of adiponectin, available for 39 subjects, correlated almost perfectly ($r$ = 0.99). Serum samples donated about 1 year apart (mean, 11.3 months; range, 3.5-12.9) available for 80 Janus participants, not part of the present study, were used to assess the reproducibility of adiponectin measurements over time.

Leptin and C-peptide concentrations or study participants have been analyzed previously by RIAs from Linco Research and DSL (Webster, TX), with mean intra-batch coefficients of variation of 4.8% and 6.8%, respectively (2).

The relationship between hormone variables was evaluated by Spearman partial correlations and the reproducibility of adiponectin measurements by intra-class correlations. Conditional logistic regression analyses was used to estimate odds ratios and 95% confidence intervals. All analyses were conducted with SAS statistical software, version 11 (SAS Institute, Cary, NC).

With 381 cases and 381 controls, we had 80% power (at a two-sided significance level of 0.05) to detect an odds ratio of 1.74 (or 0.57) across quartiles of hormone distribution (assuming normal exposure distributions, rare disease, and a log-linear relationship of exposure with disease risk).

## Results

The median age at recruitment of study participants was 44 years. The median follow-up time was 17.3 years and only two cases were diagnosed <6 months after blood collection. The median age at cancer diagnosis was 60.8 years. The median time between blood sampling and adiponectin analysis was 28.7 years.

The median and interquartile range of adiponectin measurements in samples collected on average 12 months apart were similar [5.85 μg/mL (4.35-7.45) and 5.60 μg/mL (4.30-7.25), respectively]. The intra-class correlation between the repeated measurements was 0.71 (95% confidence intervals, 0.58-0.80). Median adiponectin concentrations were also similar in subjects with follow-up time below and above the median (6.5 versus 6.5 μg/mL, respectively), as were the concentrations in samples stored more and less than the median (6.8 versus 6.4 μg/mL, respectively). Adiponectin correlated inversely with levels of leptin ($r$ = −0.13, $P$ < 0.001) and was not correlated with C-peptide.

Mean levels of adiponectin were very similar in cases and controls and there was no association between adiponectin and risk of colorectal, colon (left and/or right, data not shown), or rectal cancer in the whole study population (Table 1) or in

Cancer Epidemiol Biomarkers Prev 2006;15(2):401–2

Received 10/31/05; accepted 12/6/05.

**Grant support:** Swedish Cancer Society, The Lions Research Foundation, and Västerbotten County Council, Umeå, Sweden.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Pär Stattin, Department of Surgery and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, 901-85 Umeå, Sweden. Phone: 46-90-7852291; Fax: 46-90-125396. E-mail: par.stattin@urologi.umu.se



doi:10.1158/1055-9965.EPI-05-0836

**Table 1. Odds ratios (95% confidence intervals) of colorectal, colon, and rectal cancer by quartiles of serum adiponectin**

| | Odds ratios (95% confidence intervals) | | | | |
|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | $P_{trend}$* |
| Colorectal cancer | | | | | |
| Adiponectin (μg/mL) | ≤4.6 | 4.6-6.3 | 6.3-8.9 | >8.9 | |
| Cases/controls | 99/95 | 77/96 | 120/95 | 85/95 | 0.97 |
| Crude model | 1.00 | 0.8 (0.5-1.2) | 1.2 (0.8-1.7) | 0.9 (0.6-1.3) | |
| Adjusted model† | 1.00 | 08 (0.5-1.2) | 1.2 (0.8-1.8) | 0.9 (0.6-1.4) | |
| Colon cancer | | | | | |
| Adiponectin (μg/mL) | ≤4.6 | 4.6-6.3 | 6.3-8.9 | >8.9 | |
| Cases/controls | 53/59 | 44/59 | 83/60 | 57/59 | 0.30 |
| Crude model | 1.00 | 0.8 (0.5-1.4) | 1.5 (0.9-2.4) | 1.1 (0.7-1.8) | |
| Adjusted model† | 1.00 | 0.8 (0.5-1.4) | 1.6 (1.0-2.6) | 1.2 (0.7-1.9) | |
| Rectal cancer | | | | | |
| Adiponectin (μg/mL) | ≤4.7 | 4.7-6.4 | 6.4-8.7 | >8.7 | |
| Cases/controls | 44/36 | 35/36 | 34/36 | 31/36 | 0.30 |
| Crude model | 1.00 | 0.8 (0.4-1.5) | 0.8 (0.4-1.5) | 0.7 (0.3-1.4) | |
| Adjusted model† | 1.00 | 0.7 (0.4-1.4) | 0.7 (0.4-1.4) | 0.6 (0.3-1.3) | |

NOTE: Conditional logistic regression, with quartile 1 as referent, cutoff points of adiponectin concentrations based on adipokine distribution in the controls.
*Test for linear trend in odds ratios over quartiles by assigning quantitative scores (1, 2, 3, and 4).
†Adjusted for levels of leptin and C-peptide (after ln-transformation).

subgroups according to median follow-up or storage time (data not shown). Adjustments for leptin and/or C-peptide had a negligible effect on the risk estimates in all adiponectin-cancer models tested.

## Discussion

In contrast to the results of several recent case-control studies on endometrial, breast, gastric cancer, and colorectal adenomas (4), in this prospective study, serum adiponectin was not related to risk of colorectal, colon, or rectal cancer in men.

In preparation for the current study, we analyzed adiponectin in serum samples donated on average 1 year apart by 80 Janus Project participants. The intra-class correlations between repeated measurements was high (0.71), implying that in a given individual, circulating adiponectin is fairly stable over an at least 1 year period. However, as the median follow-up time in our study was much longer (17 years), a single adiponectin measurement may not have been sufficient to characterize an individual's long-term exposure to the adipokine and could have decreased our ability to detect an association with cancer risk.

The lack of association cannot be explained by circadian and prandial variation of the adipokine in samples collected from nonfasting cohort members, as it has been shown that adiponectin does not experience large variations throughout the day and food intake does not influence its circulating concentrations (5). We also consider it to be unlikely that our results were substantially influenced by analyte degradation during prolonged sample storage at −25°C, as mean adiponectin concentrations and risk estimates were similar in analyses stratified by the median storage time (28.7 years). Finally, it is possible that the anti-inflammatory and insulin-sensitizing effects of the adipokine are more relevant during tumor progression to clinically overt disease.

Our results do not support the hypothesis that adiponectin is associated with long-term risk of colorectal cancer. Further studies are necessary to establish the long- and short-term involvement of this adipokine in benign and neoplastic large bowel disease.

## Acknowledgments

The Janus Serum bank owned by The Norwegian Cancer Society provided the serum samples. Randi Elin Gislefoss is the data coordinator of the Janus Serum bank, and Karin Hjertkvist, Department of Clinical Chemistry, Umeå University Hospital, did the immunoassays.

## References

1. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
2. Stattin P, Lukanova A, Biessy C, et al. Obesity and colon cancer: does leptin provide a link? Int J Cancer 2004;109:149–52.
3. Tilg H, Wolf AM. Adiponectin: a key fat-derived molecule regulating inflammation. Expert Opin Ther Targets 2005;9:245–51.
4. Otake S, Takeda H, Suzuki Y, et al. Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res 2005;11:3642–6.
5. Gavrila A, Peng CK, Chan JL, Mietus JE, Goldberger AL, Mantzoros CS. Diurnal and ultradian dynamics of serum adiponectin in healthy men: comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. J Clin Endocrinol Metab 2003;88:2838–43.

# Serum Adiponectin is not Associated with Risk of Colorectal Cancer

Annekatrin Lukanova, Stefan Söderberg, Rudolf Kaaks, et al.

*Cancer Epidemiol Biomarkers Prev* 2006;15:401-402.