

## Association of Visceral Fat Accumulation and Plasma Adiponectin with Colorectal Adenoma: Evidence for Participation of Insulin Resistance

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**Abstract Purpose:** Colorectal carcinogenesis is thought to be related to abdominal obesity and insulin resistance. To investigate whether visceral fat accumulation contributes to colorectal carcinogenesis, we examined its accumulation and the levels of the adipose tissue–derived hormone adiponectin in Japanese patients with colorectal adenoma.

**Experimental Design:** Fifty-one consecutive Japanese patients ages  $\geq 40$  years and with colorectal adenoma were subjected to measurement of visceral fat area by computed tomography scanning and plasma adiponectin concentration. The patients also underwent the 75-g oral glucose tolerance test. Insulin resistance was calculated by the homeostasis metabolic assessment (HOMA-IR) method. The controls were 52 Japanese subjects ages  $\geq 40$  years and without colorectal polyp. Cigarette smokers and subjects who consumed alcohol ( $\geq 30$  g ethanol/d) were excluded.

**Results:** The patients with colorectal adenoma showed significantly more visceral fat area and significantly less plasma adiponectin concentration in comparison with the controls [odds ratio (OR), 2.19; 95% confidence interval (95% CI), 1.47–3.28;  $P < 0.001$  and OR, 0.24; 95% CI, 0.14–0.41;  $P < 0.001$ , respectively] by logistic regression analysis. HOMA-IR index was also associated with colorectal adenoma (OR 2.60; 95% CI, 1.20–5.64;  $P = 0.040$ ). Visceral fat area and adiponectin were associated with adenoma number (1, 2,  $\geq 3$ ), the size of the largest adenoma ( $< 10$  and  $\geq 10$  mm), and adenoma histology (tubular and tubulovillous/villous).

**Conclusions:** These results suggest an association of visceral fat accumulation and decreased plasma adiponectin concentration with colorectal adenoma in Japanese patients. This study may offer a new insight to understanding the relationship of colorectal carcinogenesis with abdominal obesity and insulin resistance.

A relationship between body mass index (BMI) and increased risk for colorectal cancer has been suggested, especially for males (1). Recent reports have shown that the risk of colorectal cancer is associated with abdominal obesity with hyperinsulinemia and insulin resistance (2, 3).

Intra-abdominal adipose tissue mass has been assessed by measuring visceral fat area (VFA,  $\text{cm}^2$ ) by computed tomogra-

phy (CT) scanning at the umbilical level (4–6). The area of VFA on the CT scan was shown related to the waist-to-hip circumference ratio (7). Many reports have shown VFA association with insulin resistance, diabetes mellitus, dyslipidemia, hypertension, and coronary heart disease (4–9). However, there have been few studies addressing the association between measured values of VFA and colorectal adenoma and cancer.

The adipose tissue–derived peptide hormone adiponectin has been reported to correlate inversely with whole body adipose mass (10). A decrease in plasma adiponectin with visceral fat accumulation is associated with insulin resistance, diabetes mellitus, and coronary heart disease (11–13). Recently, a low plasma concentration of adiponectin has been thought to be associated with tissue inflammation (14–16) and cancer development (17, 18). However, there has been no report on the relationship of plasma adiponectin concentration with colorectal adenoma and cancer. To clarify the role of abdominal obesity and insulin resistance in colorectal carcinogenesis, we measured VFA and plasma adiponectin concentration in Japanese subjects with and without colorectal adenoma.

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**Grant support:** The 21st Century Center of Excellence Program of the Japan Society for the Promotion of Science grant-in-aid F-1 and Ministry of Education, Science, and Culture in Japan grant-in-aid 16046202.

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## Patients and Methods

**Patient selection.** Fifty-one consecutive Japanese patients ages  $\geq 40$  years and with histologically diagnosed colorectal adenoma were enrolled in this study. The patients underwent total colonoscopy during a voluntary health check-up or because of occult fecal blood loss at the Yamagata University Hospital and hospitals affiliated with the Osaka University between January 2001 and December 2001. Patients with hyperplastic polyps, cigarette smokers, and subjects consuming alcohol ( $\geq 30$  g ethanol/d) were excluded from this study. Also excluded were those with a history of colectomy, gastrectomy, or colorectal polypectomy and those under dietary or drug treatment for diabetes mellitus. Three of the 51 patients had rectal adenoma. The controls were 52 consecutive Japanese subjects ages  $\geq 40$  years and without colorectal polyp or inflammatory bowel diseases, who underwent total colonoscopy because of a voluntary health check-up or occult fecal blood loss during the same period and at the same hospitals, with the same exclusion criteria. The controls were drawn from the same population as the patients with colorectal adenoma. The response rates for agreed participation in this study were 91% for cases and 87% for controls.

This study protocol was approved from the Yamagata University Faculty of Medicine Ethical Committee. Written informed consent was obtained in advance from all subjects.

**Assays.** A 75-g oral glucose tolerance test was done after the subjects had fasted overnight. A Teflon catheter was inserted into the antecubital vein for blood sampling, and samples were obtained for plasma glucose and free insulin concentrations in the basal period and after an oral glucose load at 30-minute intervals for 180 minutes. The subjects were classified as normal, impaired glucose tolerance, or diabetes mellitus in accordance with the WHO criteria (19). Insulin resistance was calculated by the homeostatic metabolic assessment (HOMA-IR) method as follows:  $\text{HOMA-IR} = \text{fasting plasma insulin} \times \text{fasting plasma glucose} / 405$ , whereas insulin is expressed in microunits/mL and glucose in mg/d (20). Venous blood for assay of plasma concentration of adiponectin was drawn from all subjects after overnight fasting. Plasma samples were kept at  $-80^\circ\text{C}$  for subsequent assay. The plasma concentration of adiponectin was determined with a sandwich ELISA system (adiponectin ELISA kit, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) as previously reported (10). Body weight and height were recorded, and body mass index (BMI,  $\text{kg}/\text{m}^2$ ) was used as a measure of obesity.

**Measurement of visceral fat area.** The intra-abdominal visceral fat area (VFA) was measured at the level of the umbilicus by CT scan according to a procedure previously described (21). The border of the intra-abdominal cavity was outlined on the CT image, and VFA was quantified using standard software. The CT measurements were made blinded to case status. The coefficient of variation of these measurements by a single observer was  $<1.5\%$ , and that of variation for day-to-day measurements was  $<1\%$ . All CT scans were carried out using a CT scanner (General Electric Co., Fairfield, CT) with the subjects in a supine position.

**Statistics.** Differences of age, gender, fasting glucose, and insulin concentration, oral glucose tolerance test status, HOMA-IR, BMI, VFA, and plasma adiponectin concentration between patients and controls were assessed by Wilcoxon rank sum test or  $\chi^2$  test. The relationship of VFA or plasma adiponectin with colorectal adenoma was determined using a logistic regression method (SAS Software Release 8.2, SAS Institute, Inc., Cary, NC) to obtain the odds ratio (OR) and 95% confidence interval (95% CI). Continuous variables were used for age, BMI, HOMA-IR, VFA, and plasma adiponectin concentration. The association of adenoma number with VFA or adiponectin was assessed by the nonparametric Jonckheere test. The association of other tumor characteristics such as the largest size of adenoma and histology of the adenoma with VFA or adiponectin was assessed by Wilcoxon rank sum test.  $P < 0.05$  was considered statistically significant.

## Results

Age was not significantly different between the patients ( $59 \pm 7.3$  years, mean  $\pm$  SD) with colorectal adenoma and the controls ( $58 \pm 7.1$ ; Wilcoxon rank sum test; Table 1). The patient group consisted of 35 males and 16 females, whereas the control group had 34 males and 18 females. No difference in gender was observed between the patients and the controls ( $\chi^2$  test). Fasting plasma glucose concentration was not different between the two groups. Fasting insulin concentration was not significantly different between the two groups, although it tended to be higher in patients with colorectal adenoma ( $8.5 \pm 2.3$  microunits/mL) than in controls ( $6.1 \pm 1.8$ ;  $P = 0.11$ ). Oral glucose tolerance test status was also not different between the two groups (normal/impaired glucose

**Table 1.** Baseline characteristics of Japanese patients with colorectal adenoma and controls (Wilcoxon rank sum test or  $\chi^2$  test)

Variable	Patients with adenoma (n = 51), $\pm$ SD	Controls (n = 52)	P
Age (y)	$59 \pm 7.3$	$58 \pm 7.1$	$>0.2$
Gender			
Male	35	34	$>0.2$
Female	16	18	
Fasting glucose (mg/d)	$105 \pm 21$	$91.9 \pm 18.9$	$>0.2$
Fasting insulin (microunits/mL)	$8.5 \pm 2.3$	$6.1 \pm 1.8$	0.11
HOMA-IR	$2.2 \pm 0.7$	$1.4 \pm 0.5$	0.032
OGTT			
Normal	28	36	$>0.2$
IGT	14	11	
DM	9	5	
BMI ( $\text{kg}/\text{m}^2$ )	$23.6 \pm 2.9$	$22.8 \pm 2.6$	0.14
VFA ( $\text{cm}^2$ )	$98.9 \pm 36.3$	$66.6 \pm 29.5$	$<0.001$
Adiponectin ( $\mu\text{g}/\text{mL}$ )	$7.0 \pm 2.6$	$10.6 \pm 2.5$	$<0.001$

Abbreviations: OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; DM, diabetes mellitus.

tolerance/diabetes mellitus were 28:14:9 in patients and 36:11:5 in controls;  $\chi^2$  test). However, HOMA-IR index was significantly higher in the patient than in controls ( $2.2 \pm 0.7$  versus  $1.4 \pm 0.5$ ;  $P = 0.032$ ). BMI was not significantly different between the patients ( $23.6 \pm 2.9$ ) with colorectal adenoma and the controls ( $22.8 \pm 2.6$ ), although there was a tendency to be higher in the patient group ( $P = 0.14$ ).

The mean of VFA was  $98.9 \pm 36.3 \text{ cm}^2$  in patients with colorectal adenoma, whereas it was  $66.6 \pm 29.5 \text{ cm}^2$  in controls (Fig. 1). This indicated significant accumulation of visceral adipose tissue in patients with colorectal adenoma ( $P < 0.001$ ; Wilcoxon rank sum test). In addition, the mean of plasma adiponectin was  $7.0 \pm 2.6 \text{ }\mu\text{g/mL}$  in patients, whereas it was  $10.6 \pm 2.5$  in controls, indicating that plasma adiponectin concentration was significantly lower in patients with colorectal adenoma ( $P < 0.001$ ). BMI, VFA, and plasma adiponectin showed high correlation with each other (BMI versus VFA, Pearson's correlation coefficient  $r = 0.683$ ,  $P < 0.001$ ; BMI versus adiponectin,  $r = -0.600$ ,  $P < 0.001$ ; VFA versus adiponectin  $r = -0.677$ ,  $P < 0.001$ ).

The numbers of adenomas were 1 in 23 patients, 2 in 13, and  $\geq 3$  in 15. The size of the largest adenoma was  $< 10 \text{ mm}$  in 41 patients and  $\geq 10 \text{ mm}$  in 10 patients. The histology was that of tubular adenoma in 44 patients, tubulovillous in five patients, and villous in two patients.

Logistic regression analysis showed that both VFA and plasma adiponectin concentration were significantly associated with colorectal adenoma (OR, 2.19; 95% CI, 1.47-3.28;  $P < 0.001$  and OR, 0.24; 95% CI, 0.14-0.41;  $P < 0.001$ , respectively; Table 2). HOMA-IR index was also associated with colorectal adenoma (OR, 2.60; 95% CI, 1.20-5.64;  $P = 0.040$ ). These observations suggested an association of insulin resistance with colorectal adenoma.

VFA and plasma adiponectin concentration were associated with tumor number ( $P < 0.01$  and  $P < 0.05$ , respectively; Jonckheere test; Table 3). In addition, VFA and adiponectin were associated with the size of the largest adenoma ( $P < 0.01$  and  $P < 0.01$ , respectively; Wilcoxon rank sum test) and the histology of the adenoma ( $P < 0.01$  and  $P < 0.05$ , respectively; Wilcoxon rank sum test).

**Table 2.** Factors associated with colorectal adenoma in Japanese patients assessed by logistic regression analysis

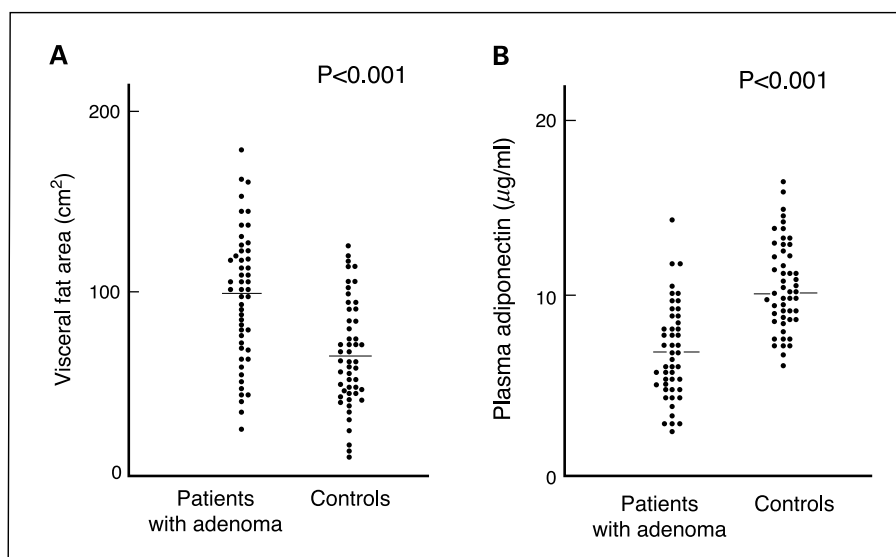
Variable	Odds ratio (95% confidence interval)	P
Age (y)	1.00 (0.95-1.06)	$> 0.2$
Gender (male versus female)	1.16 (0.51-2.64)	$> 0.2$
BMI ( $\text{kg}/\text{m}^2$ )	1.11 (0.96-1.28)	0.16
HOMA-IR	2.60 (1.20-5.64)	0.040
IGT versus normal	1.64 (0.65-4.16)	$> 0.2$
DM versus normal	2.31 (0.70-7.68)	0.17
VFA ( $\text{cm}^2$ )	2.19 (1.47-3.28)	$> 0.001$
Adiponectin ( $\mu\text{g}/\text{mL}$ )	0.24 (0.14-0.41)	$> 0.001$

Abbreviations: IGT, impaired glucose tolerance; DM, diabetes mellitus.

## Discussion

Abdominal obesity, which is known to correlate strongly with visceral fat accumulation (4, 6), has been linked to cardiovascular disease (22), diabetes mellitus (5, 23), and overall mortality (24). Data have suggested that abdominal obesity might also be associated with colon (2, 3), breast (25), and prostate (26) neoplasia. Epidemiologic studies have shown an association between waist circumference and waist-to-hip ratio and colon neoplasia (2, 3).

In this study, we examined whether VFA is associated with colorectal adenoma in Japanese patients. The results suggested that visceral fat accumulation is a risk factor of colon adenoma. To our knowledge, this is the first report to show an association between measured VFA and colorectal adenoma. On the other hand, BMI was not significantly associated with colorectal adenoma. Schoen et al. (2) reported that higher levels of waist-to-hip circumference, but not BMI, were significantly associated with colorectal cancer. These data suggest that visceral adipose



**Fig. 1.** A, comparison of VFA between Japanese patients with colorectal adenoma and controls in Japanese patients. VFA is significantly greater in the patients than in the controls ( $P < 0.001$ , Wilcoxon rank sum test). Bar, mean value of VFA in the patients and controls. B, comparison of plasma adiponectin concentration between Japanese patients with colorectal adenoma and controls. The adiponectin concentration is significantly lower in the patients than in the controls ( $P < 0.001$ , Wilcoxon rank sum test). Bar, mean value of plasma adiponectin concentration in the patients and controls.

**Table 3.** Association of adenoma number, size of the largest adenoma, and histology of adenoma with VFA or plasma adiponectin concentration in Japanese patients with colorectal adenoma

Variables	Adenoma number			P*	Size of the largest adenoma		P†	Histology of adenoma		
	1 (n = 23)	2 (n = 13)	≥3 (n = 15)		>10 mm (n = 41)	≤10 mm (n = 10)		T (n = 44)	TV/V (n = 7)	P†
VFA (cm <sup>2</sup> )										
Median	80	110	118	<0.01	92	114	<0.01	97	138	<0.01
Minimum	35	26	51		26	98		26	98	
Maximum	146	161	179		154	179		154	179	
Adiponectin (μg/mL)										
Median	7.9	6.0	5.7	<0.05	7.5	5.1	<0.01	7.1	5.0	<0.05
Minimum	4.6	2.8	2.9		2.8	5.1		2.8	2.9	
Maximum	14.4	12.0	9.0		14.4	8.2		14.4	8.2	

Abbreviations: T, tubular; TV, tubulovillous; V, villous.  
\*Jonckheere test.  
†Wilcoxon rank sum test.

tissue rather than whole body adipose tissue is associated with colorectal adenoma.

Plasma adiponectin concentration is known to decrease with obesity, especially in abdominal obesity in association with insulin resistance (27–32) and atherosclerosis (12, 33). In this study, we showed that decrease in plasma adiponectin concentration is a factor associated with the development of colorectal adenoma in Japanese patients. Low concentration of plasma adiponectin may be a risk factor of colorectal adenoma. Adiponectin also seems to participate in regulating inflammation and apoptosis possibly via inhibition of nuclear factor  $\kappa$ B signaling (14, 34). Recently, an association has been thought to exist between reduced adiponectin in blood and carcinogenesis (17, 18, 35). This study offers a new insight towards understanding the role of insulin resistance in colorectal carcinogenesis.

Logistic regression analysis showed that oral glucose tolerance test status, normal, impaired glucose tolerance, and diabetes mellitus did not show association with colorectal adenoma in this study. Several reports have shown that impaired glucose intolerance was associated with colorectal tumors (2, 36). These were large-scale studies for risks of colorectal cancer. Our findings may have been due to the small number of subjects. However, HOMA-IR index was associated with colorectal adenoma. Taken together with increased VFA and decreased plasma concentration of adiponectin, it seems that insulin resistance is associated with colorectal adenoma.

The number of colorectal adenomas and the size of the largest adenoma showed association with increased VFA and

decreased plasma adiponectin in this study. Histologic progression from tubular adenoma to tubulovillous/villous adenoma was also associated with increased VFA and decreased plasma adiponectin. Much epidemiologic evidence has suggested that the insulin-like growth factor-I (IGF-I) axis is associated with colorectal cancer risk (37). The Physician's Health Study showed that after adjustment for age, cigarette smoking, BMI, alcohol intake, and IGF-I binding protein-3 levels, men in the top quintile of circulating IGF-I had a relatively higher risk compared with those in the bottom quintile (38). Results from the Flexi-Scope trial also showed that high IGF-I and low IGFBP-3 levels increased the probability of high-risk adenomas, defined as at least one adenoma  $\geq 1$  cm in diameter of tubulovillous or villous morphology or with severe dysplasia or the presence of three or more adenomas (39). Further study is needed to examine whether there is a straightforward relationship between VFA and IGF-I and IGFBP-3.

In conclusion, our findings suggest that increased VFA and decreased concentration of plasma adiponectin are associated with the development of colon adenoma in Japanese patients. However, as this study was done with a small number of patients, a large-scale study is needed to clarify the association of visceral fat accumulation and adiponectin with the development of colon adenoma and cancer. Similar studies are also needed with other ethnic groups, including Caucasians and other Asians. Such research may warrant an intervention study on whether reduction of visceral fat accumulation and plasma adiponectin by weight loss and exercise (40) can prevent further development of colorectal adenoma.

## References

- Potter JD, Slatter ML, Bostick RM, et al. Colon cancer: a review of the epidemiology. *Epidemiol Rev* 1993;15: 499–545.
- Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999;91: 1147–54.
- Giovannucci E, Aasheri A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995;122: 327–34.
- Fujioka S, Matsuzawa Y, Tokunaga K, et al. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987;36:54–9.
- Matsuzawa Y. Pathophysiology and molecular mechanisms of visceral fat syndrome: the Japanese experience. *Diabetes Metab Res Rev* 1997;13:3–13.
- Shuman WP, Newell-Morris LL, Leonetti DL, et al. Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol* 1986;21: 483–7.
- Seidell JG, Oosterlee A, Thijssen MA, et al. Assessment of intra-abdominal and subcutaneous abdominal fat: relation between anthropometry and computed tomography. *Am J Clin Nutr* 1987;45:7–13.
- Nieves DJ, Cnop M, Retzlaff B, et al. The atherogenic

- lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. *Diabetes* 2003;52:172–9.
9. Kanai H, Tokunaga K, Fujioka S, et al. Decrease in intra-abdominal visceral fat may reduce blood pressure in obese hypertensive women. *Hypertension* 1996;27:125–9.
  10. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;257:79–83.
  11. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;20:1595–9.
  12. Kumada M, Kihara S, Sumitsuiji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003;23:85–9.
  13. Kondo H, Shimomura I, Matsukawa Y, et al. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. *Diabetes* 2002;51:2325–8.
  14. Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- $\kappa$ B signaling through a cAMP-dependent pathway. *Circulation* 2000;102:1296–301.
  15. Ouchi N, Kihara S, Funahashi T, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* 2003;107:671.
  16. Engeli S, Feldpausch M, Gorzelniak K, et al. Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 2003;52:942–7.
  17. Petridou E, Mantzoros C, Dessypris N, et al. Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. *J Clin Endocrinol Metab* 2003;88:993–7.
  18. Miyoshi Y, Funahashi T, Kihara S, et al. Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 2003;15:5699–704.
  19. The Expert Committee. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;20:11833–1197.
  20. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000;23:57–63.
  21. Tokunaga K, Matsuzawa Y, Ishikawa K, et al. A novel technique for determination of body fat by computed tomography. *Int J Obes* 1983;7:437–45.
  22. Larsson B, Svardssudd K, Welin L, et al. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 1984;288:1401–4.
  23. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982;54:254–60.
  24. Folsom AR, Kaye SA, Sellers TA, et al. Body fat distribution and 5-year risk of death in older women [published erratum appears in *JAMA* 1993;269:1254]. *JAMA* 1993;269:483–7.
  25. Sellers TA, Kushi LH, Potter JD, et al. Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer [published erratum appears in *N Engl J Med* 1992;327:1612]. *N Engl J Med* 1992;326:1323–9.
  26. Gann PH, Daviglus ML, Dyer AR, et al. Heart rate and prostate cancer mortality: results of a prospective analysis. *Cancer Epidemiol Biomarkers Prev* 1995;4:611–6.
  27. Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002;8:731–7.
  28. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;8:1288–95.
  29. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003;423:762–9.
  30. Kern PA, Di Gregorio GB, Lu T, et al. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- $\alpha$  expression. *Diabetes* 2003;52:1779–85.
  31. Goldfine AB, Kahn CR. Adiponectin: linking the fat cell to insulin sensitivity. *Lancet* 2003;362:1431–2.
  32. Snehalathan C, Mukesh B, Simon M, et al. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. *Diabetes Care* 2003;26:3226–9.
  33. Zietz B, Herfarth H, Paul G, et al. Adiponectin represents an independent cardiovascular risk factor predicting serum HDL-cholesterol levels in type 2 diabetes. *FEBS Lett* 2003;19:103–4.
  34. Yokota T, Oritani K, Ishikawa J, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 2000;96:1723–32.
  35. Mantzoros C, Petridou E, Dessypris N, et al. Adiponectin and breast cancer. *J Clin Endocrinol Metab* 2004;89:1102–7.
  36. Nishii T, Kono S, Abe H, Eguchi H, et al. Glucose intolerance, plasma insulin levels, and colon adenomas in Japanese. *Jpn J Cancer Res* 2001;92:836–40.
  37. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr* 2001;131:3109–20S.
  38. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. *J Natl cancer Inst* 1999;91:620–5.
  39. Renehan AG, Painter JE, Atkin WS, et al. High-risk colorectal adenomas and serum insulin-like growth factors. *Br J Surg* 2001;88:107–13.
  40. Kriketos AD, Gan SK, Poynten AM, et al. Exercise increases adiponectin levels and insulin sensitivity in humans. *Diabetes Care* 2004;27:629–30.

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*Clin Cancer Res* 2005;11:3642-3646.

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