

## Serum triglycerides and colorectal adenoma in a case–control study among cancer screening examinees (Japan)

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### Abstract

**Objective** Most epidemiologic studies have shown serum triglycerides to be associated with colorectal adenoma. However, whether the association can be modified by smoking is unknown. We cross-sectionally investigated the association of serum triglycerides with the risk of adenoma by smoking status.

**Methods** We identified 782 newly diagnosed adenoma cases from the examinees of a colorectal cancer screening program. All cases were diagnosed by a magnifying colonoscopy with dye spreading. We determined 738 controls without present illness or past history of adenoma from among the examinees. They provided their lifestyle information and fasting blood samples to measure their serum triglycerides. We calculated odds ratios (OR) and 95% confidence intervals (CI) of colorectal adenoma for serum triglycerides.

**Results** High serum triglycerides were associated with colorectal adenoma (OR 1.5; 95% CI 1.1–2.0 for the highest versus the lowest quartile,  $P_{\text{trend}}$ , 0.030). A stronger association was observed between three or more adenoma cases and study controls (OR 2.3; 95% CI 1.3–4.2,  $P_{\text{trend}}$ , < 0.0010). After classifying the study subjects by smoking status, a significant linear risk trend was found in ever-smokers ( $P_{\text{trend}}$ , 0.0018) but not in never-smokers ( $P_{\text{trend}}$ , 0.94;  $P_{\text{interaction}}$ , 0.067).

**Conclusions** Our results suggested that a higher serum triglyceride level may be related to a larger number of adenomas. Adenoma development involving an elevated serum triglyceride level may be modified by smoking.

**Keywords** Serum triglycerides · Smoking · Colorectal adenoma · Case–control study

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### Introduction

Physical inactivity, high body mass index, and high alcohol consumption are convincing or probable risk factors of colorectal cancer [1, 2], and also lead to hypertriglyceridemia [3]. Serum triglycerides may contribute to subsequent development of colorectal neoplasms [4].

Most epidemiologic studies [5–10] have consistently demonstrated that serum levels of triglycerides are associated with the risk of colorectal adenoma, a precursor lesion of colorectal cancer [11]. Recently, an animal study reported that an age-dependent hyperlipidemic state along with a suppressed lipoprotein lipase, which catalyzes hydrolysis of triglycerides, occurs in *Apc*-deficient mice [12]. The same study group also

showed the improvement of hyperlipidemia and the reduction of intestinal polyp formation by peroxisome proliferator-activated receptor (PPAR) agonists [12] or a lipoprotein lipase inducer without PPAR agonistic activity [13]. Moreover, the lipoprotein lipase inducer simultaneously reduces cyclooxygenase-2 expression levels [13], which are supposed to be involved in colon carcinogenesis [14]. Thus, hypertriglyceridemia is probably associated with colorectal adenoma development in humans as well as in animals.

Moreover, serum triglycerides may promote carcinogen-induced colon tumorigenesis. Some laboratory rats with hypertriglyceridemia such as Zucker obese rats [15], Nagase analbuminemic rats [16], and high-fat diet intake rats [17] are all known to be more sensitive to carcinogen treatments than rats with normal serum lipid levels. After initiating with carcinogen, a clear tumor-promoting effect of triglycerides is observed in these rats. We hypothesized that such a clear effect could be observed in those exposed to a carcinogen such as tobacco smoke. In fact, the International Agency for Research on Cancer announced that an independent effect of smoking may be weak for colorectal cancer [18]. Therefore, colorectal cancer development may need some exposure to promoting factors or environments such as hypertriglyceridemia, after initiating with tobacco smoke.

We examined the association between serum triglycerides and colorectal adenoma, and the different effects between ever- and never-smokers in a case-control study for cancer screening examinees. We conducted a colonoscopic screening with a magnifying instrument and dye spreading to identify adenoma lesions applying the pit-pattern classification. This colonoscopic diagnosis is more efficient and less time-consuming than pathologic diagnosis [19]. Moreover, the validity and reproducibility of this approach have been demonstrated [20, 21].

## Subjects and methods

### Study subjects

Study subjects were selected from 3,212 colonoscopic screening examinees during February 2004 to February 2005 who participated in the cancer screening program provided by the Research Center for Cancer Prevention and Screening, the National Cancer Center, Japan. These examinees will be annually followed by mail and then reexamined by the same screening process for the

following 5 years. Eligible examinees were 2,234 adults, after excluding those out of the age range (less than 50, or 80 or more for men; less than 40, or 80 or more for women); those with a past history of the following diseases and conditions: colorectal adenoma, any cancer, ulcerative colitis, Crohn's disease, familial adenomatous polyposis, carcinoid tumor, or colectomy; those with an unsatisfactory preparation for colonoscopy; those with an incomplete examination; those colonoscopically diagnosed as colorectal cancer. A preparatory magnesium citrate solution, which was both non-absorptive and non-secretion-inducing, was orally administered to each examinee 2 h before screening. No dietary restriction was imposed. Examinees having at least one adenoma were 782 adults (526 men and 256 women) identified by the pit-pattern classification on the magnifying colonoscopy with dye spreading (chromoendoscopy) [19] using a colonoscope (CF-H260AZI; Olympus Medical Systems Corporation, Tokyo, Japan). Of 1,452 examinees not having adenoma, 1,203 (482 men and 721 women) were eligible controls, after excluding those with inflammatory polyps, diverticulitis, submucosal tumor, bowel tuberculosis, or hyperplastic polyps. Since eligible controls were fewer than eligible cases, all 482 men were used for study controls. Of 721 eligible female controls, 256 women were selected using stratified sampling by age and screening periods of female cases. This left 782 adenoma cases and 738 controls. All examinees provided written informed consent. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan (G15-01, G16-03).

### Questionnaire

Study subjects responded to self-administered questionnaires including demographics, past medical history, family history of cancer, medication, occupation, height, weight, smoking, alcohol consumption, physical activity, working hours, reproductive factors, stress, and dietary habits. Their dietary habits were assessed by intake frequency and relative portions for 145 food items. Various nutrient and food-group intakes were estimated by multiplying the frequency, the relative portions, and the nutrient contents on the Food Composition Table for Japanese foods [22]. This food frequency questionnaire (FFQ) was modified from the FFQ for a population-based prospective study [23, 24] with additional food items. Examinees completed the questionnaire before their screening examinations.

## Blood collection and laboratory assays

Study subjects provided their samples of fasting venous blood that were drawn into vacutainer tubes for plasma or serum before any examinations. Blood samplings were mostly conducted one day before colonoscopic screening. In the blood samplings, 74% of examinees were without breakfast, i.e., overnight fasting (about 12 h), while 26% of examinees were without lunch, i.e., approximately 6 h fasting. The blood samples for plasma were divided into four 1-ml aliquots and two buffy-layers. These samples were preserved at  $-80^{\circ}\text{C}$  until analysis. The blood samples for serum were used to measure various biomarkers including serum triglycerides. Their serum triglyceride levels were measured using an enzymatic method (Kyowa Medex Co., Ltd., Tokyo, Japan) on a Hitachi 7600 auto-analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan).

## Statistical analysis

Least square means of potential risk factors for colorectal adenoma were calculated by analysis of covariance with adjustment for sex, age, and screening periods using the PROC GLM procedure. Characteristics of cases and controls were compared with the extensions of the Mantel–Haenszel procedure [25] using the PROC FREQ procedure with the CMH option. Odds ratios (OR) of colorectal adenoma for quartile categories of serum triglycerides were calculated using the logistic regression model adjusted for sex, age (less than 50, 50–54, 55–59, 60–64, 65 or more), screening periods (first, second), smoking (0, 1–29, 30–59, 60 or more pack-years), body mass index (lower than 25.0, 25.0–26.9, 27.0–29.9, 30.0 or higher; calculated by measurements at the screening examination), physical activity (METs; quartiles based on controls), alcohol consumption (0, 1–149, 150–299, 300 or more g/week ethanol), family history of colorectal cancer, aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) use, dietary fiber, folate, calcium, vitamin D, and red meat intake (quartiles based on controls; energy-adjusted by the residual method [26]). An adjustment for screening periods has two meanings. One is as a density sampling, which can serve to compare cases and controls like a cohort study. Another is as an indicator of the experience of colonoscopists, because our screening institute was established in February 2004, and all instruments were new for all colonoscopists. Togashi et al. [27] reported that diagnostic accuracy increases with the

number of experienced lesions. Serum triglyceride levels were divided into quartiles based on controls' distribution. ORs by the number of colorectal adenomas were assessed by the generalized logit model, i.e., multinomial logistic regression model. Furthermore, we examined whether the association of serum triglycerides was different between never-smokers and ever-smokers, i.e., more than 0 pack-years. The linear trend of ORs was tested using the logarithmic-transformed median serum levels of triglycerides in each category, since the measurements were log-normally distributed. Statistical interaction between serum triglycerides and smoking was assessed based on modeling serum triglycerides as a continuous variable, i.e., median values in each category, with smoking (ever = 1 or never = 0) and a one-degree of freedom test. The *p*-values for the trend and interaction were evaluated using the two-sided test with 0.05 as the significant level. We used SAS software (version 9.1; SAS institute Inc., Cary, NC) for all statistical analyses.

## Results

Adenoma cases were older, more had a family history of colorectal cancer, fewer used aspirin or other NSAIDs, more smoked, had a higher body mass index, and consumed more alcoholic beverages than controls (Table 1). Mean serum triglyceride levels were 113 mg/dl for cases and 101 mg/dl for controls ( $p < 0.0010$ ). Spearman partial rank correlation between serum triglycerides and body mass index in the controls was 0.38, adjusted for sex, age, and screening periods (data not shown in tables). Other potential confounding factors were little correlated with serum triglycerides.

The OR of colorectal adenoma for serum triglycerides was statistically significant in the highest quartile compared to the lowest quartile (OR 1.5; 95% CI 1.1–2.0; Table 2). The linear trend was also statistically significant ( $P_{\text{trend}}$ , 0.030). The greater the number of adenomas, the higher were the ORs of the highest quartile. The ORs were 1.2 (95% CI 0.85–1.8) for one adenoma, 1.5 (95% CI 0.90–2.6) for two adenomas, and 2.3 (95% CI 1.3–4.2) for three or more adenomas. Medium size (5–9 mm in diameter) adenomas were more strongly associated with serum triglycerides ( $P_{\text{trend}}$ , 0.011) than smaller (less than 5 mm;  $P_{\text{trend}}$ , 0.30) or larger ones (10 mm or more;  $P_{\text{trend}}$ , 0.22). Association of serum triglycerides did not differ among sites of the largest adenomas (data not shown in tables).

**Table 1** Characteristics of adenoma cases and controls

	Cases	Controls	<i>p</i>
<i>n</i>	782	738	
Men, <i>n</i> (%)	526 (67)	482 (65)	0.38 <sup>a</sup>
Women, <i>n</i> (%)	256 (33)	256 (35)	
First screening period, <i>n</i> (%)	322 (41)	328 (44)	0.22 <sup>b</sup>
Age, mean, year <sup>c</sup>	60.5	59.7	0.0075
Family history of colorectal cancer, <i>n</i> (%)	129 (17)	92 (12)	0.020 <sup>d</sup>
Non-steroidal anti-inflammatory drug use, <i>n</i> (%)	33 (4.2)	55 (7.5)	0.0022 <sup>d</sup>
Smoking, mean, pack-years <sup>d</sup>	15.3	9.86	<0.0010
Body mass index, mean, kg/m <sup>2</sup> <sup>d</sup>	23.0	22.5	<0.0010
Physical activity, mean, METs/day <sup>d</sup>	37.4	36.7	0.15
Alcohol consumption, mean, g/week ethanol <sup>d</sup>	153	122	0.0016
Energy intake, mean, kcal/day <sup>d</sup>	1,955	1,895	0.065
Dietary fiber intake, mean, g/day <sup>e</sup>	13.5	14.0	0.035
Folate intake, mean, μg/day <sup>e</sup>	382	394	0.064
Calcium intake, mean, mg/day <sup>e</sup>	607	620	0.44
Vitamin D intake, mean, μg/day <sup>e</sup>	8.37	7.87	0.15
Red meat intake, mean, g/day <sup>e</sup>	35.6	33.7	0.14
Serum triglycerides, mean, mg/dl <sup>d</sup>	113	101	<0.0010

*Note:* Least square means (“mean”) were calculated by analysis of covariance with adjustment for the following factors. Differences between cases and controls were tested by the extensions of the Mantel–Haenszel procedure with each adjustment

<sup>a</sup> Adjusted for age and screening periods

<sup>b</sup> Adjusted for sex and age

<sup>c</sup> Adjusted for sex and screening periods

<sup>d</sup> Adjusted for sex, age, and screening periods

<sup>e</sup> Adjusted for sex, age, screening periods, and energy intake

**Table 2** Odds ratios (OR) and 95% confidence intervals (CI) of colorectal adenoma for serum triglycerides

Range	Serum triglycerides (mg/dl)				<i>P</i> <sub>trend</sub>
	<68	68–94	95–127	128+	
Median	55	81	109	169	
Controls	176	186	184	183	
1+ adenomas	145	188	192	252	
OR <sup>1a</sup> (95% CI)	1.0 (reference)	1.2 (0.92–1.7)	1.3 (0.93–1.7)	1.7(1.2–2.2)	0.0010
OR <sup>2b</sup> (95% CI)	1.0 (reference)	1.2 (0.88–1.6)	1.1 (0.82–1.5)	1.5(1.1–2.0)	0.030
1 adenoma	95	130	98	123	
OR <sup>b</sup> (95% CI)	1.0 (reference)	1.3 (0.94–1.9)	0.93 (0.65–1.3)	1.2 (0.85–1.8)	0.59
2 adenomas	30	35	60	60	
OR <sup>b</sup> (95% CI)	1.0 (reference)	1.0 (0.58–1.7)	1.6 (0.95–2.6)	1.5(0.90–2.6)	0.058
3+ adenomas	20	23	34	69	
OR <sup>b</sup> (95% CI)	1.0 (reference)	1.0 (0.53–1.9)	1.3 (0.68–2.4)	2.3(1.3–4.2)	<0.0010

<sup>a</sup> Adjusted for sex; age (<50, 50–54, 55–59, 60–64, 65+); and screening periods (first, second)

<sup>b</sup> Adjusted for sex; age (<50, 50–54, 55–59, 60–64, 65+); screening periods (first, second); smoking (0, 1–29, 30–59, 60+ pack-years); body mass index (<25.0, 25.0–26.9, 27.0–29.9, 30.0+); physical activity (quartiles based on controls); alcohol consumption (0, 1–149, 150–299, 300+ g/week ethanol); family history of colorectal cancer; aspirin or other non-steroidal anti-inflammatory drug use; dietary fiber, folate, calcium, vitamin D, and red meat intake (quartiles based on controls; energy-adjusted)

Serum triglyceride levels were associated with colorectal adenoma in ever-smokers, but not in never-smokers (Table 3). A statistically significant OR for the highest quartile was found in ever-smokers (OR 2.0; 95% CI 1.3–3.2), in which the linear trend of OR was evident ( $P_{\text{trend}}$ , 0.0018). Serum triglyceride levels were clearly associated with three or more adenomas

(OR 3.4 for the highest versus the lowest; 95% CI 1.5–7.9;  $P_{\text{trend}}$ , < 0.0010). In contrast, no elevated OR of adenoma was shown in never-smokers (OR 1.1 for the highest versus the lowest quartile; 95% CI 0.71–1.8), where the statistical interaction between smoking and serum triglycerides was borderline significant ( $P_{\text{interaction}}$ , 0.067). A similar trend was found when

**Table 3** Odds ratios (OR<sup>a</sup>) and 95% confidence intervals (CI) of colorectal adenoma for serum triglycerides stratified by smoking

Range	Serum triglycerides (mg/dl)				<i>P</i> <sub>trend</sub>
	<68	68–94	95–127	128+	
Median	55	81	109	169	
<i>Never-smokers</i>					
Controls	108	94	103	71	
1+ adenomas	89	101	84	73	
OR (95% CI)	1.0 (reference)	1.3 (0.85–2.0)	0.87 (0.57–1.3)	1.1 (0.71–1.8)	0.94
1 adenoma	66	72	43	37	
OR (95% CI)	1.0 (reference)	1.3 (0.82–2.1)	0.64 (0.39–1.1)	0.88 (0.51–1.5)	0.24
2 adenomas	12	20	30	16	
OR (95% CI)	1.0 (reference)	1.8 (0.80–4.0)	2.3 (1.1–5.0)	1.7 (0.73–4.1)	0.18
3+ adenomas	11	9	11	20	
OR (95% CI)	1.0 (reference)	0.78 (0.29–2.1)	0.64 (0.24–1.7)	1.9 (0.76–4.6)	0.14
<i>Ever-smokers</i>					
Controls	68	92	81	112	
1+ adenomas	56	87	108	179	
OR (95% CI)	1.0 (reference)	1.3 (0.80–2.1)	1.6 (0.99–2.6)	2.0 (1.3–3.2)	0.0018
1 adenoma	29	58	55	86	
OR (95% CI)	1.0 (reference)	1.6 (0.91–2.8)	1.6 (0.87–2.8)	1.9 (1.1–3.3)	0.053
2 adenomas	18	15	30	44	
OR (95% CI)	1.0 (reference)	0.67 (0.30–1.5)	1.3 (0.64–2.7)	1.4 (0.72–2.9)	0.092
3+ adenomas	9	14	23	49	
OR (95% CI)	1.0 (reference)	1.5 (0.58–3.8)	2.2 (0.89–5.4)	3.4 (1.5–7.9)	<0.0010

<sup>a</sup> Adjusted for sex; age (<50, 50–54, 55–59, 60–64, 65+); screening periods (first, second); body mass index (<25.0, 25.0–26.9, 27.0–29.9, 30.0+); physical activity (quartiles based on controls); alcohol consumption (0, 1–149, 150–299, 300+ g/week ethanol); family history of colorectal cancer; aspirin or other non-steroidal anti-inflammatory drug use; dietary fiber, folate, calcium, vitamin D, and red meat intake (quartiles based on controls; energy-adjusted)

classified according to adenoma size (0–4 mm, 5–9 mm, or 10 or more mm in diameter; data not shown in tables).

Since the use of statin and intake of saturated, monounsaturated, or polyunsaturated fatty acid could influence the serum triglyceride levels, we repeatedly performed the same analyses with adjustment for these factors. However, the result did not substantially change compared to that without such adjustment. An analysis was made after deleting subjects taking statin, nonsteroidal anti-inflammatory drugs, or hormone replacement therapy. The association between serum triglycerides and colorectal adenoma was slightly attenuated in the overall analysis but somewhat deattenuated in stratified analysis by smoking. Moreover, we made stratified analyses by all covariates in our multivariate model to control any confounding by these covariates. As a result, we observed a clearer association between serum triglycerides and colorectal adenoma in men than women, or a lower (less than median) than a higher (median or more) red meat intake group. The association did not differ between strata classified according to the other covariates. Since the use of estrogen could reduce the incidence of colon neoplasms, we also adjusted for a history of hormone replacement therapy when separately analyzing female subjects, although it did not substantially influence the

association. We also analyzed the association of serum triglycerides and polypoid (0-Ip, 0-Is) or flat/depressed adenoma (0-IIa, 0-IIc; no 0-IIb adenoma in our study subjects) [28]. A clearer association was observed for the risk of polypoid than for flat/depressed adenoma.

## Discussion

Our results were consistent with those of previous studies that reported a positive association between serum triglycerides and colorectal adenoma [5–10]. The association was confirmed by dose-dependent relationships between serum levels of triglycerides and the number of adenomas, which is associated with the risk of colorectal cancer [11]. Total colonoscopy was sparsely used in previous epidemiologic studies [8, 10]. Our method of screening by total colonoscopy was more useful than by sigmoidoscopy in reducing the number of misclassifications, since many proximal adenomas could not be detected with sigmoidoscopy [29, 30].

Smoking seemed to play an important role in the association between serum triglycerides and colorectal adenoma. Our results showed that serum triglycerides were associated with colorectal adenoma only in ever-smokers. This suggested that serum triglycerides may be

involved in adenoma formation after DNA damage to colorectal epithelia by carcinogens within tobacco smoke. In short, serum triglycerides may be at work in the promotion phase of carcinogenesis. In fact, *Apc*-deficient mice showed age-dependent hypertriglyceridemia and a number of intestinal polyp formations, which were suppressed by anti-hyperlipidemic medicines [12, 13]. In another animal study, azoxymethane injection of obese rats with hypertriglyceridemia resulted in an increased number of advanced colon aberrant crypt foci, putative precursors of colon cancer [15]. Those animals probably showed such a clear association between triglycerides and intestinal neoplasms due to initiation by a genetic defect or carcinogen. However, the biological or molecular mechanism is unclear so far. Further laboratory and epidemiologic studies are necessary to substantiate this association among smoking, serum triglycerides, and colorectal adenoma.

However, serum triglyceride levels are not necessarily associated with colorectal cancer incidence [31, 32] or death [33]. Other factors such as hyperinsulinemia associated with physical inactivity or high body mass index may be needed for further neoplastic development [34, 35]. An elevated insulin level leads to a rise in insulin-like growth factor-I (IGF-I) [35]. IGF-I has potent anti-apoptotic and mitogenic properties in both normal and neoplastic cells. Although serum triglycerides may not be a specific predictor of subsequent risk of colorectal cancer, we might at least consider smokers with high serum triglycerides for colorectal screening and polypectomy as well as risk stratification by age and family history used in the algorithm for colorectal cancer screening [36]. This consideration might contribute to further reduction of the risk of colorectal advanced lesions or deaths [37, 38].

There are several limitations in this study. First, the adenoma cases in our study might include a few false positive cases because the overall accuracy of pit-pattern diagnosis is approximately 90%, whereas our institute data investigating overall accuracy showed more than 95% accurate diagnosis [19]. We could not analyze the association of serum triglycerides by several types of adenoma such as tubular, villous, or serrated adenoma [39] because of a lack of pathologic diagnosis. However, biopsies for all suspicious lesions including adenoma and hyperplastic polyps are unrealistic and time-consuming. Now, magnifying chromoendoscopy is a feasible and efficient method to determine neoplastic lesions such as adenoma. This method is also valid on inter- and intra-observer consistency [20, 21]. Second, serum levels of triglycerides were obtained by single measurements of study subjects. These measurements might show a wider varia-

tion due to measurement errors than would the means of multiple measurements. However, a positive association between serum triglycerides and colorectal adenoma would not be due to these diagnostic or measurement errors, which would be random misclassifications occurring in both cases and controls. If we could entirely exclude the misclassification, that positive association would be clearer than the present one. Third, smokers have unhealthy diet habits associated with hypertriglyceridemia in general. We cannot completely rule out a residual confounding with unhealthy diet associated with smoking when we explain the association between hypertriglyceridemia and adenoma only among smokers. Finally, the association between serum triglycerides and colorectal adenoma cannot be conclusively determined to be a causal relationship, since both were assessed cross-sectionally. However, colorectal adenoma could not alter serum triglycerides or dietary habits, which influence serum triglycerides in subjects with colorectal adenoma, since it is an asymptomatic lesion. Therefore, this cross-sectional assessment may be at least useful to infer a causal relationship between serum triglycerides and colorectal adenoma. A Japanese population was originally thought to be different from a Western population in terms of the high prevalence of nonpolypoid (flat and depressed) adenoma. However, such nonpolypoid lesions have now been reported around the world [40]. Therefore, our results can be generalizable not only to the Japanese population but also to other populations including Western ones.

Our results suggest that a higher level of serum triglycerides may be related to a larger number of adenomas. Adenoma development involving an elevated level of serum triglycerides may be modified by smoking.

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## References

1. World Health Organization, International Agency for Research on Cancer (2002) Chapter 5. Cancer-preventive effects; Weight and weight control; Colorectal cancer. In: IARC Handbooks of cancer prevention, vol 6. Weight control and physical activity. IARC Press, Lyon, pp 85–95

2. World Cancer Research Fund in association with American Institute for Cancer Research (1997) Chapter 4.10 Colon, rectum. In: Food, nutrition and the prevention of cancer: a global perspective. WCRF and AICR, Washington, DC, pp 216–251
3. NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease (1993) NIH Consensus Conference. Triglyceride, high-density lipoprotein, and coronary heart disease. *JAMA* 269:505–510
4. McKeown-Eyssen G (1994) Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 3:687–695
5. Kono S, Ikeda N, Yanai F, Yamamoto M, Shigematsu T (1990) Serum lipids and colorectal adenoma among male self-defence officials in northern Kyushu, Japan. *Int J Epidemiol* 19:274–278
6. Bird CL, Ingles SA, Frankl HD, Lee ER, Longnecker MP, Haile RW (1996) Serum lipids and adenomas of the left colon and rectum. *Cancer Epidemiol Biomarkers Prev* 5:607–612
7. Manus B, Adang RP, Ambergen AW, Brägelmann R, Armbrecht U, Stockbrügger RW (1997) The risk factor profile of recto-sigmoid adenomas: a prospective screening study of 665 patients in a clinical rehabilitation centre. *Eur J Cancer Prev* 6:38–43
8. Park SK, Joo JS, Kim DH, Kim YE, Kang D, Yoo KY (2000) Association of serum lipids and glucose with the risk of colorectal adenomatous polyp in men: a case-control study in Korea. *J Korean Med Sci* 15:690–695
9. Shinomiya S, Sasaki J, Kiyohara C, et al (2001) Apolipoprotein E genotype, serum lipids, and colorectal adenomas in Japanese men. *Cancer Lett* 164:33–40
10. Misciagna G, De Michele G, Guerra V, Cisternino AM, Di Leo A, Freudenheim JL (2004) Serum fructosamine and colorectal adenomas. *Eur J Epidemiol* 19:425–432
11. Muto T, Bussey HJ, Morson BC (1975) The evolution of cancer of the colon and rectum. *Cancer* 36:2251–2270
12. Niho N, Takahashi M, Kitamura T, et al (2003) Concomitant suppression of hyperlipidemia and intestinal polyp formation in Apc-deficient mice by peroxisome proliferator-activated receptor ligands. *Cancer Res* 63:6090–6095
13. Niho N, Mutoh M, Takahashi M, Tsutsumi K, Sugimura T, Wakabayashi K (2005) Concurrent suppression of hyperlipidemia and intestinal polyp formation by NO-1886, increasing lipoprotein lipase activity in Min mice. *Proc Natl Acad Sci USA* 102:2970–2974
14. Brown JR, DuBois RN (2005) COX-2: a molecular target for colorectal cancer prevention. *J Clin Oncol* 23:2840–2855
15. Raju J, Bird RP (2003) Energy restriction reduces the number of advanced aberrant crypt foci and attenuates the expression of colonic transforming growth factor beta and cyclooxygenase isoforms in Zucker obese (fa/fa) rats. *Cancer Res* 63:6595–6601
16. Ochiai M, Ogawa K, Wakabayashi K, et al (1991) Induction of intestinal adenocarcinomas by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in Nagase albuminemic rats. *Jpn J Cancer Res* 82:363–366
17. Koohestani N, Tran TT, Lee W, Wolever TM, Bruce WR (1997) Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. *Nutr Cancer* 29:69–76
18. International Agency for Research on Cancer (eds) (2004) IARC monographs on the evaluation of the carcinogenic risk to humans, vol 83. Tobacco smoking and involuntary smoking. IARC, Lyon
19. Sano Y, Saito Y, Fu KI, et al (2005) Efficacy of magnifying chromoendoscopy for the differential diagnosis of colorectal lesions. *Digest Endosc* 17:105–116
20. Fu KI, Sano Y, Kato S, et al (2004) Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. *Endoscopy* 36:1089–1093
21. Huang Q, Fukami N, Kashida H, et al (2004) Interobserver and intra-observer consistency in the endoscopic assessment of colonic pit patterns. *Gastrointest Endosc* 60:520–526
22. Science and Technology Agency (eds) (2000) Standard tables of food composition in Japan. The fifth revised edition (in Japanese). Printing Bureau, Ministry of Finance, Tokyo
23. Tsubono Y, Takamori S, Kobayashi M, et al (1996) A database approach for designing a semiquantitative food frequency questionnaire for a population-based prospective study in Japan. *J Epidemiol* 6:45–53
24. Tsugane S, Kobayashi M, Sasaki S (2003) Validity of the self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for main nutrients. *J Epidemiol* 13:S51–S56
25. Mantel N (1963) Chi-square tests with one degree of freedom; extensions of the Mantel–Haenszel Procedure. *J Am Stat Assoc* 58:690–700
26. Willett W, Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 124:17–27
27. Togashi K, Konishi F, Ishizuka T, Sato T, Senba S, Kanazawa K (1999) Efficacy of magnifying endoscopy in the differential diagnosis of neoplastic and non-neoplastic polyps of the large bowel. *Dis Colon Rectum* 42:1602–1608
28. No Author listed (2003) The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 58:S3–S43
29. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G (2000) Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 343:162–168
30. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF (2000) Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 343:169–174
31. Schoen RE, Tangen CM, Kuller LH, et al (1999) Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 91:1147–1154
32. Tsushima M, Nomura AM, Lee J, Stemmermann GN (2005) Prospective study of the association of serum triglyceride and glucose with colorectal cancer. *Dig Dis Sci* 50:499–505
33. Trevisan M, Liu J, Muti P, Misciagna G, Menotti A, Fucci F (2001) Markers of insulin resistance and colorectal cancer mortality. *Cancer Epidemiol Biomarkers Prev* 10:937–941
34. Giovannucci E (1995) Insulin and colon cancer. *Cancer Causes Control* 6:164–179
35. Sandhu MS, Dunger DB, Giovannucci EL (2002) Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst* 94:972–980

36. Winawer S, Fletcher R, Rex D, et al (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology* 124:544–560
37. Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA (1998) Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control* 9:455–462
38. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH (1999) Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Tele-mark Polyp Study I. *Scand J Gastroenterol* 34:414–420
39. Tabuchi M, Kitayama J, Nagawa H (2006) Hypertriglyceridemia is positively correlated with the development of colorectal tubular adenoma in Japanese men. *World J Gastroenterol* 12:1261–1264
40. Soetikno R, Friedland S, Kaltenbach T, Chayama K, Tanaka S (2006) Nonpolypoid (flat and depressed) colorectal neoplasms. *Gastroenterology* 130:566–576 quiz 588-9