

# Prevalence of Colorectal Neoplasm Among Patients With Newly Diagnosed Coronary Artery Disease

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**C**OLORECTAL CANCER IS THE second most prevalent cancer worldwide.<sup>1</sup> There were about 1 million new cases and 500 000 deaths due to colorectal cancer in 2002.<sup>1</sup> It has been estimated that 1 in 20 healthy individuals will eventually develop colorectal cancer. Coronary artery disease (CAD) is the single leading cause of death in the United States and other industrialized countries.<sup>2</sup> We previously published a retrospective study that reported a strong

**Context** Colorectal neoplasm and coronary artery disease (CAD) share similar risk factors, and their co-occurrence may be associated.

**Objectives** To investigate the prevalence of colorectal neoplasm in patients with CAD in a cross-sectional study and to identify the predisposing factors for the association of the 2 diseases.

**Design, Setting, and Participants** Patients in Hong Kong, China, were recruited for screening colonoscopy after undergoing coronary angiography for suspected CAD during November 2004 to June 2006. Presence of CAD (n=206) was defined as at least 50% diameter stenosis in any 1 of the major coronary arteries; otherwise, patients were considered CAD-negative (n=208). An age- and sex-matched control group was recruited from the general population (n=207). Patients were excluded for use of aspirin or statins, personal history of colonic disease, or colonoscopy in the past 10 years.

**Main Outcome Measures** The prevalence of colorectal neoplasm in CAD-positive, CAD-negative, and general population participants was determined. Bivariate logistic regression was performed to study the association between colorectal neoplasm and CAD and to identify risk factors for the association of the 2 diseases after adjusting for age and sex.

**Results** The prevalence of colorectal neoplasm in the CAD-positive, CAD-negative, and general population groups was 34.0%, 18.8%, and 20.8% ( $P < .001$  by  $\chi^2$  test), prevalence of advanced lesions was 18.4%, 8.7%, and 5.8% ( $P < .001$ ), and prevalence of cancer was 4.4%, 0.5%, and 1.4% ( $P = .02$ ), respectively. Fifty percent of the cancers in CAD-positive participants were early stage. After adjusting for age and sex, an association still existed between colorectal neoplasm and presence of CAD (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.25-2.70;  $P = .002$ ) and between advanced lesions and presence of CAD (OR, 2.51; 95% CI, 1.43-4.35;  $P = .001$ ). The metabolic syndrome (OR, 5.99; 95% CI, 1.43-27.94;  $P = .02$ ) and history of smoking (OR, 4.74; 95% CI, 1.38-18.92;  $P = .02$ ) were independent factors for the association of advanced colonic lesions and CAD.

**Conclusions** In this study population undergoing coronary angiography, the prevalence of colorectal neoplasm was greater in patients with CAD. The association between the presence of advanced colonic lesions and CAD was stronger in persons with the metabolic syndrome and a history of smoking.

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association between colorectal cancer/adenoma and CAD, possibly due to the sharing of common environmental risk factors.<sup>3</sup>

Colorectal cancer and CAD share similar environmental risks factors, such as diabetes mellitus; smoking; hyperlipidemia; sedentary lifestyle; high-fat, low-fiber diet; obesity; and hypertension.<sup>4-6</sup> The metabolic syndrome is being increasingly recognized as a significant health hazard worldwide.<sup>7</sup> It comprises a constellation of metabolic risk factors, including most of the underlying risk factors for both colorectal cancer and CAD: diabetes or impaired glucose tolerance, hypertriglyceridemia, low high-density lipoprotein cholesterol level, central obesity, and hypertension. Persons with the metabolic syndrome have been reported to have increased risk of developing CAD.<sup>8,9</sup> We postulated that the metabolic syndrome might also be an important risk factor for the development of both colorectal cancer and CAD.

Hong Kong is an industrialized region with incidences of and mortality due to colorectal cancer and CAD similar to that in western countries.<sup>10-12</sup> Although we observed an association between colorectal cancer and CAD in our previous study,<sup>3</sup> we were not able to identify the risk factors involved because of its retrospective nature.<sup>3</sup> We thus designed and conducted the current cross-sectional study, the primary aim of which was to investigate the prevalence of colorectal cancer and adenoma (colorectal neoplasms) in patients with newly diagnosed CAD. A secondary aim was to identify the underlying risk factors, after adjusting for age and sex, that predisposed to the 2 conditions. The results have important implications in prevention of both colorectal neoplasm and CAD, as well as for the screening strategy of colorectal cancer.

## METHODS

### Patient Recruitment

The study period encompassed November 2004 to June 2006. Participating hospitals include the cardiac divisions of Queen Mary Hospital, Grantham Hospi-

tal, and Ruttonjee Hospital. These are regional hospitals serving patients with heart disease in the Hong Kong West cluster.

The study was approved by the institutional review boards of the University of Hong Kong/Queen Mary Hospital, Grantham Hospital, and Ruttonjee Hospital, all in Hong Kong. All participants provided written informed consent.

Consecutive patients with suspected CAD (ie, those with angina or abnormal exercise stress test results) who presented for the first time for coronary angiography were invited to participate in the study. Because we aimed at studying the prevalence of colorectal neoplasm in patients with newly diagnosed CAD, and to avoid the potential protective effect of aspirin and statins on colorectal neoplasm, patients with a history of CAD for more than 1 year or who had been taking aspirin or a statin for more than 1 year were excluded. In addition, those presenting for coronary angiography for reasons other than suspected CAD (eg, congestive heart failure, cardiomyopathy) were also excluded. Additional exclusion criteria were history of colonic disease, such as colorectal cancer, polyp, and inflammatory bowel disease, and history of colorectal surgery or colonoscopy within the previous 10 years.

Consecutive patients with coronary angiogram were invited for colonoscopy regardless of hemoglobin status to avoid preselection in the CAD-positive group of patients with gastrointestinal tract bleeding due to aspirin or clopidogrel therapy. In accordance with American College of Cardiology/American Heart Association guidelines, patients were defined as CAD-positive if at least 50% diameter stenosis in any 1 of the major coronary arteries was found on coronary angiography; otherwise, patients were defined as CAD-negative.

Because age and sex matching was not available in the CAD-negative group, a second control group from the general population was recruited. They were healthy participants who were asymptomatic other than having functional epigastric pain but with a normal result on upper endoscopy performed in our unit.

They were age- and sex-matched to the CAD-positive group within 5 years on a nearly case-to-case basis. This group did not undergo coronary angiogram. The same exclusion criteria were also applied in this second control group.

All individuals in the 3 groups were invited to participate. Information on age, sex, history of smoking, diabetes mellitus, hypertension, family history of colorectal cancer, and use and duration of aspirin and statins was recorded. Waist circumference was measured. Blood was drawn and fasting glucose level and complete lipid profile were measured. The metabolic syndrome was defined as at least 3 of the following criteria set forth by the National Cholesterol Education Program's modified Adult Treatment Panel III (Asian Pacific Region criteria)<sup>13</sup>: (1) abdominal obesity: waist circumference of at least 36 in (91 cm) for men and 32 in (81 cm) for women; (2) low high-density lipoprotein cholesterol level: 40 mg/dL (1.03 mmol/L) or lower for men and 50 mg/dL (1.3 mmol/L) or lower for women; (3) hypertriglyceridemia: 150 mg/dL (1.7 mmol/L) or higher; (4) hypertension: blood pressure 130/85 mm Hg or higher; and (5) impaired glucose tolerance: fasting glucose 110 mg/dL (6.1 mmol/L) or higher.

### Colonoscopy

Colonoscopy was scheduled within 8 weeks after assessing for eligibility or after revascularization for critical patients. All patients received the same bowel preparation. Colonoscopies were repeated the next day for those with poor bowel preparation. Patients taking clopidogrel had their treatment changed to subcutaneous heparin 2 days before colonoscopy. Endoscopists were blinded to the CAD status of the patients. The withdrawal time of the colonoscopy procedure was more than 6 min to minimize the chance of lesions being missed.<sup>14</sup> Incomplete examination was excluded from analysis.

Advanced colonic lesion was defined as presence of cancer or adenomas with villous component, with high-grade dysplasia, or 1 cm or larger.

**Table 1.** Key Risk Factors and Assessment of Heterogeneity of the CAD-Negative and General Population Groups

Risk Factors	CAD-Negative Group (n = 208)	General Population Group (n = 207)	Adjusted P Value <sup>a</sup>
Male, No. (%)	132 (63.5)	152 (73.4)	.17
Age, mean (SD), y	62.9 (8)	62.9 (8)	.97
Family history of colorectal cancer, No. (%)	12 (5.8)	24 (11.6)	.18
Ever smoking, No. (%)	37 (17.8)	45 (21.7)	.94
Metabolic syndrome, No. (%)	38 (18.3)	20 (9.7)	.08
Fasting glucose ≥110 mg/dL, No. (%)	42 (20.2)	42 (20.3)	>.99

Abbreviation: CAD, coronary artery disease.  
 SI conversion: To convert fasting glucose to mmol/L, multiply by 0.555.  
<sup>a</sup>Adjusted using the Holm<sup>18</sup> method for multiple testing.

The size of a polyp was assessed by comparing it with an open colonoscope biopsy forcep (Bard, Murray Hill, NJ). The site of colorectal neoplasm was defined as right-sided if proximal to splenic flexure. The size, site, histologic findings, and number of polyps were recorded.

**Statistical Analysis**

The polyp prevalence in Hong Kong was assumed to be 24% (including hyperplastic polyps).<sup>15</sup> Assuming an unadjusted odds ratio of 2.0,<sup>3</sup> the sample size required to achieve a 2-tailed  $\alpha$  level of significance of .05 with a power of  $1-\beta=.9$  was 207 in the CAD-positive, CAD-negative, and general population groups.

The Pearson  $\chi^2$  test or the Fisher exact test (for small prevalences) was carried out to perform simple comparisons of prevalence based on various demographic and clinical characteristics among participants in the CAD-positive, CAD-negative, and general population groups. *F* tests based on a 1-way analysis of variance model was used to compare the ages of the patients in the 3 groups. Descriptive statistics and simple analyses were carried out using JMP software, release 6.0.2 (SAS Institute Inc, Cary, North Carolina).

A bivariate logistic regression analysis<sup>16,17</sup> was carried out to examine the association between colorectal neoplasm and CAD, adjusted accordingly for potential risk factors  $\chi_1, \dots, \chi_k$ . In the current application, we let  $Y=1$  denote presence of CAD and  $W=1$  denote presence of colorectal neoplasm, while  $Y=0$  and  $W=0$  denote the absence of CAD and co-

lorectal neoplasm, respectively. The marginal probabilities of  $Y$  and  $W$  were modeled by the usual logistic regression analysis with models

$$\text{logit}[P(Y_i=1)] = \alpha_1 + \alpha_2 x_{1i} + \dots + \alpha_{k+1} x_{k,i}$$

and

$$\text{logit}[P(W_i=1)] = \beta_1 + \beta_2 x_{1i} + \dots + \beta_{k+1} x_{k,i}$$

for  $i = 1, \dots, n$ .

The odds ratio [OR] is defined as

$$\gamma_i = \frac{P(Y_i=1, W_i=1) \times P(Y_i=0, W_i=0)}{P(Y_i=1, W_i=0) \times P(Y_i=0, W_i=1)}$$

This OR measures the association of CAD and colorectal neoplasm. An OR of  $\gamma_i=1$  corresponds to no association between CAD and colorectal neoplasm, and  $\gamma_i>1$  means that a patient with CAD is also more likely to have colorectal neoplasm, with larger values of  $\gamma_i$  indicating a stronger association. While it is possible to model this OR  $\gamma_i$  as a constant  $\gamma$ , forcing it to be the same for all participants in the population, we chose to also let it depend on covariates, thus allowing patients with certain characteristics to have a stronger association between CAD and colorectal neoplasm than others. This relationship is mitigated through the equation

$$\log(\gamma_i) = \theta_1 + \theta_2 x_{1i} + \dots + \theta_{k+1} x_{k,i}.$$

With this specification, the joint probabilities of  $Y$  and  $W$  are given by

$$P(Y_i=1, W_i=1) = \frac{(\gamma_i - 1)[P(Y_i=1) + P(W_i=1)] + 1 - \delta_i^{1/2}}{2(\gamma_i - 1)}$$

where

$$\delta_i = 1 + (\gamma_i - 1)\{ \gamma_i [P(Y_i=1) - P(W_i=1)]^2 - [P(Y_i=1) + P(W_i=1)]^2 + 2[P(Y_i=1) + P(W_i=1)] \}$$

and

$$P(Y_i=1, W_i=0) = P(Y_i=1) - P(Y_i=1, W_i=1),$$

$$P(Y_i=0, W_i=1) = P(W_i=1) - P(Y_i=1, W_i=1),$$

$$P(Y_i=0, W_i=0) = 1 - P(Y_i=1) - P(W_i=1) + P(Y_i=1, W_i=1).$$

Maximum likelihood estimates of the regression coefficients, namely  $\alpha$ ,  $\beta$ , and  $\theta$ , were computed using a tailor-made computer program in FORTRAN language. The 95% confidence intervals (CIs) were computed based on the asymptotic  $\chi^2$  distributed properties of the log-likelihood ratio. The CAD-negative and general population groups were pooled together as the control group in the bivariate logistic regression analysis because they were not statistically significantly different in terms of sex and age distribution, family history of colorectal cancer, smoking history, metabolic syndrome, or diabetes (TABLE 1). Our aim was to (1) assess if any association existed between CAD and colorectal neoplasm and (2) identify the risk factors that predispose to both diseases simultaneously.

There are a number of potential covariates, but not all of them are useful predictors in the marginal probabilities of  $Y$  or  $W$  or the ORs of the 2 events. The effects of age and sex were included in the modeling of the marginal probabilities  $P(Y=1)$  and  $P(W=1)$  since they are well known to be the risk factors that predispose to the development of both CAD and colonic lesions. We did not consider other factors in the marginal models because our primary objective was to investigate the effect of factors on the association between CAD and colorectal neoplasm or advanced lesions, and the inclusion of too many simultaneous factors in the model could result in colinearity or other difficulties fitting the model.

In the first phase of our analysis, we simply assumed that the OR  $\gamma$  was a constant that, thus, was not affected by any covariates. We tested the null hypothesis of no association between CAD and

colorectal neoplasm using a Wald test. In the second phase of the bivariate logistic regression analysis, we allowed the OR  $\gamma$  to depend on some explanatory variable that may play an important role in mitigating the association of the 2 diseases. The factors of age, sex, metabolic syndrome, smoking history, and family history of colon cancer were included in the regression model for the log OR,  $\log(\gamma_i)$ ; while the effects of age and sex were adjusted in the modeling of  $P(Y_i=1)$  and  $P(W_i=1)$ . A backward-elimination procedure was adopted to remove the most insignificant variable in the regression model for  $\log(\gamma_i)$  at each step until the  $P$  values for the variables remained in the working model were all less than .10.

The  $P$  values reported are based on 2-tailed alternatives in the cases in which comparisons were made between 2 groups and for the regression coefficients of the log OR in the bivariate logistic regression analyses. The method of Holm<sup>18</sup> was used to adjust the  $P$  values in multiple testing, where appropriate, particularly on the demographic variables and prevalence of colonic lesions of the 3 groups. For example, when reporting  $K$   $P$  values for  $K$  distinct tests, the Holm method is to compare the  $r^{\text{th}}$  smallest  $P$  value (for  $r=1, \dots, K$ ) among the  $KP$  values with  $.05/(K-r+1)$ , and the test result is considered statistically significant after adjustment for the multiple tests if the  $r^{\text{th}}$  smallest  $P$  value is less than  $.05/(K-r+1)$ . However, if the  $r^{\text{th}}$  smallest  $P$  value is the first that exceeds  $.05/(K-r+1)$ , then the test results associated with the  $(K-r+1)$  largest  $P$  values are considered statistically nonsignificant according to the Holm method. To make the presentation simpler, we let the adjusted  $P$  value be  $(K-r+1)$  times the original  $P$  value and simply compare the adjusted  $P$  value with .05 to determine whether a particular test result is statistically significant after adjustment.

**RESULTS**

**Baseline Characteristics**

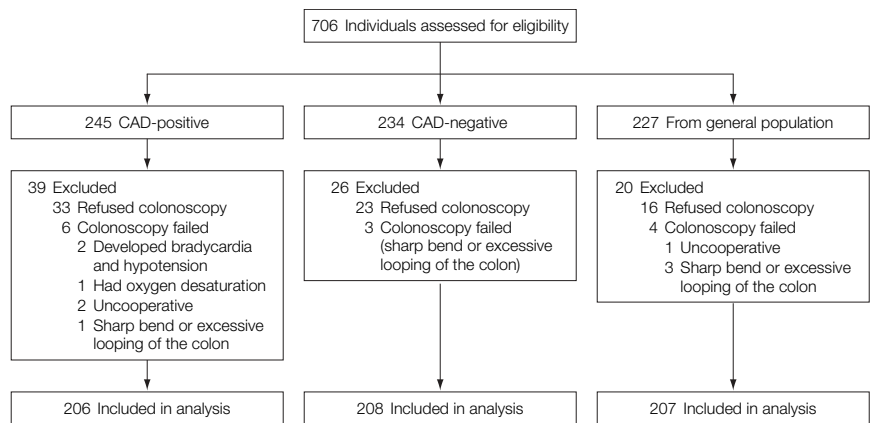
There were 706 participants assessed for eligibility in the 3 groups. The response rates are summarized in the

FIGURE. The final numbers of participants for analysis were 206, 208, and 207 in the CAD-positive, CAD-negative, and general population groups, respectively.

The baseline demographic and clinical characteristics in each group are summarized in TABLE 2. The CAD-positive and general population group were age- and sex-matched. Accord-

ing to the Holm adjustment, we concluded that the mean age and distributions of family history of colorectal cancer were insignificantly different among the 3 groups, but there were differences in the distributions of sex, smoking history, the metabolic syndrome, and the individual factors of the metabolic syndrome among the 3 groups (Table 2). Eighty-five percent

**Figure.** Study Recruitment and Participant Flow



CAD indicates coronary artery disease.

**Table 2.** Baseline Demographic and Clinical Characteristics of the CAD-Positive, CAD-Negative, and General Population Groups

Characteristics	CAD-Positive Group (n = 206)	CAD-Negative Group (n = 208)	General Population Group (n = 207)	P Value Comparing the 3 Groups <sup>a</sup>	Adjusted P Value (Rank) <sup>b</sup>
Age, mean (SD), y	64.7 (8)	62.9 (8)	62.9 (8)	.04	.07 (9)
Male, No. (%)	161 (78.2)	132 (63.5)	152 (73.4)	.003	.009 (8) <sup>c</sup>
Metabolic syndrome, No. (%)	78 (37.9)	38 (18.3)	20 (9.7)	<.001	.001 (1) <sup>c</sup>
Waist circumference ≥91.4 cm for men or ≥81.3 cm in for women, No. (%)	77 (37.6)	74 (35.6)	47 (22.8)	.002	.01 (6) <sup>c</sup>
Fasting glucose ≥110 mg/dL, No. (%)	87 (42.2)	42 (20.2)	42 (20.3)	<.001	.001 (2) <sup>c</sup>
Triglycerides ≥150 mg/dL, No. (%)	70 (34.0)	53 (25.5)	40 (19.3)	.003	.01 (7) <sup>c</sup>
HDL-C ≤40 mg/dL for men or ≤50 pmg/dL for women, No. (%)	78 (37.9)	61 (29.3)	28 (13.5)	<.001	.001 (3) <sup>c</sup>
Blood pressure ≥130/85 mm Hg, No. (%)	88 (42.7)	54 (26.0)	28 (13.5)	<.001	.001 (4) <sup>c</sup>
Ever smoking, No. (%)	78 (37.9)	37 (17.8)	45 (21.7)	<.001	.001 (5) <sup>c</sup>
Family history of colorectal cancer, No. (%)	12 (5.8)	12 (5.8)	24 (11.6)	.04	.04 (10) <sup>d</sup>

Abbreviations: CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol. SI conversions: To convert fasting glucose to mmol/L, multiply by 0.555; to convert triglycerides to mmol/L, multiply by 0.0113; to convert HDL-C to mmol/L, multiply by 0.0259. <sup>a</sup> $P$  values calculated from 1-way analysis of variance and/or  $\chi^2$  or Fisher exact tests. <sup>b</sup>Adjusted  $P$  values using the Holm<sup>18</sup> method for multiple testing, with the first entry being the adjusted  $P$  value and the rank in parentheses the rank of the associated original  $P$  value in ascending order from most to least significant. <sup>c</sup>Statistically significant ( $P < .05$ ) after adjustment for multiple tests using the Holm method. <sup>d</sup>The variable of age (rank = 9) is not statistically significant at the  $P < .05$  level and, hence, the family history of colorectal cancer (rank = 10) is not statistically significant using the Holm method.

**Table 3.** Type and Prevalence of Colonic Lesions in the CAD-Positive, CAD-Negative, and General Population Groups

Type of Colonic Lesion	No. (%)			P Value Comparing the Prevalence in All 3 Groups <sup>a</sup>	Adjusted P Value Comparing All 3 Groups Using Holm Method (Rank) <sup>b</sup>	P Value Comparing CAD-Positive and General Population Groups (Holm-Adjusted P Value) <sup>c</sup>
	CAD-Positive Group (n = 206)	CAD-Negative Group (n = 208)	General Population Group (n = 207)			
Endoscopic polyp	84 (40.8)	59 (28.4)	69 (33.3)	.03	.055 (4)	.12 (.24)
Colorectal neoplasm	70 (34.0)	39 (18.8)	43 (20.8)	<.001	.002 (2) <sup>d</sup>	<.001 (.01)
Hyperplastic polyp	17 (8.3)	10 (4.8)	15 (7.2)	.33	.33 (5)	.70 (.70)
Advanced lesion	38 (18.4)	18 (8.7)	12 (5.8)	<.001	.001 (1) <sup>d</sup>	<.001 (.001)
Colorectal cancer	9 (4.4)	1 (0.5)	3 (1.4)	.02	.06 (3)	.09 (.26)

Abbreviation: CAD, coronary artery disease.

<sup>a</sup>P values calculated from  $\chi^2$  or Fisher exact tests.

<sup>b</sup>Adjusted P values using the Holm<sup>18</sup> method for multiple testing, with the first entry being the adjusted P value and the rank in parentheses the rank of the associated original P value in ascending order from most to least significant.

<sup>c</sup>P values in this column are for 2-tailed alternative hypotheses.

<sup>d</sup>Statistically significant ( $P < .05$ ) after adjustment for multiple tests using the Holm method.

of the patients in the CAD-positive group underwent revascularization and 10% underwent coronary artery bypass graft surgery; the remaining 5% were treated noninvasively. None of the participants in the CAD-negative and general population groups underwent revascularization or coronary artery bypass graft surgery. The prevalence of the metabolic syndrome in the CAD-positive patients in our study is similar to that reported in the Asia/Pacific region.<sup>19,20</sup>

**Prevalence and Characteristics of Colorectal Neoplasms**

The characteristics and prevalence of colonic lesions in the 3 groups are summarized in TABLE 3 together with the original and Holm-adjusted P values. Colorectal neoplasm and advanced lesion were more prevalent (34.0% and 18.4%, respectively) in the CAD-positive group than in the CAD-negative (18.8% and 8.7%) and general population (20.8% and 5.8%) groups ( $P < .001$  for both by Pearson  $\chi^2$  test and adjusted  $P = .002$  and  $P = .001$ , respectively). In addition, using the Holm method, there was no difference in the prevalence of endoscopic polyps (40.8% vs 28.4% vs 33.3%; adjusted  $P = .055$  by Pearson  $\chi^2$  test), hyperplastic polyps (8.3% vs 4.8% vs 7.2%; adjusted  $P = .33$  by Fisher exact test), and adenocarcinoma (4.4% vs 0.5% vs 1.4%; adjusted  $P = .06$  by Fisher exact test). Differences in the prevalence of colorectal neoplasm (34.0% vs 20.8%; adjusted  $P = .01$  by Pearson  $\chi^2$  test) and advanced lesions (18.4% vs 5.8%; adjusted  $P < .001$  by Pearson  $\chi^2$  test) were still observed when comparing only the CAD-positive and general population groups, which were age- and sex-matched.

Of the 9 adenocarcinomas (4.4%) detected in the CAD-positive group, 8 were asymptomatic. Five (55%) of the 9 cancers detected were at an early stage (Dukes A or B) and were small (<3 cm). In contrast, only 1 cancer (0.5%) and 3 cancers (1.4%) were detected in the CAD-negative and general population groups, respectively. All were asymptomatic and 75% (3/4) were of small size (1-2 cm) and early stage (Dukes A).

**Bivariate Logistic Regression Analysis**

The 2 control groups were merged for the bivariate logistic regression analysis because no significant differences between them were found for any demographic or clinical characteristics (age, sex, family history of colorectal cancer, smoking status, presence of the metabolic syndrome, and high fasting glucose level) and the 2 groups appeared to be reasonably homogeneous (Table 1).

**Bivariate Logistic Regression Analysis**

Assuming that the OR of the association of the 2 diseases was constant (ie, not affected by any independent variables) when adjusting only for the

marginal probabilities for age and sex, we observed evidence of a strong association between colorectal neoplasm and CAD (OR, 1.88; 95% CI, 1.25-2.70; 2-tailed  $P = .002$ ; TABLE 4), and between advanced lesions and CAD (OR, 2.51; 95% CI, 1.43-4.35; 2-tailed  $P = .001$ ; TABLE 5). If all explanatory variables (age, sex, smoking status, family history of colon cancer, and the metabolic syndrome) were included in the estimate of the marginal probabilities  $P(Y_i=1)$  and  $P(W_i=1)$  and assuming the OR did not depend on any explanatory variables, the constant OR for CAD and colorectal neoplasm is estimated to be 1.54 (95% CI, 1.04-2.30; 2-tailed  $P = .048$ ).

In the second part of the bivariate logistic regression analysis, we allowed the OR for the association of the 2 diseases to depend on explanatory variables like age, sex, smoking status, metabolic syndrome, and family history of colorectal cancer. To identify the risk factors and/or predictors that predispose to the development of both CAD and colorectal neoplasm, the variables of age, sex, smoking history, metabolic syndrome, and family history of colorectal cancer were included as the explanatory variables for the log of the OR while adjusted for the variables of age and sex in the marginal probabilities  $P(Y_i=1)$  and  $P(W_i=1)$ . A backward-elimination procedure was adopted to remove the most nonsignificant variable in the regression of the log of the

OR at each step. The final model indicated that the association between CAD and colorectal neoplasm did not depend on any of the aforementioned explanatory variables ( $P > .05$ ) and that the OR (estimated to be 1.88; Table 4) was constant across all participants.

However, we found that both the metabolic syndrome and history of smoking were strong independent predictive factors for the positive association between advanced lesions and CAD (for metabolic syndrome, OR, 5.99; 95% CI, 1.43-28.0; 2-tailed  $P = .02$ ; for smoking, OR, 4.74; 95% CI, 1.38-19.0; 2-tailed  $P = .02$ ; TABLE 6). This indicates that participants who were smokers and/or who had the metabolic syndrome were much more likely to develop both CAD and advanced lesions. The OR of the metabolic syndrome in predicting the positive association of the 2 diseases was higher than the OR of the individual components of the metabolic syndrome (TABLE 7) after adjustment for age and sex. The wide CI for this OR was because the OR was larger in magnitude and fewer participants had the metabolic syndrome than had its individual components.

**Complications**

One patient from the CAD-positive group developed colonic perforation during polypectomy for a 2-cm sessile villous adenoma. She recovered after operation. Another patient in the CAD-positive group developed congestive heart failure after bowel preparation for colonoscopy and was treated conservatively.

**COMMENT**

Previous studies have reported the association between colorectal neoplasm and CAD,<sup>21-23</sup> and some have refuted the association.<sup>24</sup> The current study confirms the association between the 2 diseases and our previous retrospective study observation.<sup>3</sup> The design of the current study is robust compared to others<sup>21-24</sup> in that CAD was defined by coronary angiogram, which is the criterion standard for diagnosing CAD, and that patients were re-

cruited prospectively for colonoscopy. We observed that there was a strong association between colorectal neoplasm and CAD (OR, 1.88) and between advanced colonic lesion and CAD (OR, 2.51). The prevalence of colorec-

**Table 4.** Results of the Bivariate Logistic Regression Analysis on CAD and Colorectal Neoplasm Assuming a Constant Odds Ratio  $\gamma$

	Factor ( $\alpha, \beta, \text{ or } \gamma$ ) (95% Confidence Interval)	P Value
Coefficients for the marginal probability of CAD ( $\alpha$ )		
Intercept	-4.53 (-5.77 to -3.21)	<.001
Age/100	4.97 (2.94 to 6.79)	<.001
Male	0.98 (0.63 to 1.35)	<.001
Coefficients for the marginal probability of colorectal neoplasm ( $\beta$ )		
Intercept	-4.97 (-6.32 to -3.54)	<.001
Age/100	5.00 (2.80 to 7.02)	<.001
Male	0.88 (0.40 to 1.30)	<.001
Coefficients for the log odds ratio ( $\gamma$ )		
Intercept	0.61 (0.22 to 0.99)	.002
Odds ratio	1.88 (1.25 to 2.70)	.002

Abbreviation: CAD, coronary artery disease.

**Table 5.** Results of Bivariate Logistic Regression Analysis on CAD and Advanced Lesions Assuming a Constant Odds Ratio  $\gamma$

	Factor ( $\alpha, \beta, \text{ or } \gamma$ ) (95% Confidence Interval)	P Value
Coefficients for the marginal probability of CAD ( $\alpha$ )		
Intercept	-3.98 (-5.19 to -2.89)	<.001
Age/100	4.14 (2.51 to 5.95)	<.001
Male	0.96 (0.61 to 1.36)	<.001
Coefficients for the marginal probability of advanced lesions ( $\beta$ )		
Intercept	-5.06 (-7.03 to -3.43)	<.001
Age/100	3.76 (1.28 to 6.62)	.005
Male	0.78 (0.18 to 1.40)	.01
Coefficients for the log odds ratio ( $\gamma$ )		
Intercept	0.88 (0.35 to 1.47)	.001
Odds ratio	2.51 (1.43 to 4.35)	.001

Abbreviation: CAD, coronary artery disease.

**Table 6.** Final Results of the Bivariate Logistic Regression Analysis on CAD and Advanced Lesions Allowing the Odds Ratio  $\gamma$  to Depend on Some Explanatory Variables

	Factor ( $\alpha, \beta, \text{ or } \gamma$ ) (95% Confidence Interval)	P Value
Coefficients for the marginal probability of CAD ( $\alpha$ )		
Intercept	-4.01 (-5.11 to -2.46)	<.001
Age/100	4.10 (1.73 to 5.70)	<.001
Male	0.95 (0.57 to 1.34)	<.001
Coefficients for the marginal probability of colorectal neoplasm ( $\beta$ )		
Intercept	-5.96 (-7.93 to -3.42)	<.001
Age/100	5.09 (1.10 to 8.02)	.002
Male	0.71 (0.09 to 1.36)	.03
Coefficients for the log odds ratio ( $\gamma$ )		
Intercept	-0.29 (-1.35 to 0.62)	.58
Smoking status	1.56 (0.32 to 2.94) <sup>a</sup>	.02
Metabolic syndrome	1.79 (0.35 to 3.33) <sup>b</sup>	.02

Abbreviation: CAD, coronary artery disease.

<sup>a</sup>Estimated odds ratio for smoking status:  $\exp(1.56) = 4.74$ .

<sup>b</sup>Estimated odds ratio for the metabolic syndrome:  $\exp(1.79) = 5.99$ .

**Table 7.** Age- and Sex-Adjusted Odds Ratios for Independent Predictive Factors for Association of Advanced Colonic Lesions and CAD

	No. (%) of Sample With Characteristic	Odds Ratio (95% Confidence Interval)	P Value <sup>a</sup>
Metabolic syndrome	136 (21.9)	5.99 (1.43-27.94) <sup>b</sup>	.02
Individual components of the metabolic syndrome			
Diabetes	171 (27.5)	2.39 (1.33-3.98)	.002
Hypertension	170 (27.4)	2.41 (1.33-4.03)	.002
Triglycerides	163 (26.2)	2.17 (1.21-3.74)	.007
High-density lipoprotein cholesterol	167 (26.9)	2.12 (1.15-3.47)	.008
Waist circumference	198 (32.0)	2.29 (1.29-3.72)	.002

Abbreviation: CAD, coronary artery disease.

<sup>a</sup>P values are for 2-tailed alternative hypotheses.

<sup>b</sup>The odds of the metabolic syndrome in predicting the association of the 2 diseases was higher than the odds of its individual components after adjustment for age and sex in the marginal probabilities of the events.

tal neoplasm (34%) was much higher in the CAD-positive group than in the CAD-negative group (18.8%) or in the age- and sex-matched general population group (20.8%), as well as that reported by Sung et al<sup>15</sup> (21%). Moreover, the prevalence of advanced lesions (18.4%) and adenocarcinoma (4.4%) was also observed to be much higher in the CAD-positive group.

The high prevalence of advanced lesions in CAD-positive patients in the study is remarkable. This is much higher than the 12.5% reported in the general population in Hong Kong by Sung et al<sup>15</sup> and the 10.5% in the US general population.<sup>25</sup> Importantly, we observed that the metabolic syndrome and smoking, after adjusting for age and sex, were important predictive factors for the association of advanced colonic lesions and CAD. It has been well documented that old age and male sex are important risk factors for CAD and colorectal neoplasm. However, these 2 factors are not modifiable. But the metabolic syndrome and smoking are environmental factors that can be reversed. Smoking has been demonstrated as a major risk factor in the development of the 2 diseases.<sup>26,27</sup> There are also reports on insulin resistance syndrome and colorectal cancer,<sup>28,29</sup> as well as metabolic syndrome, predisposing to colorectal adenomas.<sup>30,31</sup>

Both colorectal neoplasm and CAD probably develop through the mechanism of chronic inflammation. Inflammation is now recognized as being

pivotal in the pathogenesis of atherosclerosis and, hence, CAD.<sup>32,33</sup> Colorectal cancer is also thought to progress through the pathway of inflammation.<sup>34</sup> This is evidenced by the development of colorectal cancer in patients with ulcerative colitis. Inflammation, which may result from underlying risk factors, may be the culprit for the simultaneous development of the 2 conditions. In addition, insulin resistance is recognized as an important metabolic defect linking the components of the metabolic syndrome. The direct proliferative/antiapoptotic effects of insulin and related insulinlike growth factor 1 on both colorectal neoplasm and CAD has gained support recently.<sup>35,36</sup> Peroxisome proliferator-activated receptor  $\gamma$  may play an important role in metabolic syndrome to regulate metabolic and vascular pathways. These may be important potential mechanisms for the simultaneous evolution of the 2 diseases. Interestingly, statins have been shown to have beneficial effects in both colorectal cancer and CAD, probably through an anti-inflammatory mechanism.<sup>37</sup> Aspirin has long been proven to be beneficial in both conditions, albeit through different mechanisms.

It would be ideal to perform an age- and sex-matched study in both the CAD-positive and CAD-negative groups to study the association of the 2 diseases. However, in reality, this is nearly impossible. Asymptomatic men with healthy coronary arteries (the control group) would rarely undergo a coro-

nary angiogram. Similarly, few young women have CAD (the study group). Therefore, we have included the age- and sex-matched general population as another control group. In addition, the factors of age and sex were further adjusted in the marginal logistic regression part of the analysis. We chose coronary angiogram to be the diagnostic criterion for the presence of CAD because diagnosis based on symptoms alone is not reliable and coronary angiogram has the highest sensitivity among the tests (treadmill, thallium scan, or computed tomography angiogram). However, the current design might have potential bias in that we were only assessing the prevalence of colorectal neoplasm in CAD patients who presented for coronary angiogram. The study might not be able to estimate the true magnitude of association between CAD and colorectal neoplasm because there might be a percentage of patients in the general population with CAD who have not had a coronary angiogram. However, the study highlights the important point that, at least in those with CAD presenting for coronary angiogram, a high prevalence of colorectal neoplasm was observed. The predictive value of the metabolic syndrome and smoking on predisposing the positive association of colorectal neoplasm and CAD is limited by the nature of the cross-sectional study. A prospective study evaluating the role of the metabolic syndrome and smoking on the 2 conditions is desirable.

In this study population undergoing coronary angiography, the prevalence of colorectal neoplasm was greater in patients with CAD. The association between the presence of advanced colonic lesions and CAD was stronger in persons with the metabolic syndrome and a history of smoking.

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## REFERENCES

- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74-108.
- Miniño AM, Heron MP, Murphy SL, Kochanek KD. Deaths: final data for 2004. *Natl Vital Stat Rep*. 2007;55(19):1-120.
- Chan AO, Lam KF, Tong TS, et al. Coexistence between colorectal cancer/adenoma and coronary artery disease: results from 1382 patients. *Aliment Pharmacol Ther*. 2006;24(3):535-539.
- Winawer SJ. Natural history of colorectal cancer. *Am J Med*. 1999;106(1A):3S-6S.
- Framingham Heart Study Web site. <http://www.framinghamheartstudy.org>. Accessed August 30, 2007.
- Multiple Risk Factor Intervention Trial Group. *Multiple Risk Factor Intervention Trial Proceedings of the Nutrition Behavioral Research Conference*. Bethesda, MD: National Institutes of Health; 1975. DHEW publication (NIH) 76-978.
- Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287(3):356-359.
- Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288(21):2709-2716.
- Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary artery disease. *Arch Intern Med*. 1999;159(10):1104-1109.
- Hospital Authority of Hong Kong Special Administrative Region. Hong Kong Cancer Registry. <http://www3.ha.org.hk/cancereg/>. Accessed August 29, 2007.
- American Cancer Society. *Cancer Facts and Figures 2000*. Atlanta, GA: American Cancer Society; 2000.
- Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol*. 2001;2(9):533-543.
- National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
- Simmons DT, Harewood GC, Baron TH, et al. Impact of endoscopist withdrawal speed on polyp yield: implications for optimal colonoscopy withdrawal time. *Aliment Pharmacol Ther*. 2006;24(6):965-971.
- Sung JJ, Chan FK, Leung WK, et al. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. *Gastroenterology*. 2003;124(3):608-614.
- Chan JS, Kuk AY, Bell J. A likelihood approach to analyzing longitudinal bivariate binary data. *Biom J*. 1997;4:409-421.
- Ananth CV, Preisser JS. Bivariate logistic regression: modelling the association of small for gestational age births in twin gestations. *Stat Med*. 1999;18(15):2011-2023.
- Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65-70.
- Kwon HS, Prak YM, Lee HJ, et al. Prevalence and clinical characteristics of the metabolic syndrome in middle-aged Korean adults. *Korean J Intern Med*. 2005;20(4):310-316.
- Lin RT, Lee WJ, Jeng CY, Sheu WH, Chen YT. Metabolic syndrome and its contribution to CAD in non-DM participants. *J Formos Med Assoc*. 2004;103(4):317-320.
- Correa P, Strong JP, Johnson WD, et al. Atherosclerosis and polyps of the colon: quantification of precursors of coronary heart disease and colon cancer. *J Chronic Dis*. 1982;35(5):313-320.
- Neugut AI, Jacobson JS, Sherif G, et al. Coronary artery disease and colorectal neoplasia. *Dis Colon Rectum*. 1995;38(8):873-877.
- Reicher-Reiss H, Jonas M, Goldbourt U, Boyko V, Modan B. Selectively increased risk of cancer in men with coronary heart disease. *Am J Cardiol*. 2001;87(4):459-462, A6.
- Neugut AI, Rosenberg DJ, Ahsan H, et al. Association between coronary heart disease and cancers of the breast, prostate, and colon. *Cancer Epidemiol Biomarkers Prev*. 1998;7(10):869-873.
- Lieberman DA, Prindiville S, Weiss DG, Willett W; VA Cooperative Study Group 380. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA*. 2003;290(22):2959-2967.
- Lakier JB. Smoking and cardiovascular disease. *Am J Med*. 1992;93(1A):8S-12S.
- Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2001;10(7):725-731.
- Bowers K, Albanes D, Limburg P, et al. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers. *Am J Epidemiol*. 2006;164(7):652-664.
- Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. *Cancer*. 2006;107(1):28-36.
- Morita T, Tabata S, Mineshita M, Mizoue T, Moore MA, Kono S. The metabolic syndrome is associated with increased risk of colorectal adenoma development: the Self-Defense Forces health study. *Asian Pac J Cancer Prev*. 2005;6(4):485-489.
- Wang YY, Lin SY, Lai WA, Liu PH, Sheu WH. Association between adenomas of rectosigmoid colon and metabolic syndrome features in a Chinese population. *J Gastroenterol Hepatol*. 2005;20(9):1410-1415.
- Tiong AY, Brieger D. Inflammation and coronary artery disease. *Am Heart J*. 2005;150(1):11-18.
- Sepulveda JL, Mehta JL. C-reactive protein and cardiovascular disease: a critical appraisal. *Curr Opin Cardiol*. 2005;20(5):407-416.
- Clevers H. At the crossroads of inflammation and cancer. *Cell*. 2004;118(6):671-674.
- Renahan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*. 2004;363(9418):1346-1353.
- McEwen JE, Zimniak P, Mehta JL, Reis RJ. Molecular pathology of aging and its implications for senescent coronary atherosclerosis. *Curr Opin Cardiol*. 2005;20(5):399-406.
- Demierre MF, Higgins PD, Gruber SB, et al. Statins and cancer prevention. *Nat Rev Cancer*. 2005;5(12):930-942.