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Familial Aggregation of Diabetes and Hypertension in a Case-Control Study of Colorectal Neoplasia

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Familial aggregation of diseases potentially associated with metabolic syndrome (diabetes mellitus, hypertension, and cardiovascular diseases) was assessed in a colonoscopy-based case-control study of colorectal neoplasia in Toronto and Ottawa, Canada, in 1993–1996. Each familial disease was analyzed by logistic regression using generalized estimating equations. Case probands had incident adenomatous polyps (n = 172) or incident (n = 25) or prevalent (n = 132) colorectal cancer (CRC), while control probands (n = 282) had a negative colonoscopy and no history of CRC or polyps. Significant effect modification was evident in the data, with the strongest positive associations between familial diabetes and colorectal neoplasia among older probands with symptoms (parents: odds ratio (OR) = 2.4, 95% confidence interval (CI): 1.2, 4.8; siblings: OR = 5.8, 95% CI: 2.6, 13.3). Familial hypertension was also associated with colorectal neoplasia among probands with symptoms (OR = 1.7, 95% CI: 1.1, 2.6). In stratified analyses, familial diabetes, hypertension, and stroke were positively associated with adenomatous polyps in subgroups of probands who were older and/or had symptoms, while only familial diabetes was possibly associated with CRC. Associations in other proband groups may have been obscured by high cumulative incidence of parental CRC. Family studies are needed to understand the contribution of specific environmental and genetic factors in accounting for the disease aggregations.

adenomatous polyps; case-control studies; colorectal neoplasms; diabetes mellitus; family; family health; hypertension; insulin resistance

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FHQ, family history questionnaire; OR, odds ratio.

Colorectal cancer (CRC), cardiovascular diseases, and non-insulin-dependent diabetes mellitus share several etiologic lifestyle risk factors—notably western dietary patterns, physical inactivity, and obesity (1, 2)—suggesting that underlying biologic factors link these conditions. One candidate factor is insulin resistance, as first suggested by McKeown-Eyssen (3) and Giovannucci (4). Insulin resistance is one feature of metabolic syndrome, which is also

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characterized by an increased visceral abdominal fat depot, hypertriglyceridemia, reduced levels of high density lipoprotein cholesterol, and elevated blood pressure (5). These syndrome features are already well-known independent risk factors for diabetes and/or cardiovascular diseases (5, 6).

Evidence supporting the hypothesis has been accumulating from studies of diabetes mellitus (7–17) and hypertension (18–23) in CRC, physiologic biomarkers (24–31), and animal models (32). Evidence of associations between metabolic syndrome-associated diseases in families of those with CRC or adenomatous polyps would provide additional evidence to support or refute the hypothesis. This case-control study was therefore undertaken to assess familial aggregation of diabetes, hypertension, and cardiovascular conditions in first-degree relatives of persons with and those without CRC or adenomatous polyps.

MATERIALS AND METHODS

Study design

Probands for this case-control study were drawn from a study of associations between physiologic markers of the metabolic syndrome and adenomatous polyps and either incident or prevalent CRC (McKeown-Eyssen et al., manuscript in preparation). Both studies were approved by the ethics review boards of the University of Toronto and the participating hospitals.

From July 1993 to November 1996, patients scheduled for a colonoscopy at three teaching hospitals in Toronto and one in Ottawa were approached if chart review indicated that they were aged 40–79 years; had no history of ulcerative colitis, Crohn's disease, or familial adenomatous polyposis; and had not had surgery within the previous 12 months. In addition, patients treated for primary CRC in the participating hospitals in the previous 5 years and during the study period were invited to participate, even if they were not scheduled for a colonoscopy.

At least a week before colonoscopy, study probands were interviewed and had a fasting blood sample taken. At the interview, probands were given an envelope containing 1) a letter explaining the familial aggregation study, 2) a family history questionnaire (FHQ) (available at: www.uoguelph.ca/FAMILY/pbrauer), and 3) a stamped, self-addressed envelope. They were asked to complete the FHQ and return it by mail. Refusals to complete the FHQ or special circumstances for nonreceipt of an FHQ, such as poor reading ability, were noted by the interviewers. Two follow-up mailings to nonrespondents were conducted over the course of the 3-year study. These mailings included a follow-up letter and a second copy of the FHQ. Therefore, some nonrespondents received the second questionnaire several months after the clinic visit. This delay was unavoidable, since the work was carried out by the staff of physicians' offices to preserve the confidentiality of subjects, and personnel time was limited.

Questionnaire development

The format and content of the FHQ were adapted from a questionnaire developed by Williams et al. (33). Probands were asked to indicate, for each first-degree relative, whether the relationship was a "blood" relationship or one by adoption or marriage, their year of birth, current age and/or year of death, sex, and disease status, as well as age at diagnosis, if applicable. A "don't know" option was provided. The lay terms used to describe the diseases of interest were "cancer of the large bowel" (colon or rectum), "diabetes" for diabetes mellitus, "high blood pressure" for hypertension, "stroke" for cerebrovascular disease, and "heart attack" and "angina" for coronary heart diseases. Because of the potential for false-positive reports, each disease had to have been diagnosed by a physician, and only hypertension and angina requiring medication and heart attack requiring hospitalization were to be reported. It was not felt that participants would be able to report accurately on the pattern of high triglycerides and low high density lipoprotein cholesterol levels most associated with the metabolic syndrome, so probands were asked to report on presence of high blood cholesterol, terminology used in some population surveys (34, 35).

Case definitions

All study probands underwent a colonoscopy within 4 months after interview except probands with a previous CRC who had not been scheduled for a follow-up colonoscopy or those with incident CRC who went directly to surgery. Colonoscopies were performed by gastroenterologists on the Faculty of Medicine at the University of Toronto or the University of Ottawa. Probands were categorized according to current and past lesions, from pathologic review of lesions removed during colonoscopy and from medical history and pathology reports. Controls had no history of any polyps and no lesions on colonoscopy. The three case groups had adenomatous polyps detected on colonoscopy and no history of CRC, prevalent CRC that had been diagnosed at least 1 year previously, or incident CRC that was newly diagnosed. Probands with past polyps and no lesions on colonoscopy were excluded, as were probands with hyperplastic polyps.

Analyses

The data were organized as a series of reconstructed cohorts of case and control relatives (36), and each disorder in relatives was modeled as a function of the case-control status of probands (37). Questionnaires were excluded from analysis if the case-control status of the probands could not be adequately determined because of failure of the colonoscopy to examine the entire colon, absence of pathologic assessment of polyps, cancellation of the colonoscopy, or a delay of more than 4 months after completion of the questionnaire. Only data on full biologic relatives were analyzed.

The generalized estimating equations algorithm was used to calculate parameter estimates (PROC GENMOD) using SAS 6.12 (38), assuming an exchangeable correlation matrix. Under this assumption, correlations within families were $r \sim 0.15$ for both hypertension and hypercholesterolemia and $r < 0.1$ for colorectal cancer, diabetes, stroke, myocardial infarction, and angina. The data for the three case groups (adenomatous polyps, previous CRC, and inci-

dent CRC) were analyzed together as a combined group of colorectal neoplasia because of the similar etiology proposed for these conditions and to increase statistical power.

Confounding and effect modification were assessed by using a hierarchal backwards elimination approach (39), with two-way interaction terms between proband status and other variables assessed first. Those that significantly contributed to models ($p < 0.05$ by Wald and likelihood ratio test) were retained. Each potential confounder was then considered, and those that changed the point estimate for proband case-control status by 10 percent or contributed to the model ($p < 0.10$) were retained.

A systematic search of previous family history studies in CRC suggested that the following possible confounders and effect modifiers be considered in analysis: presence of a family history of CRC (12, 40); proband age at diagnosis (41–47); generation (47–49); and reason for referral (50); as well as probands' body mass index (BMI), age, and sex; and relatives' age and sex. Family history of CRC was measured as a binary variable for history of parental CRC. Proband age at diagnosis was described by a binary variable (≥55 and <55 years) based on the median age of the control group probands. Proband age at diagnosis was taken as the age at diagnosis for probands with CRC and present age for those with adenomatous polyps. Generation of family members was described by indicator variables for parents, siblings, and children. Reasons for referral were determined from proband responses to two sets of questions. The first reason was coded as positive for surveillance if probands reported being seen for colonoscopy for a family history of CRC, follow-up of previous polyps or CRC, or other surveillance reason (written in). The second reason was coded as positive for symptoms if probands reported being seen to investigate recent symptoms, including abdominal pain, rectal bleeding, or change in bowel habit.

Some probands, especially among those who did not undergo colonoscopy, did not complete questions on referral (prevalent ($n = 44$) and incident ($n = 7$) CRC). Since the majority of these probands were being followed for surveillance purposes, they were coded as positive for surveillance and negative for symptoms. The robustness of this assumption was tested.

For assessment of effects of possible recall bias, a binary variable that indicated whether the FHQ had been returned prior to or after the colonoscopy date was added to each disease model, and the odds ratios for case-control status were recalculated.

RESULTS

Response rates

Study probands were drawn from the 4,338 patients (2,191 men and 2,147 women) who were scheduled for colonoscopy at participating hospitals or who had had CRC in the previous 5 years. Thirty-three percent were excluded prior to determination of eligibility because of refusal to be considered, missed appointments, missing contact information, etc. Among the 2,911 remaining probands, 1,279 were eligible and were approached to participate in the physiologic marker study, and 1,185 agreed (figure 1). Of the 1,632 ineligible patients, 54 percent did not meet the age criteria, 19 percent had either ulcerative or Crohn's colitis, 18 percent had had chemotherapy or general anesthetic in the previous 12 months, 3 percent could not communicate in English, 2.1 percent had another cancer, 0.4 percent had familial adenomatous polyposis, and 3.5 percent were ineligible for other miscellaneous reasons.

Only 1,104 of the 1,185 probands received an FHQ; 26 were ill or refused to participate and 55 interviewed in Ottawa were not given a questionnaire. Questionnaires were received from 911 probands, for a response rate of 83 percent (911/1,104). There were no differences between respondents and nonrespondents regarding age, sex, or ethnic origin.

For 106 probands, case-control status could not be accurately determined because of failure of the colonoscopy to reach the cecum, absence of pathologic assessment of polyps, etc., and these probands were excluded. An additional 12 probands were excluded because they did not report any first-degree relatives, and 182 were excluded because they did not meet the criteria for the diagnosis. After categorization by diagnosis, there were 282 control probands and 329 with colorectal neoplasia (172 adenomatous polyps, 132 prevalent CRC, and 25 incident CRC).

Characteristics of probands

Case probands were, on average, 6 years older, were more likely to be male (68 vs. 46 percent), and were heavier (mean BMI, 27 vs. 26) than were control probands (table 1). Of case probands who had a colonoscopy, 61 percent reported that they were having the colonoscopy for surveillance purposes only, 19 percent because of symptoms only, 16 percent for both reasons, and 4 percent for neither reason. Among control probands, 34 percent reported having the colonoscopy for surveillance purposes only, 39 percent because of symptoms only, 19 percent for both reasons, and 8 percent for neither reason. Personal medical history of diabetes and myocardial infarction differed between groups in crude analyses, but not after adjustment for proband age, sex, and BMI. There were only two persons from the same family who both contributed family history data.

Characteristics of relatives

Years of birth, ages of relatives at questionnaire completion, and cumulative incidences of the diseases of interest in parents and siblings are shown in table 2. Data for children are not shown, since few (<3 percent) had any of the conditions of interest. Mean ages of case ($n = 657$) and control ($n = 484$) children were 34 (standard deviation, 10) and 28 (standard deviation, 11) years, respectively. Sex distributions were equal in all groups. As expected, disease in relatives was associated with a history of the same disease in the proband, adjusted for age, sex, and proband BMI (diabetes, hypertension, and hypercholesterolemia, $p < 0.001$; myocardial infarction, $p < 0.05$).

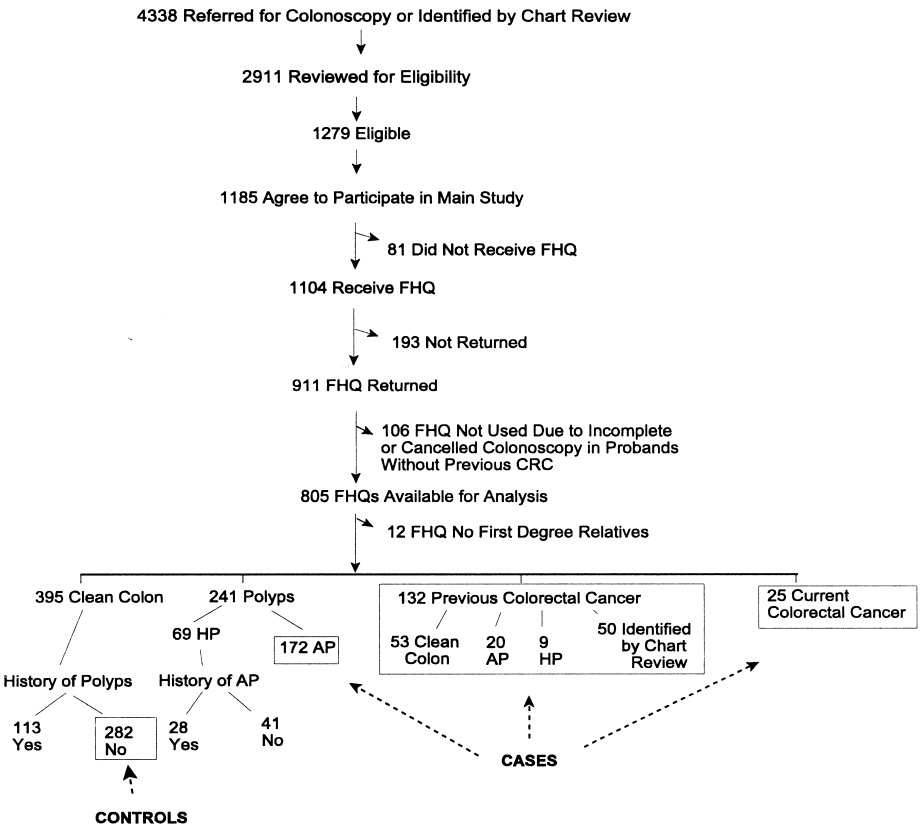

FIGURE 1. The number of case and control probands at each stage of the Toronto/Ottawa Colorectal Cancer Study, 1993–1996. FHQ, family history questionnaire; CRC, colorectal cancer; HP, hyperplastic polyps; AP, adenomatous polyps. All probands completed questions on reasons for referral and had colonoscopies except the following. Of the 50 probands identified by chart review who had CRC previously, only six answered questions on reasons for referral and three had colonoscopies. In addition, of the 25 probands with current CRC, only 18 answered questions on reasons for referral, while 24 had a surgery or a colonoscopy.

Familial disease associations

No significant associations between the familial diseases of interest and case-control status were seen when adjusted for confounders only (table 3, columns 2 and 3). The inverse association between familial CRC and proband case-control status (odds ratio (OR) = 0.6, 95 percent confidence interval (CI): 0.4, 0.8) was notable, since familial aggregation of CRC is well recognized (51).

Significant effect modification was evident in three diseases. Familial CRC was significantly inversely associated with case-control status of probands who were under surveillance but was positively associated with case-control status when probands were not under surveillance. The latter positive association between familial CRC and proband status was significant only when the BMI of the proband was greater than 25 (table 3, columns 5 and 6).

The results for diabetes were particularly complex, with simultaneous effect modification by all of proband age at diagnosis, presence of symptoms, and generation. Among younger probands, null and inverse associations were evident. Significant positive associations were seen, however, among three of the four older proband groups, particularly when older case and control probands had symptoms (parents: OR = 2.4, 95 percent CI: 1.2, 4.8, $p < 0.01$; siblings: OR = 5.8, 95 percent CI: 2.6, 13.3, $p < 0.001$).

There was also a significant positive association between familial hypertension and colorectal neoplasia among probands with symptoms.

Removal or recoding on reasons for referral for the 51 probands who did not answer the questions on reason for referral did not alter any of the results substantially, and these probands are included in the results.

Adenomatous polyps and colorectal cancer considered separately

When the adenomatous polyps and CRC case groups were considered separately, most of the familial disease associations were limited to the group with adenomatous polyps (table 4). In this group, familial CRC was inversely associated with proband status, and the association was significant when probands had a lower BMI. In the group with CRC, familial CRC was inversely associated with case-control status among probands under surveillance and was positively associated among probands not under surveillance.

TABLE 1. Baseline characteristics of probands in the Toronto/Ottawa Colorectal Cancer Study, 1993–1996

	Controls (n = 282)	Cases with colorectal neoplasia† (n = 329)
Year of birth (mean (SD‡))	1938 (10)	1931(9)
Age (years) (mean (SD))	58 (10)	64 (9)
Sex (% male)	46	68**
BMI‡ (mean (SD))	26 (4)	27 (5)**
Ethnicity (% Caucasian)	92	95
No. of relatives/proband (median (range))	6 (1–14)	6 (1–14)
Seen for surveillance, family history (%)§	53	78**
Have symptoms (%)§	58	35**
Medical history (%)		
Diabetes¶	5.0	12.8**
Hypertension	23.4	29.5
Myocardial infarction¶	4.3	9.1*
Hypercholesterolemia	21.3	20.4

* $p < 0.05$; ** $p < 0.001$.

† There were a total of 172 probands with adenomatous polyps, 132 with prevalent colorectal cancers, and 25 with incident colorectal cancers.

‡ SD, standard deviation.

§ A total of 51 probands (44 prevalent and seven incident colorectal cancers) in the case group did not complete these questions and are not included in these percentages.

¶ No longer significantly different after adjustment for proband age, sex, and body mass index.

Proband age, presence of symptoms, and generations were all still significant interaction terms in the familial diabetes model for the group with adenomatous polyps. Associations between familial diabetes and case-control status were significant among siblings of older probands (older probands with no symptoms: OR = 3.6, 95 percent CI: 1.2, 10.1; older probands with symptoms, OR = 7.2, 95 percent CI: 1.6, 31.8). While effect modification was also evident in the group with CRC, a possible positive association among older probands (OR = 1.7, 95 percent CI: 0.8, 3.6) was not statistically significant.

In the group with adenomatous polyps, but not the group with CRC, familial hypertension was positively associated with case-control status among older probands, while familial stroke was positively associated when probands had symptoms. All other familial disease associations were null.

Recall bias

Because some FHQs were completed before and some after colonoscopy, it was possible to evaluate the possibility of recall bias associated with current colonoscopy in those who were and those who were not aware of the colonoscopy results at completion of the questionnaire (table 5). There was suggestive evidence of recall bias for the presence of familial diabetes, although confidence intervals were wide. For example, the odds ratio for familial diabetes precolonoscopy among siblings of older probands with symptoms was 4.1 (95 percent CI: 1.7, 9.7) compared with 10.7 (95 percent CI: 4.5, 25.5) postcolonoscopy. In contrast, the statistically significant associations for familial CRC and hypertension were nearly identical, regardless of whether the questionnaire had been completed before or after colonoscopy.

Summary

Strong positive associations were observed for familial diabetes and hypertension primarily among the probands aged 55 years or more at diagnosis who had come for a colonoscopy because of abdominal symptoms of pain, altered bowel habit, and/or rectal bleeding. Associations were more pronounced in siblings than in parents. Strong positive associations with familial diabetes, hypertension, and stroke were evident for adenomatous polyps, with a possible association between familial diabetes and CRC among older probands. Recall bias did not account for the results.

DISCUSSION

The results add new evidence to the metabolic syndrome hypothesis, with the finding of an association between colorectal neoplasia and metabolic syndrome diseases in the families of probands who are older and/or have had symptoms. Because this investigation is, to our knowledge, the first to examine associations between colorectal neoplasia and family history of these diseases and because of findings of substantial effect modification, it is important to consider whether the findings are supported by other evidence of

TABLE 2. Characteristics of first-degree relatives in the Toronto/Ottawa Colorectal Cancer Study, 1993–1996*

	Controls		Cases with colorectal neoplasia	
	Cumulative incidence (%)	Mean age at onset (years) (SD†)	Cumulative incidence (%)	Mean age at onset (years) (SD)
Parents	(*n* = 515)		(*n* = 612)	
Year of birth (mean (SD))	1907 (12)		1899 (12)	
Age at questionnaire completion or at death (mean (SD))	74 (14)		72 (14)	
Familial disease				
Colorectal cancer	19	66 (13)	12	70 (11)
Diabetes mellitus	8	61 (12)	8	63 (11)
Hypertension	24	60 (13)	22	59 (12)
Stroke	15	71 (11)	16	72 (11)
Hypercholesterolemia	8	63 (12)	5	59 (12)
Angina pectoris	12	66 (10)	10	64 (12)
Myocardial infarction	17	67 (13)	16	67 (12)
Siblings	(*n* = 621)		(*n* = 784)	
Year of birth (mean (SD))	1938 (12)		1929 (13)	
Age at questionnaire completion or at death (mean (SD))	55 (13)		60 (16)	
Familial disease				
Colorectal cancer	4	58 (10)	5	63 (9)
Diabetes mellitus	2	49 (14)	6	56 (16)
Hypertension	11	52 (12)	17	56 (13)
Stroke	2	63 (7)	4	67 (10)
Hypercholesterolemia	7	52 (8)	9	54 (11)
Angina pectoris	3	54 (8)	4	58 (10)
Myocardial infarction	4	58 (12)	6	56 (11)

* When reported by probands.
† SD, standard deviation.

effect modification in the literature or could have arisen through bias or by chance.

Effect modification by proband age was found in one previous study of the relation between CRC and personal medical history of diabetes, with an association observed only among cases over age 60 years (13). Effect modification by proband age has also been observed in numerous studies of familial CRC. In these studies, however, the strongest associations between personal and familial CRC have occurred at younger ages (41, 52–57), in contrast to our results. Because the diseases under study are diseases of older age rather than of youth, it is perhaps to be expected that the strongest associations would be found among the relatives of older probands, who had reached ages when these diseases are more frequently observed.

Effect modification by generation, with stronger associations among siblings than among parents, has been observed in previous CRC familial aggregation studies (41, 55, 58, 59). More pronounced associations in siblings could be due to a combination of factors, including changes in disease incidence, more recently recognized disease, and more accurate diagnosis.

Effect modification by reason for colonoscopy has not been reported previously but could have resulted because of the known referral bias in colonoscopy-based studies (50). The majority of probands were undergoing colonoscopy because of previous neoplasia, because of a family history of CRC, or for investigation of symptoms of bowel disease. In the analysis of familial diabetes, the strongest case-control differences were observed in the older probands with symptoms. Seven percent of case parents and 9 percent of control parents of these probands had CRC, percentages that are similar to the lifetime probability of CRC in Canada of 6.3 percent (60). All of the other groups reported higher cumulative incidences of parental CRC, especially control probands (older probands without symptoms: 14 percent of cases and 23 percent of controls; younger probands with symptoms: 12 percent of cases and 16 percent of controls; younger probands without symptoms: 18 percent of cases and 36 percent of controls). This finding suggests that older

TABLE 3. Odds ratios and 95% confidence intervals for associations between familial diseases and colorectal neoplasia in the Toronto/Ottawa Colorectal Cancer Study, 1993–1996

Adjusted for confounders†			Stratified analyses		
	OR‡	95% CI‡		OR	95% CI
CRC‡,§	0.6***	0.4, 0.8	Not under surveillance		
			BMI ≤25	1.8	0.6, 5.1
			BMI >25	3.3*	1.3, 8.9
			Under surveillance		
			BMI ≤25	0.3***	0.2, 0.5
			BMI >25	0.6*	0.4, 0.9
Diabetes mellitus¶	1.3	0.8, 2.0	Younger		
			No symptoms, siblings	0.2***	0.1, 0.5
			No symptoms, siblings	0.5	0.2, 1.4
			Symptoms, parents	0.5	0.2, 1.4
			Symptoms, siblings	1.3	0.4, 3.5
			Older		
			No symptoms, parents	1.0	0.5, 2.1
			No symptoms, siblings	2.5*	1.0, 6.0
			Symptoms, parents	2.4**	1.2, 4.8
			Symptoms, siblings	5.8***	2.5, 13.3
Hypertension#	1.2	0.9, 1.7	No symptoms	0.9	0.6, 1.3
			With symptoms	1.7*	1.1, 2.6
Stroke††	1.3	0.9, 1.9			
Hyperchole-sterolemia‡‡	1.1	0.7, 1.8			
Angina pectoris§§	1.0	0.7, 1.5			
Myocardial infarction‡‡	0.9	0.6, 1.3			

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† Adjusted for proband body mass index (BMI), age, and sex, and for the age of a relative at questionnaire completion or at death, their sex, and their year of birth, unless otherwise indicated.

‡ OR, odds ratio; CI, confidence interval; CRC, colorectal cancer.

§ Also adjusted for symptoms, under surveillance, and generation.

¶ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, and generation.

Also adjusted for parental history of CRC, symptoms, and generation.

†† Also adjusted for symptoms and generation.

‡‡ Also adjusted for parental history of CRC, symptoms, under surveillance, and generation.

§§ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, under surveillance, parental history of CRC, and generation.

probands with symptoms were being examined more frequently because of their symptoms, while other proband groups were being examined more frequently because of a family history of CRC. The strongest positive disease associations were observed in the proband group with reported rates of parental CRC that were similar to each other and to the Canadian average, suggesting less referral bias than for other proband groups. To the extent that parental CRC was caused by metabolic syndrome factors, referral bias could have masked relevant associations.

Several forms of selection and recall bias could plausibly have occurred in this study, and the possibility of effect modification resulting from such biases was considered. Analysis of results pre- and postcolonoscopy suggested the presence of some recall bias associated with probands' knowledge of the study colonoscopy results but was not of sufficient magnitude to account for the findings. The strongest argument against the possibility of selection and other biases having a substantial impact on the results was that the

TABLE 4. Odds ratios and 95% confidence intervals for associations between familial diseases and adenomatous polyps or previous and current colorectal cancer in the Toronto/Ottawa Colorectal Cancer Study, 1993–1996†

Adenomatous polyps			Previous and current CRC‡		
	OR‡	95% CI‡		OR	95% CI
Familial colorectal cancer§,¶			Familial colorectal cancer§		
BMI ≤25	0.4**	0.2, 0.7	Under surveillance	0.3***	0.2, 0.5
BMI >25	0.8	0.5, 1.3	Not under surveillance	3.9**	1.4, 10.8
Diabetes#			Diabetes§,††		
Younger, no symptoms, parents	0.1*	0.2, 0.8	Younger	0.5	0.2, 1.2
Younger, no symptoms, siblings	0.5	0.07, 2.8	Older	1.7	0.8, 3.6
Younger, with symptoms, parents	0.2	0.02, 2.4			
Younger, with symptoms, siblings	0.9	0.1, 8.5			
Older, no symptoms, parents	0.9	0.4, 2.1			
Older, no symptoms, siblings	3.6*	1.2, 10.1			
Older, with symptoms, parents	1.8	0.4, 7.5			
Older, with symptoms, siblings	7.2**	1.6, 31.8			
Hypertension‡‡			Hypertension§§		
Younger	0.6	0.3, 1.2		1.0	0.6, 1.6
Older	1.7*	1.1, 2.6			
Stroke¶¶			Stroke§§		
No symptoms	0.8	0.4, 1.5		1.0	0.6, 1.5
With symptoms	2.3**	1.4, 3.9			
Hypercholesterolemia##	1.2	0.7, 1.9	Hypercholesterolemia§§	0.9	0.5, 1.6
Angina†††	0.8	0.5, 1.4	Angina‡‡‡	1.2	0.7, 2.2
Myocardial infarction§§§	0.9	0.6, 1.4	Myocardial infarction¶¶¶	1.0	0.6, 1.6

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† Adjusted for proband body mass index (BMI), age, and sex, and for the age of a relative at questionnaire completion or at death, their sex, and their year of birth, unless otherwise indicated.

‡ CRC, colorectal cancer; OR, odds ratio; CI, confidence interval.

§ Also adjusted for symptoms, under surveillance, and generation.

¶ Interaction significant by Wald test only.

Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, and generation.

†† Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, and parental history of CRC.

‡‡ Also adjusted for proband age at diagnosis (<55 and ≥55 years) and generation.

§§ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, parental history of CRC, and generation.

¶¶ Also adjusted for symptoms, under surveillance, and generation.

Also adjusted for parental history of CRC, symptoms, surveillance, and generation.

††† Also adjusted for proband age at diagnosis (<55 and ≥55 years), under surveillance, and generation.

‡‡‡ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, and under surveillance.

§§§ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, under surveillance, and generation.

¶¶¶ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, under surveillance, parental history of CRC, and generation.

metabolic syndrome hypothesis was unknown to subjects and physicians at the time of the study (61, 62).

Sensitivity analyses were also undertaken to assess possible bias in the odds ratio due to measurement error using Monte Carlo simulated data that incorporated information about family composition (age, sex, etc.), estimates of cumulative incidence of disease, nondifferential proband reporting error (63–68), and diagnostic error for adenomatous polyps (69–72), taken from previously published validation studies. These analyses, reported elsewhere (73), demonstrated that attenuation toward the null was more likely than creation of spurious associations and that the

TABLE 5. Recall bias assessment: odds ratios and 95% confidence intervals for associations between familial diseases and colorectal neoplasia in probands who had a colonoscopy for the Toronto/Ottawa Colorectal Cancer Study, 1993–1996†

Proband n_{con}‡, n_{ca}‡	Cases and controls completed questionnaire			
	Before colonoscopy (n_{con} = 126, n_{ca}= 121)		After colonoscopy (n_{con} = 156, n_{ca} = 161)	
	OR‡	95% CI‡	OR	95% CI
CRC‡,§				
Not under surveillance				
BMI ≤25	2.1	0.6, 6.8	1.5	0.4, 5.2
BMI >25	3.7	0.8,16.9	2.7	0.6, 12.6
Under surveillance				
BMI ≤25	0.4**	0.2, 0.7	0.3***	0.2, 0.5
BMI >25	0.7	0.2, 2.3	0.5	0.2, 1.6
Diabetes¶				
Younger				
No symptoms, parents	0.1***	0.04, 0.3	0.3**	0.1, 0.9
No symptoms, siblings	0.3*	0.1, 1.0	0.9	0.3, 2.6
With symptoms, parents	0.3*	0.1, 0.9	0.7	0.2, 2.4
With symptoms, siblings	0.8	0.3, 2.7	2.2	0.7, 7.0
Older				
No symptoms, parents	0.5	0.2,1.2	1.4	0.6, 3.3
No symptoms, siblings	1.6	0.6, 4.2	4.3**	1.7, 11.1
With symptoms, parents	1.3	0.6, 3.0	3.5**	1.5, 7.9
With symptoms, siblings	4.1**	1.7, 9.7	10.7***	4.5, 25.5
Hypertension#				
No symptoms	0.9	0.5, 1.5	1.0	0.6,1.6
With symptoms	1.7*	1.0, 2.8	1.8*	1.1, 3.1

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† Adjusted for proband body mass index (BMI), age, and sex, and for the age of a relative at questionnaire completion or at death, their sex, their year of birth, and other confounders.

‡ n_{con}, number of control group probands; n_{ca}, number of case group probands; OR, odds ratio; CI, confidence interval; CRC, colorectal cancer.

§ Also adjusted for symptoms, under surveillance, and generation.

¶ Also adjusted for proband age at diagnosis (<55 and ≥55 years), symptoms, and generation.

Also adjusted for parental history of CRC, symptoms, and generation.

degree of attenuation would vary, even if the true population association was the same for each disease. Under the scenarios tested for a true population OR = 2, associations for familial hypertension and hypercholesterolemia would be highly attenuated to OR ~ 1.0–1.1; myocardial infarction intermediate to OR ~ 1.2; and CRC, diabetes, stroke, and angina moderately attenuated to a mean observed OR ~ 1.3–1.4.

Thus, effect modifications by proband age and generation have been found previously and are biologically interpretable, while effect modification by reason for colonoscopy has not been reported previously and may have arisen because of the patterns of referral for CRC. Other biases that could account for the findings were not identified.

There is literature to support our results in studies of persons with diabetes. Of the 11 cohort studies that have examined incidence of CRC since 1970, all seven of the null studies were small and were based on analyses of fewer than 200 cases of CRC (74–80), while the four studies demonstrating significant positive associations were based on more than 700 cases of CRC (14–17). Six (8–13) of nine (8–13, 40, 81, 82) case-control studies of CRC also demonstrated significant associations, but only one (7) of three (7, 30, 83) studies of adenomatous polyps did so. Point estimates from the four largest cohort studies ranged from 0.66 to 1.55, similar to the odds ratio of 1.2 to 1.3 we observed for familial diabetes before consideration of effect modification. Thus, our data extend previous results in three ways: first, by showing associations between diabetes and CRC in families

and not only in persons; second, by demonstrating associations in subgroups; and third, by suggesting stronger associations in adenomatous polyps than in CRC.

Familial hypertension was not associated with colorectal neoplasia prior to consideration of effect modification in this study, and the majority of previous studies of personal hypertension or blood pressure have also reported null associations. Only four (18–21) of 12 studies reported statistically significant positive associations with CRC or adenomatous polyps, seven a null association (13, 30, 79, 83–86), and one an inverse association (81). Of the five studies that assessed use of various hypertension medications, two reported statistically significant positive associations (22, 23), and three found null associations (10, 87, 88). None of the previous studies reported effect modification of hypertension associations.

Our findings of an association between familial stroke and adenomatous polyps in probands with symptoms have not been reported previously. Only two case-control studies of CRC have examined a personal history of stroke; a null association was found in the first (13) and an inverse association in the second (81).

Our failure to find strong associations between colorectal neoplasia and familial myocardial infarction and hypercholesterolemia is consistent with three previous reports of null or inverse associations between personal history of myocardial infarction and CRC (13, 81) or adenomatous polyps (89) as well with a large body of evidence showing either null or inverse associations between serum cholesterol level or low density lipoprotein cholesterol and CRC or adenomatous polyps (90). A recent study using imaging (carotid sonography and echocardiography) also found no evidence of increased subclinical atherosclerosis in those who later developed CRC (25). Associations between familial cardiovascular diseases and colorectal neoplasia might not be seen, even if metabolic syndrome factors were important in causation, because mortality from cardiovascular diseases rises sharply at least 10 years before mortality from CRC increases (91), so that probands who live long enough to develop adenomatous polyps or CRC may not come from families that are more susceptible to myocardial infarction than is the population at large, in spite of familial aggregation of diabetes and hypertension.

Study design issues merit additional comment. A population-based study of polyps or CRC would not be subject to the referral patterns necessarily involved in a colonoscopy-based study. Our sensitivity analyses indicated that unless all subjects of such a study underwent colonoscopy, however, misclassification error in categorization of the control group due to the presence of undiagnosed polyps could limit one's ability to detect relevant associations if the etiologic factor affected polyp formation and prevalence of polyps was similar to that seen in recent studies (mean, 30 percent in one review (92)). Colonoscopy-confirmed, population-based controls would be difficult to obtain, but would be desirable (93).

Two main approaches (marginal and conditional models) to analyzing familial aggregation data have gained popularity in the past few years (62), with marginal approaches, such as that used in this study, being particularly appropriate when attempting to establish the existence of familial associations (94). Marginal models estimate associations between probands and the average disease experience of relatives, while conditional models estimate possible associations among all family members. This advantage of conditional models is offset by the limitation that parameter estimates may have different interpretations for different family sizes, a problem in this study since family size varied from 2 to 15 members (including probands). Neither approach is ideal. If the familial associations found in this study are confirmed, then conditional models could provide additional insights into the nature of the associations (62, 94).

Familial clustering of diabetes and hypertension was observed in a subset of probands with colorectal neoplasia who were older than age 55 years, with the strongest associations in probands with symptoms. While biases could not be identified that might account for the results, it appears possible that similar associations could have been masked among other probands because of patterns of referral for colonoscopy. The findings require confirmation to determine whether the observed effect modification occurred because of referral patterns, chance, or etiologically relevant differences among subgroups in the population.

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