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Original Paper

Allergy and Other Selected Diseases and Risk of Colorectal Cancer

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It has been reported that allergy and other diseases may be related to colorectal cancer risk. The aim of this study was to perform a systematic analysis using information about medical histories specifically to see if there was any relation between allergies or other medical conditions and colorectal cancer risk. A multicentric case–control study was conducted in six Italian areas between 1992 and 1996 on 1225 incident cases of colon cancer, 728 cases of rectal cancer and 4154 controls comparable with cases according to sex and age group, admitted for acute conditions to the same network of hospitals where cases had been identified. Unconditional logistic regression models including terms for sex, age, study centre, years of education, body mass index, physical activity, smoking, history of colorectal cancer in first-degree relatives and energy intake were used to estimate the odds ratios (OR) of colon and rectal cancer according to history of allergy and other selected diseases. The OR for history of allergy was 0.88 (95% confidence interval, CI, 0.67–1.14) for colon and 0.64 (95% CI, 0.44–0.92) for rectal cancer, and the inverse association was stronger when allergy was diagnosed at age 35 years or more, or less than 10 years before the cancer diagnosis. No clear pattern emerged in strata of age and sex. History of other selected diseases, including hypertension and cholelithiasis, was not related to colon or rectal cancer risk, though there was a moderate increase in the risk of colon cancer (OR = 1.18, 95% CI, 0.66–2.14) in patients with a history of intestinal polyps. This study lends support to the hypothesis that allergic individuals may be at a lower risk of developing colorectal cancer.
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INTRODUCTION

In a previous article from a large multicentric case–control study conducted in Italy, we found that subjects with diabetes mellitus had an approximately 30% increase in risk of colorectal cancer (CRC) [1]. Several other conditions, including intestinal polyps and gallbladder disease, have been linked to CRC risk [2, 3]. Possible explanations for such associations include: (1) a direct effect of the disease; (2) (a) common aetiological factor(s); and (3) an effect of treatment.

Several studies found an inverse relation between the history of allergies and risk of CRC. A case–control study conducted in Canada on 207 large bowel cancer cases reported a non-significant odds ratio (OR) of approximately 0.6 for history of allergy [4], and a case–control study on 715 cases in Australia reported a non-significant OR of 0.8 [5]. In a previous study from our group, conducted on 1078 cases in the Greater Milan area, the OR was 0.7 (95% confidence interval (CI), 0.5–1.0) [2]. However, a prospective study using the data of the First National Health and Nutrition Examination Survey (NHANESI) found an OR of colorectal cancer of 1.7 based on 45 cases [6], and a cohort study of 34 198 Seventh-Day Adventists in California reported an OR of 0.96 for colon ($n = 138$) and 0.86 for rectum ($n = 58$) [7]. None of these estimates were significant.

Other conditions, including hypertension, hypercholesterolaemia, gastro-duodenal ulcer and various conditions

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affecting women, may also be related to colorectal cancer risk on account of dietary, nutritional or hormonal factors [2, 3] since CRC risk may be related to female hormones [8].

PATIENTS AND METHODS

A case–control study of cancers of the colon and rectum was conducted between January 1992 and June 1996 in six Italian areas: the Provinces of Pordenone and Gorizia in North-eastern Italy, the urban areas of Milan and Genoa and the Province of Forlì, in the north of the country, Latina and the urban area of Naples in the south. The general design of the investigation has already been described [1]. The same structured questionnaire and coding manual were used in all study centres, and all interviewers were centrally trained and routinely supervised. Data were checked centrally for consistency. On average, less than 4% of cases and controls approached for interview refused to participate.

Cases were 1225 patients (688 men and 537 women) with histologically confirmed cancer of the colon (International Classification of Diseases, ICD-9 153.0–153.9) and 728 (437 men and 291 women) with cancer of the rectum and rectosigmoid junction (ICD-9, 154.0 and 154.1). All cases were diagnosed within 1 year from interview and did not have a previous history of cancer. The age range was 23–74 years and the median age was 62 years.

Controls were subjects with no history of cancer, residing in the same areas and admitted for acute conditions to the same network of hospitals where cases had been identified. Controls were not included if they had been admitted for intestinal or neoplastic diseases. A total of 4154 controls (2073 men and 2081 women) aged 20–74 years (median age 58 years) were interviewed. Controls were not individually matched to cases, but their distribution according to age, sex and geographical area was similar to that of the cases [1]. They were admitted to hospital for a wide spectrum of acute conditions, unrelated to known or likely risk factors for colorectal cancer. Of these, 27% had traumatic conditions (mostly fractures and sprains), 24% other orthopaedic disorders (mostly low back pain or disc disorders), 18% had acute surgical conditions, 24% eye diseases and 7% other miscellaneous diseases such as ear, nose and throat, skin and dental conditions.

The questionnaire included information on personal characteristics and habits, education and other socio-economic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, a validated food frequency section, physical activity, menstrual and reproductive history, history of lifetime use of aspirin and hormone preparations and family history of cancer. The subjects were also asked if they had in the past a medical diagnosis of a list of selected diseases, and the age of first diagnosis was recorded. A single general question on allergy covered a broad spectrum of conditions such as allergic rhinitis, asthma, atopic dermatitis, etc. No data were collected on treatment.

Statistical analysis

We estimated the OR of colon and rectal cancer by means of unconditional multiple logistic regression [9]. Cases tended to be older than controls, and colon, but not rectal cases, were more educated than controls [1]. Thus, the models included terms for sex, age (quinquennia), study centre, years of education, body mass index, physical activity, smoking, history of CRC in first-degree relatives and energy intake.

RESULTS

Table 1 shows the number of cases and controls who reported selected conditions other than allergy, and the corresponding OR for colon and rectal cancers separately and together. The OR of CRC were 1.23 (95% CI, 0.96–1.59) for diabetes, 0.94 (95% CI, 0.81–1.09) for (drug-treated) hypertension, 0.96 (95% CI, 0.82–1.12) for hypercholesterolaemia, 0.91 (95% CI, 0.75–1.12) for cholelithiasis, 0.97 (95% CI, 0.80–1.18) for gastro-duodenal ulcer, and 1.10 (95% CI, 0.65–1.85) for intestinal polyps. When men and women were analysed separately, no significant difference emerged (data not shown). In women, the OR was 0.81 (95% CI, 0.53–1.22) for breast nodules, 1.09 (95% CI, 0.34–3.48) for endometriosis, 1.05 (95% CI, 0.82–1.33) for uterine fibromyomas, 0.73 (95% CI, 0.50–1.07) for ovarian cysts and 1.04 (95% CI, 0.39–2.77) for Stein–Leventhal syndrome.

Table 1. *Relation of colorectal cancer with selected diseases, Italy,* 1992–1996

Disease	No. (%) with the disease			OR (95% CI)		
	Colon	Rectum	Controls	Colon	Rectum	Colorectum
Men and women	1225 (100)	728 (100)	4154 (100)			
Diabetes	66 (5.4)	50 (6.9)	185 (4.5)	1.15 (0.85–1.57)	1.44 (1.02–2.03)	1.23 (0.96–1.59)
Hypertension	225 (18.4)	128 (17.6)	743 (17.9)	1.01 (0.86–1.20)	0.84 (0.67–1.04)	0.94 (0.81–1.09)
Hypercholesterolaemia	194 (15.8)	89 (12.2)	588 (14.2)	1.05 (0.87–1.26)	0.82 (0.64–1.05)	0.96 (0.82–1.12)
Cholelithiasis	119 (9.7)	62 (8.5)	397 (9.6)	0.94 (0.75–1.18)	0.86 (0.64–1.15)	0.91 (0.75–1.11)
Gastro-duodenal ulcer	126 (10.3)	65 (8.9)	374 (9.0)	1.04 (0.83–1.30)	0.87 (0.66–1.16)	0.97 (0.80–1.18)
Intestinal polyps	18 (1.5)	8 (1.1)	39 (0.9)	1.18 (0.66–2.14)	0.90 (0.41–1.98)	1.10 (0.65–1.85)
Women	537 (100)	291 (100)	2081 (100)			
Breast nodules	24 (4.5)	10 (3.4)	110 (5.3)	0.91 (0.56–1.46)	0.65 (0.33–1.29)	0.81 (0.53–1.22)
Endometriosis	3 (0.6)	2 (0.7)	10 (0.5)	1.00 (0.25–4.05)	1.49 (0.31–7.23)	1.09 (0.34–3.48)
Uterine fibromyomas	91 (16.9)	37 (12.7)	305 (14.7)	1.19 (0.90–1.57)	0.83 (0.57–1.22)	1.05 (0.82–1.33)
Ovarian cysts	23 (4.3)	18 (6.2)	146 (7.0)	0.63 (0.39–1.02)	1.01 (0.60–1.71)	0.73 (0.50–1.07)
Stein–Leventhal syndrome	5 (0.9)	2 (0.7)	13 (0.6)	1.16 (0.39–3.49)	0.87 (0.18–4.15)	1.04 (0.39–2.77)

OR, odds ratio; CI, confidence interval. Estimates from multiple logistic regression models including terms for age, sex, centre, education, body mass index, physical activity, tobacco smoking, family history of colorectal cancer and energy intake. Reference category: no history of the disease.

Table 2. Distribution of cases of colon cancer, rectal cancer and controls, according to various aspects of history of allergy, and corresponding odds ratios (OR) and 95% confidence intervals (CI), Italy, 1992–1996

	Patient no.			OR* (95% CI)		
	Colon 1225	Rectum 728	Controls 4154	Colon	Rectum	Colorectum
Allergy						
No	1145	694	3823	1†	1†	1†
Yes	80	34	331	0.88 (0.67–1.14)	0.64 (0.44–0.92)	0.80 (0.63–1.00)
Age at first diagnosis‡ (years)						
<35	37	19	149	1.00 (0.68–1.47)	0.92 (0.56–1.52)	0.97 (0.70–1.34)
≥35	40	14	164	0.80 (0.56–1.15)	0.47 (0.27–0.82)	0.69 (0.50–0.96)
Years since diagnosis‡						
<10	17	6	112	0.62 (0.36–1.05)	0.38 (0.17–0.88)	0.55 (0.34–0.88)
10–24	28	8	102	1.01 (0.65–1.56)	0.50 (0.24–1.04)	0.83 (0.56–1.24)
≥25	32	19	99	1.03 (0.68–1.56)	1.04 (0.63–1.74)	1.03 (0.72–1.47)
Strata of covariates						
Sex						
Males	32	21	144	0.73 (0.48–1.09)	0.77 (0.47–1.25)	0.74 (0.53–1.04)
Females	48	13	187	1.08 (0.76–1.54)	0.53 (0.30–0.96)	0.89 (0.65–1.23)
Age (years)						
<60	46	14	216	1.02 (0.72–1.44)	0.50 (0.29–0.89)	0.84 (0.62–1.14)
≥60	34	20	115	0.70 (0.47–1.05)	0.76 (0.46–1.25)	0.73 (0.52–1.03)

*Estimates from multiple logistic regression models including terms for age, sex, centre, education, body mass index, physical activity, tobacco smoking, family history of colorectal cancer and energy intake. †Reference category. ‡The sum of strata does not add up to the total because of some missing values.

Table 2 shows the OR of CRC for patients reporting a history of allergy, also according to age at first diagnosis and years since first diagnosis of allergy. The OR for history of allergy is presented separately in strata of sex and age. Overall, it was 0.88 (95% CI, 0.67–1.14) for colon and 0.64 (95% CI, 0.44–0.92) for rectal cancer. For both cancers, the inverse association was apparently stronger when allergy was diagnosed at age 35 years or older, and less than 10 years before diagnosis. Thus, the OR of CRC was 0.97 (95% CI, 0.70–1.34) for patients whose allergy was first diagnosed below age 35 years, and 0.69 (95% CI, 0.50–0.96) when the allergy first occurred at age 35 years or over. When time since diagnosis was considered, the OR was 1.03 (95% CI, 0.72–1.47) for allergies diagnosed 25 or more years before, 0.83 (95% CI, 0.56–1.24) for diagnosis 10–24 years before and 0.55 (95% CI, 0.34–0.88) for those first diagnosed less than 10 years prior to CRC. No clear pattern emerged in strata of sex and age.

When subsites of the colon and rectum were considered separately, the OR for history of allergies was 0.50 (95% CI, 0.23–1.09) for right colon, 0.58 (95% CI, 0.29–1.16) for transverse and descending colon, 1.16 (95% CI, 0.80–1.66) for sigma, 0.75 (95% CI, 0.38–1.50) for the rectosigmoid junction and 0.60 (95% CI, 0.39–0.92) for rectum (data not shown).

DISCUSSION

In this study, a history of selected diseases, including hypertension and cholelithiasis, was not related to CRC risk, but patients with a history of allergies first diagnosed in the last 10 years had a lower risk of CRC.

The association between diabetes mellitus and CRC in this study has previously been discussed [1] and may be related to increased plasma levels of insulin-like growth factor-I (IGF-I) [10, 11].

Adenomatous polyps are precursor lesions of colon cancer, and several studies have found an approximately doubled risk of colon cancer in individuals with a history of adenomas, but no consistent excess in the risk of developing rectal cancer [12]. In this study, the OR of colon cancer was 1.18 (95% CI, 0.66–2.14) for patients with a history of polyps, but the upper 95% confidence limit was consistent with a doubled risk. The estimate was broadly consistent across the major geographical areas included in the study. However, no histological confirmation was available of the diagnosis of intestinal polyps, and the inclusion of non-neoplastic conditions of the colon and rectum (non-adenomatous polyps) in the self-reported history of polyps may have lowered the OR. Adjustment for other risk factors may well introduce an over-adjustment, since some colon cancer risk factors may act by increasing the risk of adenomas [13]. In fact, the OR adjusted only for age, sex and centre were 1.5 (95% CI, 0.9–2.6) for colon and 1.0 (95% CI, 0.5–2.1) for rectum.

In our study the risk of colorectal cancer was lower in subjects reporting a history of allergy. This is in agreement with some [2, 4, 5], but not all [6, 7], previous reports and, therefore, provides further support for the observation that allergy is inversely related to CRC risk. An inverse relationship with history of allergy was also found for pancreatic [14–16] and liver [17] cancer. Allergic individuals may be protected against cancer in general because of their altered immune response and modulation, although how immunological factors affect CRC and cancer in general remains unclear [18]. The association between cancer and allergies appears to be complex and may vary according to the type of allergy and cancer site [7]. However, in the present study we were unable to distinguish between different types of allergies, and no information was collected on the treatment adopted.

Hospital controls may differ from the general population in several aspects as regards medical history. However, we

excluded from the comparison group all diagnoses known or likely to be related to CRC and to the conditions considered, including chronic auto-immune conditions leading to rheumatic disorders. Moreover, when we computed OR across different disease categories of controls we obtained comparable results. The estimated prevalences for several of the diseases considered, including diabetes, hypertension, gallbladder disease and gastro-duodenal ulcer were consistent with age-specific estimates derived from National Health Surveys [19, 20]. Information on the history of selected conditions was self-reported, and this may have introduced a certain degree of misclassification. However, the hospital setting itself may have improved the comparability of information on medical history [21]. In our study, moreover, there was no excess of any condition considered, suggesting that cases did not tend to recall diseases more than controls. Participation was practically complete, and the catchment areas of cases and controls were comparable. Allowance was made for major identified potential confounding factors.

In conclusion, none of the medical conditions examined showed a strong association with colorectal cancer. The association with intestinal polyps was moderate and there was a suggestion of a reduced risk in allergic individuals, which may be worth further investigation.

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