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History of Selected Diseases and the Risk of Colorectal Cancer

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The relationship between selected aspects of medical history and the risk of colorectal cancer was analysed using data from a case-control study of 673 cases of colon cancer, 405 of rectal cancer and 1501 controls in hospital for acute, non-neoplastic, non-digestive tract conditions, unrelated to known or suspected risk factor for large bowel cancer. Significantly elevated risks (RR) were observed for history of cholelithiasis (RR = 1.5 [95% confidence interval (CI) 1.1–2.1] for colon; 1.6 [1.2–6.4] for rectum) and diabetes (1.6 [1.1–2.3] for colon; 1.3 [0.8–2.0] for rectum), and a significant protection emerged for history of drug allergy (0.6 [0.4–0.9] for colon; 0.6 [0.5–1.0] for rectum). No significant association was found with thyroid disease, gastroduodenal ulcer, liver cirrhosis, hepatitis, pancreatitis, gastrectomy, appendicectomy, treatment with cimetidine/ranitidine, treatment with chenodesoxycholic acid or with blood transfusions. The associations with cholelithiasis, diabetes and drug allergy were not materially modified by allowance for major identified potential confounding factors, and were not restricted to the diseases diagnosed within 5 or 10 years before large bowel cancer diagnosis. Thus, the analysis of this large dataset offered further quantitative evidence suggesting a possible, however moderate, association between gallbladder disease and colorectal cancer risk, which may be related to enhanced or continuous secretion of secondary bile acids. The associations with diabetes and drug allergy were unexpected, and probably indirect, lacking previous epidemiological support or any obvious biological interpretation. Thus, they should be simply regarded as working hypotheses worthy of further consideration.
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INTRODUCTION

COLORECTAL cancer is the second most common cancer site in Italy, as in most western countries [1, 2] but its causes are still largely undefined. Besides diet, which is likely to play an important role in large bowel carcinogenesis, even in the absence of a clear association with specific nutrients [3], other factors which have been related to colorectal cancer risk include reproductive and menstrual factors [4, 5] and medical history.

Among medical conditions known to be associated with the incidence of colorectal cancer, there are diseases of the large bowel, such as adenomatous polyps [6, 7] and ulcerative colitis [8], but also conditions, such as Barrett's oesophagus [9], which probably reflect common predisposing factors. Other associations, such as those with cholelithiasis or cholecystectomy [10–17] and pernicious anaemia [18], have emerged in some studies, but there is at present no clear consensus on them [19–24]. Some of the associations between aspects of medical history and colorectal cancer may be of potential interest from an aetiological viewpoint, since they may shed light on possible aetiopathogenic mechanisms.

Thus, in order to provide further information on this issue, we considered information on history of selected diseases in a large case-control study conducted in northern Italy.

SUBJECTS AND METHODS

The data were derived from an ongoing study of digestive tract neoplasms, based on a network including major teaching and general hospitals in the Greater Milan area. Recruitment of

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Table 1. Distribution of 673 cases of colon cancer, 405 of rectal cancer and 1501 controls according to socio-demographic variables and smoking. Milan, Italy, 1985–1990

	Colon cancer	Rectal cancer	Controls
Sex			
Males	332 (49.3)	234 (57.8)	885 (59.0)
Females	341 (50.7)	171 (42.2)	616 (41.0)
Age group (years)			
<45	64 (9.5)	32 (7.9)	292 (19.5)
45–54	125 (18.6)	66 (16.3)	387 (25.8)
55–64	238 (35.4)	158 (39.0)	469 (31.2)
65–74	246 (36.6)	149 (36.8)	353 (23.5)
Education (years)			
<7	353 (52.5)	242 (59.8)	755 (50.3)
7–11	187 (27.8)	98 (24.2)	428 (28.5)
≥12	132 (19.6)	62 (15.3)	317 (21.1)
Unknown	1 (0.1)	3 (0.7)	1 (0.1)
Tobacco smoking			
Never smokers	381 (56.6)	214 (52.8)	663 (44.2)
Ex-smokers	124 (18.4)	72 (17.8)	266 (17.7)
Current smokers	168 (25.0)	119 (29.4)	572 (38.1)

No. of patients (percentage).

cases of colorectal cancer started in January 1985, and the present report is based on data collected before February 1990.

The general scheme of this investigation has already been described [25]. Briefly, trained interviewers identified and questioned cases and controls in the hospitals under surveillance. On the average, less than 3% of eligible subjects refused to participate.

The structured questionnaire included information on socio-demographic factors and general lifestyle habits, a short dietary history including 29 indicator foods, and a problem-oriented medical history including 14 selected diseases or medical procedures. By definition, the diseases or medical procedures considered had to anticipate by at least 1 year the onset of the disease which led to admission. Age at onset/first diagnosis was recorded.

The cases were patients below the age of 75 with histologically confirmed colorectal cancer diagnosed within the year preceding the interview, who had been admitted to the National Cancer Institute, to several specialised university clinics and to the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan. A total of 673 cases of colon cancer (331 males, 342 females, median age 61 years) and 405 rectal cancers (234 males, 171 females, median age 62 years) were interviewed.

The comparison group included 1501 subjects (885 males, 616 females, median age 58 years) admitted to the same network of hospitals for acute, non-neoplastic or digestive tract conditions. 40% were admitted for trauma, 18% had non-traumatic orthopaedic diseases, 27% surgical conditions, including plastic surgery, and 15% other miscellaneous illnesses, such as acute infections, skin, nose, throat and eye disorders, etc. The catchment area of cases and controls was comparable: 84% of the cases and 85% of the controls came from the same region, Lombardy; 91% of the cases and 93% of the controls came from northern Italy.

Relative risks (RR), and the corresponding 95% confidence intervals (CI) [26], according to selected aspects of medical history were first computed from data stratified for sex and 5-year age groups using stratification and the Mantel–Haenszel procedure [27]. Secondly, to account simultaneously for the potential confounding effect of various risk factors, unconditional logistic regression, with maximum likelihood fitting [28], was used. Included in the regression equations were terms for age, sex, area of residence, education, body mass index and selected indicator foods.

RESULTS

Table 1 gives the distribution of cases of cancer of the colon, rectum and controls according to sex, age group, and smoking. Cases were slightly older than the comparison groups, less educated (particularly rectal cancers) and less frequently smokers. After allowance for age and sex, however, only the inverse association between education and rectal cancer was significant.

Table 2 considers the relationship between colorectal cancer and selected aspects of medical history. 8.2% of colon cancer and 6.9% of rectal cancer as opposed to 4.6% of the controls reported a history of diabetes mellitus. The association was significant for colon cancer (RR = 1.6 [95% CI 1.1–2.3]),

Table 2. Relationship of colorectal cancer with selected aspects of medical history

Disease or medical intervention	No. (%) with the disease			Relative risk (95% CI)	
	Colon	Rectal	Controls	Colon	Rectal
Diabetes	55 (8.2)	28 (6.9)	69 (4.6)	1.6 (1.1–2.3)	1.3 (0.8–2.0)
Thyroid disease	21 (3.1)	11 (2.7)	56 (3.7)	0.7 (0.4–1.2)	0.7 (0.3–1.4)
Gastric ulcer	14 (2.1)	14 (3.5)	71 (4.7)	0.4 (0.2–0.7)	0.7 (0.4–1.2)
Duodenal ulcer	36 (5.3)	28 (6.9)	94 (6.3)	0.9 (0.6–1.4)	1.1 (0.7–1.7)
Cholelithiasis	81 (12.0)	50 (12.3)	107 (7.1)	1.5 (1.1–2.1)	1.6 (1.2–2.4)
Liver cirrhosis	4 (0.6)	4 (1.0)	8 (0.5)	1.0 (0.3–3.4)	1.7 (0.5–5.3)
Hepatitis	28 (4.2)	5 (1.2)	58 (3.9)	1.1 (0.7–1.8)	0.4 (0.2–1.0)
Pancreatitis	3 (0.4)	3 (0.7)	10 (0.7)	0.8 (0.2–2.8)	1.1 (0.3–4.5)
Drug allergy	41 (6.1)	23 (5.7)	133 (8.9)	0.6 (0.4–0.9)	0.6 (0.4–1.0)
Gastrectomy	8 (1.2)	8 (2.0)	33 (2.2)	0.5 (0.8–1.2)	0.8 (0.4–1.8)
Appendicectomy	245 (36.4)	128 (31.6)	551 (36.7)	1.0 (0.8–1.2)	0.8 (0.6–1.0)
Cimetidine/ranitidine treatment	18 (2.7)	11 (2.7)	59 (3.9)	0.6 (0.4–1.1)	0.7 (0.4–1.4)
Chenodesoxycholic acid treatment	11 (1.6)	5 (1.2)	24 (1.6)	0.9 (0.4–1.7)	0.7 (0.3–1.6)
Blood transfusion	59 (8.8)	30 (7.4)	132 (8.8)	1.0 (0.7–1.3)	0.8 (0.6–1.3)

Mantel-Haenszel estimates adjusted for age and sex.

Table 3. Relationship of colorectal cancer with selected diseases according to time since diagnosis

Disease	Years since diagnosis	No. (%) with the disease			Relative risk (95% CI)	
		Colon	Rectal	Controls	Colon	Rectal
Diabetes	<5	17 (2.5)	10 (2.5)	26 (1.7)	1.3 (0.7–2.5)	1.3 (0.6–2.7)
	5–9	14 (2.1)	8 (2.0)	11 (0.7)	2.5 (1.1–5.8)	2.4 (1.0–6.0)
	≥10	24 (3.6)	10 (2.5)	32 (2.1)	1.4 (0.8–2.3)	0.9 (0.5–1.9)
Cholelith-iasis	<5	17 (2.5)	12 (3.0)	22 (1.5)	1.5 (0.8–3.1)	1.9 (1.0–4.0)
	5–9	11 (1.6)	13 (3.2)	26 (1.7)	0.9 (0.4–1.8)	1.8 (0.9–3.7)
	≥10	52 (7.7)	25 (6.2)	58 (3.9)	1.7 (1.2–2.5)	1.5 (0.9–2.4)
	Unknown	1 (0.1)	—	1 (0.1)	—	—
Drug allergy	<5	8 (1.2)	7 (1.7)	44 (2.9)	0.4 (0.2–0.9)	0.7 (0.3–1.4)
	5–9	6 (0.9)	6 (1.5)	19 (1.3)	0.8 (0.3–2.0)	1.4 (0.5–3.5)
	≥10	25 (3.7)	9 (2.2)	68 (4.5)	0.7 (0.4–1.1)	0.4 (0.2–0.9)
	Unknown	2 (0.5)	1 (0.2)	2 (0.1)	—	—

Mantel-Haenszel estimates adjusted for age and sex.

but not for rectal cancer (1.3 [0.8–2.0]). Cholelithiasis was significantly more frequent among cancers of the colon (1.5 [1.1–2.1]) and rectum (1.6 [1.2–2.4]). A further significant association was observed with drug allergy, which was less frequent among cases of cancer of the colon (0.6 [0.4–0.9]) and rectum (0.6 [0.4–1.0]) than among controls. No significant association was observed with thyroid disease, gastroduodenal ulcer, liver cirrhosis, hepatitis, pancreatitis, gastrectomy, appendicectomy, treatments with cimetidine/ranitidine (H_2-receptor-antagonists), with chenodesoxycholic acid or blood transfusions.

The three diseases showing significant associations with colorectal cancer are further examined in Table 3 in terms of time elapsed since diagnosis. For none of them was there evidence of any clear pattern in relation to time since diagnosis, although each single point estimate is clearly appreciably affected by larger random variation.

Similar analyses are presented in Table 4 in relation to age at diagnosis of colorectal cancer or interview. No appreciable interaction was observed, and the relative risk estimates were similar in younger and older age groups.

Multiple logistic regression estimates for diabetes, cholelithiasis and drug allergy are given in Table 5. None of the estimated relative risks was appreciably modified by allowance for major identified potential confounding factors, including sociodemographic variables and dietary indicators.

DISCUSSION

The findings of the present study suggest that history of diabetes and cholelithiasis may be related to some (however moderate) subsequent increased risk of colorectal cancer, while history of drug allergy may indicate or confer a relative protection. None of the other diseases considered, including thyroid disease, gastroduodenal, liver, pancreatic diseases, or medical procedures, including gastrectomy, appendicectomy, blood transfusions and treatments with cimetidine or chenodesoxycholic acid appeared to be associated with any change in risk.

Table 4. Relationship of colorectal cancer with selected disease according to age

Disease	Patients' age	No. (%) with the disease		Relative risk (95% CI)	
		Colon	Rectal	Colon	Rectal
Diabetes	<60	10 (3.4)	8 (4.9)	1.3 (0.6–2.7)	1.8 (0.8–4.1)
	≥60	45 (11.8)	20 (8.2)	1.7 (1.1–2.7)	1.1 (0.6–2.0)
Cholelithiasis	<60	23 (7.9)	17 (10.4)	1.4 (0.8–2.4)	2.1 (1.2–3.7)
	≥60	58 (15.2)	33 (13.6)	1.6 (1.1–2.3)	1.5 (0.9–2.3)
Drug allergy	<60	16 (5.5)	10 (6.1)	0.5 (0.3–0.9)	0.6 (0.3–1.2)
	≥60	25 (6.6)	13 (5.4)	0.8 (0.5–1.3)	0.7 (0.4–1.2)

Mantel-Haenszel estimates adjusted for age.

Thus, the present study adds further information on the cholelithiasis-cholecystectomy-large bowel cancer issue, which includes studies showing a direct association [10–17] and others showing no clear relationships [19–24]. However, such an association, if real, is moderate, and can easily be missed in studies of small or relatively small size, and the lower confidence limit in this study (of the order of 1.1–1.2) is compatible with published evidence from most studies. The proposed biological interpretation is in terms of continuous bile secretion following gallbladder disease/cholecystectomy, and consequent enhanced formation of secondary bile acids in the intestinal lumen, which were found to act as carcinogen promoters in animals [29–31].

While a direct link between gallbladder disease and colorectal cancer is plausible, the two other significant results observed in this study (the elevated risk for diabetes and the protection

Table 5. Multivariate relative risks of colorectal cancer according to selected aspects of medical history

Disease	Relative risk (95% CI)	
	Colon	Rectal
Diabetes	1.7 (1.1–2.5)	1.5 (1.0–2.5)
Cholelithiasis	1.4 (1.0–2.0)	1.7 (1.1–2.4)
Drug allergy	0.7 (0.5–1.0)	0.7 (0.4–1.1)

Estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, body mass index, and selected indicator foods (pasta or rice, meat, green vegetables, fresh fruits and coffee).

for drug allergy) should be viewed as generating hypotheses potentially worthy of further investigation. At least two previous studies [19, 32] reporting on diabetes and large bowel cancer found no consistent association. Although allowance for a number of sociodemographic and dietary correlates failed to totally account for the association in this study, it is still possible that the apparent association between diabetes and colorectal cancer is due to a series of common correlates of both diseases which may vary from one population to another, in the absence of any direct relationship.

Likewise, little information is available on the possible protection conferred by allergies against colorectal cancer. One plausible interpretation includes the role of aspecific immunologic stimulation induced by allergic conditions. Protections by asthma, allergic skin reactions or allergic diseases in general have already been observed in an Australian case-control study on colorectal cancer [32], although the association was not significant, as well as in relation to pancreatic [33, 34] and liver cancer (unpublished observation from the present study scheme), but these results require further confirmation.

Further caution is also suggested by the limitations of this study, with reference to the restricted list of diseases considered, and the lack of details on them, other than age at first diagnosis. On the other hand, the hospital-based design probably represents an optimal framework for investigating medical histories. Cases and controls, in fact, are similarly investigated in relation to major diseases, and similarly sensitised towards recalling diseases in the past. A large hospital-based case-control study conducted in the United States, Canada and Israel [35], for instance, found excellent reliability of interview data for diabetes, with a correlation coefficient between repeated interviews of 0.93, and a good reliability for all medical conditions or procedures requiring hospital admission or prolonged medical care. The disease prevalences observed in this study, moreover, were comparable with those observed in the 1983 Italian National Health Survey, based on a sample of about 90 000 subjects representative of the whole Italian population [36]. Among other strengths of the study are the comparable catchment area of cases and controls, the almost complete participation and the absence of important confounding by major identified potential covariates.

Thus, despite some drawbacks in available data, in consideration of the large series of the dataset and the characteristics of the design, this study has offered further relevant documentation to clarify the influence of selected aspects of medical history on subsequent colorectal cancer risk. In particular, it provides further quantitative estimates on the possible gallbladder disease/colorectal cancer relationship, and found unexpected relationships with diabetes (direct) and drug allergy (inverse), which however lack epidemiological support or convincing biological interpretation, and can therefore only be considered working hypotheses of potential interest for future work.

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Factors Predicting Late Mortality from Breast Cancer

Sakari P. Toikkanen, Harry P. Kujari and Heikki Joensuu

Survival data of a cohort of 160 patients with breast cancer, who were still alive 10 years after the primary diagnosis, and who had been followed up for at least 22 years, were investigated to find out those factors that predict late mortality from breast cancer. The 13 factors investigated included age at diagnosis, histological type and grade, mitotic count, type of tumour margin, inflammatory cell reaction, extent of tumour necrosis, primary tumour size, axillary nodal status, DNA ploidy and index, S-phase fraction and occurrence of a second primary breast cancer. Advanced age at diagnosis (> 49 years, $P = 0.002$), occurrence of a second primary breast cancer during the follow-up ($P = 0.01$), and primary tumour size (T_{3-4}, $P = 0.03$) were significantly associated with mortality from breast cancer after the 10th year of follow-up in a multivariate analysis, and the ductal invasive histological type ($P = 0.03$) and a large DNA index (> 1.2; $P = 0.06$) in univariate analyses.
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INTRODUCTION

UNLIKE IN many other forms of human cancer, a late recurrence 10 or even 20 years after the primary diagnosis is not uncommon in breast cancer [1, 2]. Most survival studies have shorter than 10-year follow-up, and because the great majority of all deaths in breast cancer take place during the first 10 years, the most important prognostic factors found in these studies, such as the axillary nodal status, size of the primary tumour and histological grade, are those that predict relatively early mortality in breast cancer [3–5]. Surprisingly little is known about the factors that predict mortality in breast cancer among patients who have survived for more than 10 years after the primary diagnosis [1, 6, 7]. Yet, due to the worldwide increase in the incidence of breast cancer and improved treatment results, the number of such patients is increasing.

The purpose of the present study was to investigate the factors predicting mortality in breast cancer among those patients who have survived the first 10 years following the diagnosis.

MATERIALS AND METHODS

Patients

According to hospital records and data from the Finnish Cancer Registry, 461 women were diagnosed to have with a biopsy verified breast cancer in the city of Turku, South-Western Finland, during the years 1945–1965. Sufficient clinico-pathological and follow-up information was available for 439 patients. The survival analysis of this larger original material is published earlier elsewhere [8]. 279 patients died within the first 10 years and a total of 160 (36%) patients were alive after the 10th year of follow-up. These 160 patients constitute the actual study material.

These patients were followed up for at least 12 additional years (range 12–32 years, median 17) or until death. 15 (9%) of the 160 patients had Paget's disease of the breast or intraductal cancer *in situ* (none of the patients with either of these two tumour types had died during the first 10 years of follow-up). 12 of the 23 patients who developed a second primary breast cancer in the remaining breast were alive after the 10th year. The clinical data and cause of death were obtained from the hospital records, the files of the Finnish Cancer Registry, the Central Statistical Office of Finland, and from local authorities. All autopsy protocols and histological slides were reviewed.

Autopsy was performed on 10 of the 31 patients who died from breast cancer after the 10th follow-up year, and a histological and/or cytological confirmation of metastatic breast cancer was available in further 10 cases. In 6 of the remaining 11 cases dissemination of breast cancer was based on radiological evidence of distant metastases, and in 5 cases on a death certificate only. 9 patients died from cancer of another organ, and the cause of death was confirmed by autopsy in 4 cases, by a histological or

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