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Short communication

Aspirin and colorectal cancer

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Summary The relationship between aspirin use and colorectal cancer risk was examined by a case–control study in Italy. Regular aspirin use was reported by only 47 (3.5%) cases and 77 (4.1%) control subjects, giving a multivariate odds ratio (OR) of 0.7 (95% CI 0.5–1.0) after allowance for education, physical exercise and selected dietary factors.

Keywords: aspirin; non-steroidal anti-inflammatory drugs; colorectal neoplasms; pharmacoepidemiology

At least six case–control studies (Kune et al, 1988; Rosenberg et al, 1991; Suh et al, 1993; Muscat et al, 1994; Peleg et al, 1994), based on over 3700 cases, have suggested that the risk of colorectal cancer may be reduced in regular aspirin users. Likewise, four (Thun et al, 1991, 1993; Schreinemachers and Everson, 1994; Giovannucci et al, 1994, 1995) out of five (Paganini-Hill et al, 1989; Paganini-Hill, 1994) cohort studies showed a protection of between 20% and 40% among regular aspirin users, although in the American Nurses' Health Study (Giovannucci et al, 1995) the protection was only evident for frequent use (≥ four times per week) and after 20 years of use. Thus, the role of time factors, including latency, in the possible relationship between aspirin and colorectal cancer are not yet fully understood (Paganini-Hill, 1994; Greenberg and Baron, 1996). In addition, few studies have investigated the potential confounding role of factors such as diet and exercise. We have therefore examined aspirin use and certain lifestyle factors in a case–control study in Italy.

SUBJECTS AND METHODS

The data were derived from a case–control study of colorectal cancer, conducted between January 1992 and June 1996 in six Italian areas: Greater Milan; the provinces of Pordenone and Gorizia; the urban area of Genoa; the province of Forli, in northern Italy; the province of Latina in central Italy; and the urban area of Naples, in southern Italy. Only 2.4% of cases and 3.2% of controls approached for interview refused to participate. Information on aspirin was included from January 1993.

Cases were 1357 subjects with incident, histologically confirmed colorectal cancer, admitted to the major teaching and general hospitals within the area of study. For 860 cases, the site of origin of the cancer was the colon and for 497 the rectum. Controls were 1891 subjects residing in the same geographical areas who had been admitted to the same hospitals in which cases had been identified for acute conditions unrelated to known or likely risk factors for colorectal cancer. Of these, 23% had traumatic conditions, 27% acute non-traumatic orthopaedic disorders, 19% acute surgical conditions, 22% eye diseases and 9% miscellaneous other illnesses, such as ear, nose and throat and dental disorders.

The structured questionnaire included information on personal characteristics, education and other socioeconomic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, a validated food frequency section (based on 79 foods, food groups or recipes; Franceschi et al, 1993), a few indicators of physical activity (occupational and leisure time), gynaecological and obstetric data, related medical history, and history of lifetime use of aspirin, including indication, time, frequency and duration of use before diagnosis of the disease which led to hospital admission. A comprehensive list of major aspirin-containing preparations (including most common combinations of multiple non-steroidal antiinflammatory drugs, NSAIDS) in Italy was supplied.

Odds ratios (ORs) of colorectal cancer, and the corresponding 95% confidence intervals (CI), according to various measures of aspirin use were derived using unconditional multiple logistic regression (Breslow and Day, 1980), including terms for study centre, sex, quinquennia of age, education (< 7, 7–11, ≥ 12 years), marital status (never married, married), family history of colorectal cancer (yes/no), measures of energy intake (quintiles), alcohol drinking (abstainer, plus tertiles), vegetable and meat intake (approximate tertiles) and an overall indicator of physical exercise (approximate tertiles).

RESULTS

Table 1 gives the distribution of colorectal cancer cases and of the control group according to sex, age, education and family history. Cases were 793 men and 564 women, aged 23–74 years (median age 62 years); controls were 1253 men and 638 women, aged 20–74 years (median age 59 years). Cases reported a family history of colorectal cancer more frequently in first-degree relatives, while there was no appreciable difference for education.

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Table 1 Distribution of 1357 cases of colorectal cancer and 1891 controls according to sex, age and selected covariates. Italy, 1993–96

	Colorectal cancer cases		Controls	
	No.	%	No.	%
Sex				
Male	793	58.4	1253	66.3
Female	564	41.6	638	33.7
Age				
< 45	99	7.3	267	14.1
45–54	220	16.2	420	22.2
55–64	476	35.1	600	32.7
65–74	562	41.4	604	31.9
Education (years)				
< 7	727	53.6	986	52.1
7–11	352	25.9	550	29.1
≥ 12	278	20.5	355	18.8
Family history of colorectal cancer[a]				
No	1224	90.2	1810	95.7
Yes	133	9.8	81	4.3

[a]$P < 0.01$.

Various measures of aspirin use are examined in Table 2. A total of 47 (3.5%) cases vs 77 (4.1%) controls reported regular use (more than four times per week for > 6 months) of aspirin. The corresponding multivariate odds ratio was 0.7 (95% CI 0.5–1.0). The risk tended to decrease with increasing duration of use (OR = 0.6 for use > 2 years) and was somewhat lower among current users (OR = 0.6). No material pattern of risk was observed with reference to time since first, last use or indication (pain vs antithrombosis). The protection was appreciably, though not significantly, stronger for rectal (OR = 0.4) than for colon cancer (OR = 0.9). The association was also somewhat stronger in women (OR = 0.5) and below age 60 years (OR = 0.6), although the interaction terms were not significant.

DISCUSSION

This study provides further support for the hypothesis that aspirin may decrease the risk of colorectal cancer, which is of interest as it is based on a southern European population with specific patterns of aspirin use and prevalence of exposure to dietary and other possible correlates of colorectal cancer.

Table 2 Relationship between various measures of aspirin use and colorectal cancer risk. Italy, 1993–96

	Colorectal cancer cases		Controls		Odds ratio (95% CI)[a]
	No.	%	No.	%	
Non-users	1310	96.5	1814	95.9	1[b]
Regular users	47	3.5	77	4.1	0.7 (0.5–1.0)
Duration of use (years)[c]					
< 2	14	1.0	20	1.1	0.9 (0.5–1.7)
≥ 2	32	2.4	56	3.0	0.6 (0.4–1.0)
Time since first use (years)[c]					
< 5	19	1.4	29	1.5	0.8 (0.4–1.5)
≥ 5	28	2.1	46	2.4	0.7 (0.4–1.2)
Time since last use[c]					
< 1 year and current	25	1.8	47	2.5	0.6 (0.4–1.0)
≥ 1 years	21	1.5	28	1.5	0.9 (0.5–1.6)
Indication[c]					
Pain	20	1.5	33	1.7	0.7 (0.4–1.2)
Antithrombosis	25	1.8	43	2.3	0.7 (0.4–1.2)
Site					
Colon	37	4.3	–	–	0.9 (0.6–1.4)
Rectum	10	2.1	–	–	0.4 (0.2–0.9)

[a]Obtained from multiple logistic regression equations including terms for age, sex, centre, education, body mass index, total energy, alcohol and meat intake, and physical exercise. [b]Reference category. [c]The sum of the strata does not add up to the total because of missing values.

Although this is one of the largest case–control investigations of colorectal cancer and aspirin, the number of regular aspirin users (and hence the statistical power) is relatively low, reflecting the pattern of aspirin use in Italy. Some of the diagnostic categories of the controls may have been associated with increased NSAID use, however separate comparison of cases with each of the major diagnostic categories of controls yielded similar results, thus providing reassurance against potential selection bias. In particular, the frequency of regular aspirin users was 3.7% among subjects with traumatic conditions and 4.2% among those with non-traumatic orthopaedic diseases.

Among the strengths of the study are the similar catchment areas of cases and controls and the almost complete participation. Furthermore, the choice of hospital controls has the advantage with regard to the reliability and validity of drug use information, as cases and controls should be similarly sensitized towards various aspects of their past medical history (Paganini-Hill and Ross, 1982; Kelly et al, 1990). Finally, allowance for potential confounding factors, including measures of social class, an indicator of physical exercise and selected dietary factors did not materially modify any of the estimates.

Colorectal cancer is the commonest neoplasm in non-smokers of both sexes in western countries (Levi et al, 1994), and a 30% reduction of risk would be of considerable public health benefit. Plausible biological mechanisms exist for a protective effect of NSAIDS in colorectal carcinogenesis (Gann et al, 1993; Greenberg and Baron, 1993). However, although we tried to avoid or minimize the limitations of case–control studies, namely possible selection, information bias and confounding, a 30% reduction in an observational study of this kind is only modest, and long-term clinical trials may still be required to properly address the issue of aspirin and colorectal cancer.

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