International Journal of Epidemiology 1998;27:397–404

Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study

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Background Using data from a case-control study carried out in Italy 1989–1992, we estimated the odds ratios (OR) and the population attributable risks (AR) for inflammatory bowel diseases (IBD) in relation to smoking, oral contraception and breastfeeding in infancy.

Methods The study focused on 819 cases of IBD (594 ulcerative colitis: UC; 225 Crohn's disease: CD) originating from populations resident in 10 Italian areas, and age-sex matched paired controls.

Results Compared with non-smokers, former smokers were at increased risk of UC (OR = 3.0; 95% confidence interval [CI] : 2.1–4.3), whereas current smokers were at increased risk of CD (OR = 1.7; 95% CI : 1.1–2.6). Females who reported use of oral contraceptives for at least one month before onset of symptoms had a higher risk of CD (OR = 3.4; 95% CI : 1.0–11.9), whereas no significant risk was observed for UC. Lack of breastfeeding was associated with an increased risk of UC (OR = 1.5; 95% CI : 1.1–2.1) and CD (OR = 1.9; 95% CI : 1.1–3.3). Being a 'former smoker' was the factor with the highest attributable risk of UC both in males (AR = 28%; 95% CI : 20–35 %) and in females (AR = 12%; 95% CI : 5–18%). Smoking was the factor with the highest attributable risk for CD in males (AR = 31%; 95% CI : 11–50%). Lack of breastfeeding accounted for the highest proportion of CD in females (AR = 11%; 95% CI : 1–22%). Oral contraceptive use accounted for 7% of cases of UC and for 11% of cases of CD.

Conclusions Taken together, the considered factors were responsible for a proportion of IBD ranging from 26% (CD females) to 36% (CD males). It is concluded that other environmental and genetic factors may be involved in the aetiology of IBD.

Keywords Attributable risk, ulcerative colitis, oral contraceptives, Crohn's disease, regression models, smoking, breastfeeding

Accepted 14 July 1997

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The term inflammatory bowel disease (IBD) refers to two related diseases, namely ulcerative colitis (UC) and Crohn's disease (CD). Their aetiology remains poorly understood but it is currently accepted that both environmental and genetic factors interact in the occurrence of these diseases. However, the fact that migrants from different geographical areas acquire similar rates after living in a common location, suggests that environmental factors play an important role in the risk both of UC[1] and CD.[2]

Although many environmental and lifestyle factors have been implicated, only tobacco smoking and oral contraceptives (OC) have been amply investigated.[3,4] It has also been suggested that lack of breastfeeding during infancy might influence the onset of IBD later in life.[5]

Different patterns of cigarette smoking in patients with IBD have been observed. Patients with UC are less likely to smoke.[3] However, the hypothesized protective effect seems to be limited to current smokers, since the risk of UC has actually been reported to be higher in former smokers.[6] On the other hand, patients with CD are more likely to be smokers.[3] The few studies, however, taking into consideration the dose-response relationship between smoking and the risk of IBD showed contrasting results.[7–11]

Evidence exists for an association between OC use and risk of IBD.[4] However, contradictory results have been reported not only concerning the effect of smoking as a putative confounding factor of OC,[12–15] but also the joint effect of smoking and OC on the risk of IBD.[16]

We carried out a matched case-control study using incident cases recruited by an Italian nationwide population-based study.[17] The main aims of this study were: (1) to evaluate the independent effect of smoking, oral contraception and breastfeeding in infancy on the risk of IBD; (2) to identify the model that would better explain the combined action of these factors, and (3) to estimate the proportion of IBD attributable to these factors in Italy.

Material and Methods

Study subjects

This study focused on a population aged 18–65 years, resident in the years 1989–1992, in 10 Italian cities: Genoa (Northern Italy); Bologna, Forlì, Modena (North-Central Italy); Florence, Rome, L'Aquila (Central Italy); Bari, Messina and Naples (Southern Italy).

We considered both in and out patients in whom the first diagnosis of IBD had been made between 1 January 1989 and 31 December 1992. In each area, potential cases were identified with the collaboration of all the public and private services involved in the diagnosis and management of IBD (gastroenterology, radiology, and endoscopy departments as well as medical and surgical divisions). All general practitioners were also asked to flag new cases. In addition, all diagnoses of IBD made by the pathology services during the study period were cross-checked. We excluded from this study those cases diagnosed within the study areas but resident elsewhere. Patients with a diagnosis of IBD made prior to 1989 were also excluded.

Clinical information was collected by evaluating medical records. Definitive diagnosis was made using standardized diagnostic criteria according to Binder *et al.*[18] for UC, and Gollop *et al.*[19] for CD. A local committee of experts reviewed the forms of all patients to check that the diagnostic criteria had been fulfilled. Furthermore, the committee discussed the cases that did not fit the diagnostic criteria. If uncertainty remained, the cases were classified as 'undefined' and were not included in the analysis (10 cases).

According to these criteria, 858 patients (626 UC and 232 CD) were included as eligible cases.

Controls were randomly selected from the patients resident in the areas considered, who were either examined by or admitted to the same hospital as the cases and 1:1 matched to each case by gender and age at diagnosis (±3 years). Controls had acute diseases not related to smoking, oral contraceptive use or immunological disorders. We excluded patients with infectious disease, from pneumology, gynaecology and obstetric departments and patients with gastrointestinal, metabolic, neoplastic and cardiovascular diseases. Thus, control patients were selected from patients admitted for minor surgery (18.3%), acute urinary tract infections (26.7%), dental/ocular diseases (30.6%), ear-nose-throat infections (19.%) and orthopaedic diseases (5.3%).

Data collection

One month after diagnosis, each eligible patient was invited to come to the department where the diagnosis had been made for routine clinical monitoring. On that occasion, the patient was interviewed by a trained interviewer blinded with respect to the aim of the study. The interview was presented as part of the routine recording of the medical history. Thus, no specific patient consent was required by the local ethics committee. A standardized questionnaire was used to collect anamnestic and lifestyle information, including breastfeeding in infancy, smoking habits and use of OC.

Information on breastfeeding in infancy, including duration of nursing, was collected from the patients with the help of their relatives when possible or when needed due to their lack of recall. Since many patients and relatives did not remember the duration of breastfeeding, we considered this variable in a dichotomous form (childhood breastfeeding, yes or no).

Questions regarding smoking concerned one of the three following conditions related to onset of symptoms: lifetime non-smoker, former or current cigarette smoker. For smokers, the following information was obtained: average number of cigarettes per day and age when the patient started smoking. For former smokers, the time period elapsed from when the patient stopped smoking was also recorded. Other smoking habits, such as cigar and pipe smoking, are not very common in Italy and were, therefore, not considered in the present study.

The OC questions concerned one of the three following conditions: lifetime non-user, former or current contraceptive user. Oral contraceptive use (former or current) was defined as use for at least one month for any indication including birth control, hormone replacement therapy, regulation of menstrual disorders or others. Only two UC patients, no CD patients and three controls had taken OC for reasons other than birth control. Current use was defined as use <12 months before onset of symptoms and former use was defined as use >12 months prior to onset of symptoms. Duration of contraceptive use was also recorded.

Of the eligible patients, 83 (4.8%) did not present themselves (28 UC patients, 5 CD patients and 35 controls) or refused to answer questions at the interview (4 UC patients, 2 CD patients and 9 controls). Thus we included in the analysis only the 819 patients responding (594 UC patients and 225 CD patients). Some non-responding controls were replaced by other matched controls that would not otherwise have been used. A 94.5% response rate was obtained for the control group.

Exploring the representativeness of the controls

The distribution of smokers and OC users in our referents was compared with that reported in two national surveys in order to ascertain whether our control group could be considered a representative sample of the Italian population as far as the variables of interest were concerned. In particular, the proportions of never, former and current cigarette smokers in the Italian population were derived from the Fifth Multipurpose Survey on the Italian Families which was conducted in 1991 by the Italian National Institute of Statistics (ISTAT). They interviewed a sample of 67 400 subjects (33 025 males and 34 375 females). The prevalence of females using OC was derived from the Italian Multicentre Gallstone Disease Study (Multicentrica Italiana Colelitiasi: MICOL Study), carried out between 1984 and 1987, which interviewed 29 739 subjects (13 750 females) aged 18–65 years, sampled from the populations resident in 14 Italian areas.[20] The expected number of smokers and OC users in the control group was calculated on the basis of the proportion of smokers and OC users in each age class of the sample of the Italian population (indirect standardization for age).

Data analysis

The risk of IBD associated with lack of breastfeeding in infancy, smoking habit and use of OC was estimated fitting several logistic regression models and expressed as odds ratio (OR) and the corresponding 95% confidence interval (CI) adjusted for potential confounding variables. Since the logistic model assumes a multiplicative joint effect of explicative variables,[21] we verified the adequacy of this last assumption, also fitting additive regression models.[22] For all considered models, we estimated the parameters by maximizing the conditional likelihood function. The goodness-of-fit of each model was assessed by the statistic D = –2 log of the likelihood ratio. Since the D-statistic provides a measure of unexplained variability, the lower its value, the better the goodness-of-fit of the model to the data. The D-statistics have asymptotic χ^2 distribution under the null hypothesis with degrees of freedom obtained by the difference between the numbers of strata and parameters estimated.[23] The corresponding calculations were carried out using the GLIM package.[24]

The risk of IBD attributable to smoking, lack of breastfeeding and OC use was estimated according to Kuritz and Landis.[25] In brief, by combining information across the strata determined by the matched sets, and using the Mantel-Haeszel estimator of OR and the proportion of exposed cases, this approach provides an estimator of the population AR. Asymptotic variance of AR, and corresponding CI, were derived under the assumption that the frequencies of disagreeing response patterns follow the multinomial distribution.

For all hypotheses tested, *P*-values <0.05 were considered as significant.

Results

The characteristics of the study population are presented in Table 1. The proportion of males was higher in the UC series than in the CD series whereas there was no appreciable difference between mean ages at diagnosis of the two series. The time elapsing before diagnosis was significantly lower in UC patients than in CD patients (χ^2 approximation of Wilcoxon test: $\chi^2_1 = 5.27$; $P < 0.05$).

Table 1 General characteristics of cases and controls: 1989–1992, Italy

	Ulcerative colitis				**Crohn's disease**			
	Cases		Controls		Cases		Controls	
Characteristic	N°	(%)	N°	(%)	N°	(%)	N°	(%)
Gender								
Males	354	(59.6)	354	(59.6)	119	(52.9)	119	(52.9)
Females	240	(40.4)	240	(40.4)	106	(47.1)	106	(47.1)
Age at diagnosis (years)								
Mean (SD)	37.5	(15.0)	37.3	(15.1)	38.3	(14.9)	38.1	(14.7)
Diagnostic delay[a] (months)								
Median (range)	3	(0–60)	not applicable		6	(0–78)	not applicable	
Smoking status								
Never	272	(45.8)	328	(55.2)	116	(51.6)	125	(55.5)
Former	185	(31.1)	84	(14.1)	31	(13.8)	31	(13.8)
Current	137	(23.1)	182	(30.6)	78	(34.7)	69	(30.7)
Breastfeeding								
No	111	(18.7)	81	(13.6)	42	(18.7)	30	(13.3)
Yes	483	(81.3)	513	(86.4)	183	(81.3)	195	(86.7)
Contraceptive use								
Never	182	(75.8)	202	(84.2)	88	(83.0)	89	(84.0)
Former	18	(7.5)	14	(5.8)	7	(6.6)	6	(5.7)
Current	40	(16.7)	24	(10.0)	11	(10.4)	11	(10.4)

[a] Interval between onset of symptoms and diagnosis

Table 2 Relations between inflammatory bowel disease and smoking status, breastfeeding and oral contraceptive use: 1989–1992, Italy

	Ulcerative colitis		Crohn's disease	
	Odds ratio[a]	(95% CI)[b]	Odds ratio[a]	(95% CI)[b]
Smoking status				
Never	1.0	(reference)	1.0	(reference)
Former	3.0*	(2 1–4.3)	1.7	(0.9–3.3)
Current	0.9	(0.7–1.2)	1.7*	(1.1–2.6)
Breastfeeding				
Yes	1.0	(reference)	1.0	(reference)
No	1.5*	(1.1–2.1)	1.9*	(1.1–3.3)
Contraceptive use				
Never	1.0	(reference)	1.0	(reference)
Former	1.3	(0.6–2.8)	1.8	(0.4–7.3)
Current	1.6	(0.9–3.0)	3.4*	(1.0–11.9)

[a] Odds ratio estimated by fitting conditional logistic regression model.
[b] 95% confidence interval of odds ratio
* $P < 0.05$.

Table 3 Dose-response relations between inflammatory bowel disease and smoking status, in accordance with duration of smoking and number of cigarettes per day: 1989–1992, Italy

	Ulcerative colitis		Crohn's disease	
	Odds ratio[a]	(95% CI)[b]	Odds ratio[a]	(95% CI)[b]
Duration of smoking				
Lifetime non-smokers	1.0	(reference)	1 0	(reference)
Former smokers				
<10 years	4 6*	(2.5–8.3)	2.2	(0.8–6.1)
10–20 years	3.8*	(2.1–6.9)	1 5	(0.5–4.3)
>20 years	1.8*	(1.1–2.9)	1 5	(0.8–4.4)
Current smokers				
<10 years	1.0	(0.6–1.6)	1.3	(0.6–2.6)
10–20 years	1.0	(0.6–1.6)	1.3	(0.7–2.6)
≥20 years	0.7	(0.4–1.2)	2.4*	(1.2–5.0)
No. cigarettes				
Lifetime non-smokers	1.0	(reference)	1 0	(reference)
Former smokers				
<10/day	3.6*	(1.1–8.9)	1.2	(0.4–3.4)
10–20/day	2.8*	(2.1–5.3)	1.3	(0.7–5.3)
>20/day	0.8	(0.5–2.7)	2.9*	(1.0–12.1)
Current smokers				
<10/day	0.9	(0.6–1.8)	1.2	(0.5–2.5)
10–20/day	1.0	(0.5–1.9)	1.4	(0.8–2.7)
>20/day	0.9	(0.4–1.9)	2.8*	(1.6–5.1)
Time between stopping smoking and symptom onset				
Never or current smokers	1.0	(reference)	1.0	(reference)
Former smokers				
<1 year	5.0*	(2.7–9.5)	7.7*	(1.0–62.2)
1–5 years	3.9*	(2.3–6.5)	2.0	(0 8–5.4)
>5 years	2.1*	(1.4–3.3)	0.6	(0.2–1.4)

[a] Odds ratio estimated by fitting conditional logistic regression models
[b] 95% confidence interval of odds ratio
* $P < 0.05$.

The distributions of smoking, breastfeeding and OC categories were similar in the two series of controls. We observed a total of 453 lifetime non-smokers, 115 former smokers and 251 current smokers in the pooled control group. The corresponding expected figures calculated by comparison with the Italian national survey of ISTAT were very similar (454 lifetime non-smokers, 112 former smokers and 253 current smokers). Moreover, for OC users, we observed 291 never users and 55 former or current OC users in the pooled control females. Analogously, very similar expected figures, calculated by comparison with the Italian MICOL survey, were observed (279 never users and 67 former or current users).

Ulcerative colitis patients showed a higher proportion of former smokers and a lower frequency of current smokers than the corresponding controls, while CD patients showed a higher proportion of current smokers and an equal frequency of former smokers.

Both diagnostic categories showed a lower proportion of patients who had been breastfed in infancy and a higher frequency of OC users than the control groups.

The relationship between the three factors and the risk of IBD are summarized in Table 2. The risk of UC was statistically >1 in former smokers, while the risk of CD was increased both in former and current smokers. Significant risks of UC and CD were observed in patients who had not been breastfed in infancy. The risks of IBD were increased both in former and current OC users, but an increase of the CD risk statistically >1 was observed only for current users. Moreover, OR for UC were lower than those for CD.

Table 3 shows the dose-response relationships between IBD and smoking status, according to two classifications of exposure levels and with the time elapsed from stopping smoking. A decreasing trend in UC risk by increasing exposure level was observed in former smokers. A direct dose-response relationship between exposure levels and risk of CD was generally observed, the only exception being duration of smoking in former smokers. An inverse trend towards a decreasing risk with increasing time between having stopped smoking and symptom onset was observed both for UC and CD.

The gender-specific relationships between the three factors and the risk of IBD estimated by different models are shown in Table 4. Smoking status and OC use have been dichotomized for this analysis comparing the higher risk category to the other two, with the aim of increasing the precision of the estimates. The risk of UC associated with the condition of former smoker was statistically >1 both in males and females, while the risk of CD associated with being a smoker (former or current) was statistically >1 only in males. Although an increase in the risk of IBD was detected in subjects who had not been breastfed, the OR were statistically significant only in females. The risk of CD was significantly increased for the condition of OC use, while the risk of UC, although >1, was not significant.

The values of the D-statistics show that neither the additive model nor the logistic multiplicative one significantly fitted our data. Nevertheless, lower values of D-statistics were observed for additive regression models. Moreover, the inclusion of interaction terms confirmed that the additive model, which includes only main effects, better fitted our data than the logistic model. This suggests that each factor did not modify the effect of the other factors considered.

Table 4 Relations between inflammatory bowel disease and smoking status, breastfeeding and oral contraceptive use, according by diagnosis and gender. 1989–1992, Italy

		Males		Females	
		Odds ratio[a]	(95% CI)[b]	Odds ratio[a]	(95% CI)[b]
			Ulcerative colitis		
Smoking status at onset					
Former versus never + actual	multiplicative	3.3*	(2.2–4.9)	3.0*	(1.5–5.3)
	additive	3.3*	(1.9–4.6)	2.9*	(1.0–5.1)
Breastfeeding					
No versus yes	multiplicative	1.2	(0.8–1.9)	2.2*	(1.2–3.6)
	additive	1.2	(0 6–1.7)	2.1*	(1.0–3.5)
Oral contraceptive use					
Current + former versus never	multiplicative	–	–	1.6	(0.9–2.4)
	additive	–	–	1.4	(0 7–2.5)
D-statistics (multiplicative model)		450.426		312.895	
D-statistics (additive model)		446.165		309.035	
d.f.		351		236	
			Crohn's disease		
Smoking status at onset					
Current + former versus never	multiplicative	2.2*	(1.2–3.9)	1.1	(0.6–2.2)
	additive	2.3*	(1.0–3.6)	1.1	(0.3–2.0)
Breastfeeding					
No versus yes	multiplicative	1.8	(0.8–3.8)	2.5*	(1.0–4.9)
	additive	1.9	(0.2–3.7)	2.2*	(1.0–4.8)
Oral contraceptive use					
Current + former versus never	multiplicative	–	–	3.1*	(1.0–6.8)
	additive	–	–	2.6*	(1.0–6.6)
D-statistics (multiplicative model)[c]		156.121		138.318	
D-statistics (additive model)[c]		150.800		137.552	
d.f [c]		116		102	

[a] Odds ratio estimated by fitting multiplicative logistic and additive multiple regression models; each model includes the three (or two in males) risk factors as covariates.

[b] 95% confidence interval of odds ratio.

[c] Goodness-of-fit D-statistics of multiplicative and additive models and corresponding degrees of freedom.

* $P < 0\ 05$.

The estimated AR for the three factors are presented in Table 5. Being a former smoker was the factor with the highest percentage of attributable cases of UC both in males (27%) and females (12%). The condition of smoker (current or former) accounted for 31% of CD cases in males, while in females only 4% of CD was attributable to smoking. The percentage of cases attributable to lack of breastfeeding ranged from 3% (UC males) to 11% (CD females). The proportion of cases attributable to the use of OC was 7% for UC and 11% for CD. A wide variability in the confidence intervals of the AR was observed, particularly for OC use.

Assuming an additive structure of the interactions, the factors considered accounted for 30% (males) and 28% (females) of UC cases and for 36% (males) and 26% (females) of CD cases.

Discussion

One of the aims of this case-control study was to estimate the independent effect of smoking habits, OC use and lack of breastfeeding on the risk of IBD.

Our results confirm that the risk of UC is markedly increased in former smokers,[3] but showed that current cigarette smokers are not at a higher risk of UC with respect to lifetime non-smokers. Moreover, this study showed no clear relationship between exposure levels of cigarette smoking and risk of UC among current smokers. Conflicting results have been reported in previous studies which investigated the relationship between current cigarette smoking and the risk of UC with OR ranging from 0.1 to 1.3.[10,26] A previous case-control study in Italy[9] reported that female current smokers had a risk of UC similar to those who had never smoked. Thus, the present study suggests that the risk of UC is independent of the condition of current smoker in the Italian population and, consequently, allows us to reject the hypothesis of a protective effect of smoking against the development of this disease. Our results support the hypothesis that stopping smoking favours the onset of symptoms in subjects in whom the disease had already previously occurred.[27] In agreement with other studies,[3,27] our results suggest that this is a chronic effect, since the intervals between giving up smoking and onset of symptoms were widely distributed and

Table 5 Risk of inflammatory bowel disease attributable to smoking status, breastfeeding and oral contraceptive use, according by diagnosis and gender: 1989–1992, Italy

	Males		Females	
	AR[a]	(95% CI)[b]	AR[a]	(95% CI)[b]
		Ulcerative colitis		
Smoking status at onset				
Former versus never + actual	27.4	(20.0–34.7)	11.8	(0.4–18.3)
Breastfeeding				
No versus yes	2.5	(<0–9.3)	8.9	(1.9–15.9)
Oral contraceptive use				
Current + former versus never	–	–	7.0	(<0–16.5)
		Crohn's disease		
Smoking status at onset				
Current + former versus never	30.6	(11.0–50.2)	4.0	(<0–26.1)
Breastfeeding				
No versus yes	5.6	(<0–15.4)	11.4	(1.0–21.9)
Oral contraceptive use				
Current + former versus never	–	–	10.6	(1.4–19.8)

[a] Population attributable risk (AR) expressed as fraction of 100
[b] 95% confidence interval (CI) of AR

an excess of risk persisted more than 5 years after giving up smoking.

As expected, a clear dose-effect relationship between the level of exposure to smoke and risk of CD has been observed in the present study, especially in current smokers. As an original finding, we observed that in former smokers the risk of CD quickly decreased with the increase in years since giving up smoking. This suggests that the smoke-induced bowel damage, related to onset of the disease and/or to its clinical expression, is quickly reversible.

Our results on the association between OC and IBD risk showed a higher risk for CD and perhaps UC in women who used OC. These findings are consistent with those recently summarized in a meta-analysis.[4]

Differential recall of OC use could have biased our results. For example, controls might differentially underreport the use of contraceptives.[12] However, the different results for CD and UC argue against such a systematic bias.

Despite the fact that, of the various epidemiological studies on this topic, we can boast the largest sample size, our study is affected by a low power to assess the dose-effect relationship between OC use and risk of IBD. This is due to the low prevalence of OC use in our female controls (15%), which probably reflects the negligible use of this contraception method by Italian women. In another large case-control investigation, 302 women resident in the US and affected by IBD were studied together with a comparable number of healthy controls.[16] Despite the smaller sample size, an accurate dose-effect analysis was possible because of the higher prevalence of OC use in controls (57%).

Results of previous studies showed a positive association between lack of breastfeeding during infancy and IBD risk in adults,[5,28] while several reports showed that IBD patients were breastfed for comparatively shorter periods, if at all.[29–32] In the present study, we found that lack of breastfeeding during infancy was positively associated with the risk of CD and UC. Recall bias, however, cannot be completely excluded. Since there are no apparent reasons why cases and controls should differ for recall on nursing practice during infancy, such a bias might generate a non-differential misclassification of the exposure measure and, consequently, we can speculate on the fact that our relations, as well as those reported elsewhere, might be underestimated.

Other sources of bias, such as selection of the sample and confounding effects, might affect the validity of our results.

Both cases and controls might be selected for the factors of interest. To avoid the incomplete inclusion of all the IBD diagnoses, we used multiple information sources including all the medical services involved in the diagnosis and management of IBD within each investigated area. Use of the capture-recapture technique[33] showed that, with our approach, we recruited 81% of newly diagnosed IBD patients in the defined reference populations, without appreciable differences between the areas.[17] Some doubts remain concerning the control group, since the selected patients may not represent the frequency of exposure in the population that gave rise to the cases.[34] Attempts were made to minimize this possible bias by selecting control patients with acute conditions from the same geographical area as cases, excluding patients with diseases potentially associated with the factors of interest, and using a wide range of diagnostic categories as sources of our controls. In addition, our estimates of the independent effects of cigarette smoking and OC use on the risk of IBD were remarkably consistent with those reported in two meta-analyses.[3,4] Nevertheless, we cannot exclude that such a selection bias might affect our results.

The existence of confounding effects might affect each one of the observed relations. We estimated the effect of each factor of interest after correcting for the effects of others. However, other uncontrolled confounders might have affected the validity of our results. Thus, socioeconomic status, potentially associated with the risk of disease, as well as smoking habits, OC use and breastfeeding might have affected the observed relations. However, it has been reported that smoking[35] and OC use[12,16] effects on IBD risk persist after adjustment for income, education and occupation.

Another aim of this study was to assess the joint action of the factors of interest on IBD risk. Several authors have used logistic models to estimate the effects of potential risk factors, but the assumption of a multiplicative structure is not always the most appropriate for representing the combined effect of two or more factors.[36] We assessed the structure of the interaction by fitting the two most commonly assumed models of combined effect (additive and multiplicative).[37] In comparing the goodness-of-fit of models, the additive one better fitted our data than the logistic model. Although the difference between models in goodness-of-fit was little, such a result suggests that each of the factors of interest act independently from the others. This is consistent with the hypothesis that smoking, OC and lack of breastfeeding act through different mechanisms. This finding disagrees with the results reported by Sandler *et al.*[12] who found a higher CD risk among women who used OC in combination with smoking and with the study published by Katschinski *et al.*[16] who found that the risk of CD was higher only among non-smokers. However, the small difference observed between the models obtained in the present study (thus allowing only a very feeble discrimination between them), and the lack of knowledge of the biological mechanisms, suggests caution in interpretation of our results.

The third aim of this study was to estimate the proportion of IBD attributable to the investigated factors in Italy. Population attributable risk is usually interpreted as the fraction of disease in a target population that might be avoided by eliminating exposure to a risk factor.[38] We attempted to identify the actual target population of the present study with that of the Italian population.

As far as the representativeness of IBD cases goes, doubts may be derived from the fact that the study population did not coincide with that of the Italian one and, therefore, the proportion of IBD cases exposed to the factors of interest in Italy remains unknown. Although the agreement of collaborative centres was on voluntary basis, we included both urban and rural areas widely distributed in Northern, Central and Southern Italy. Consequently, there is no reason to suspect that IBD cases had been differently included in the present investigation according to smoking, OC use or breastfeeding from all Italian IBD cases.

As for the representativeness of the controls, no appreciable differences in exposure to smoking and OC use were observed between our referents and in the Italian population. However, although the lack of information on breastfeeding practice in Italy, as well as the already recalled potentially presence of selecting and/or confounding factors could have biased our results, we believe that our estimates of AR are the best available approximation of the proportion of IBD cases explained by the investigated factors in Italy. Alternatively, our estimates might be interpreted as referring to the resident populations of the 10 Italian cities, but not to the whole Italian population.

If taken together, the factors we investigated were responsible for 30% (UC) and 36% (CD) of cases in males, and 28% (UC) and 26% (CD) in females. Assuming that every year in Italy 3059 new cases of UC and 1354 of CD[17] occur, we estimate that only 889 cases of UC and 419 cases of CD are explained by the factors considered. These figures suggest that other important factors are involved in the aetiology of IBD. Several risk indicators, including limited physical activity,[39] dietary factors,[40–42] previous diseases such as psoriasis[43] and early infections,[31,44] absence of appendectomy,[45] alcohol intake,[26] and contact with animals[30] have been investigated, but the results are conflicting. In addition, genetic factors might be involved in susceptibility to these, or to others, environmental factors.

Acknowledgement

The authors are grateful to the Steering Committee of the MICOL study, for having made available the data on the surveys used in this investigation to estimate the prevalence of OC users in the Italian population.

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