

PAPERS AND SHORT REPORTS

Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age

MARTIN VESSEY, DEREK JEWELL, ALISON SMITH, DAVID YEATES, KLIM McPHERSON

Abstract

Since the start in 1968 of the Oxford Family Planning Association contraceptive study 31 women have developed ulcerative colitis and 18 have developed Crohn's disease, giving incidences of 0.15 and 0.09/1000 woman years respectively. The incidence of ulcerative colitis in women who were non-smokers on entry to the study was 0.17/1000 woman years and the incidence in smokers was 0.11/1000 woman years. The findings for Crohn's disease were entirely different, the corresponding incidences being 0.05 and 0.17/1000 woman years respectively. Both ulcerative colitis and Crohn's disease were more common among women currently using oral contraceptives than among those not doing so. Incidences per 1000 woman years for ulcerative colitis were 0.26 in users and 0.11 in non-users; for Crohn's disease the incidences were 0.13 and 0.07 respectively.

Though the association between the use of oral contraceptives and chronic inflammatory bowel disease cannot be regarded as established, the effects of smoking have been shown consistently in many studies. This observation provides an important clue to the aetiology of chronic inflammatory bowel disease.

Introduction

The results of recent work have suggested that patients with ulcerative colitis tend to be non-smokers^{1,2} and that patients with

Crohn's disease tend to be smokers.^{1,6,7} There is also evidence that women with Crohn's disease, especially of the colon, tend to be users of oral contraceptives.^{8,9} These findings encouraged us to examine the data on chronic inflammatory bowel disease obtained in the Oxford Family Planning Association contraceptive study; we report our findings here.

Methods

The methods used in the study have been described in detail elsewhere.¹² Briefly, 17 032 white married women aged 25-39 were recruited at 17 family planning clinics in different parts of England and Scotland during the period May 1968 to July 1974. On entry 9653 (56%) were using oral contraceptives, 4217 (25%) were using a diaphragm, and 3162 (19%) were using an intrauterine device. These women are being followed up at the clinics or, when necessary, by post, telephone, or home visiting; the annual rate of lapse for reasons other than death or emigration is only about 0.3%. Information collected about each woman during follow up is coordinated at each clinic by a research assistant and includes details of pregnancies and their outcome, changes in contraceptive practices, and reasons for referral to hospital as an outpatient or inpatient. Diagnoses on discharge from hospital are confirmed by obtaining copies of discharge letters or summaries.

We started the present analysis by identifying the study records for each woman in whom ulcerative colitis or Crohn's disease had been diagnosed. These records were then reviewed, and those women for whom the date of onset of chronic inflammatory bowel disease clearly preceded the date of entry to the study were excluded. The medical information available on each patient was also reviewed (by DJ). If there was insufficient evidence to confirm the diagnosis of ulcerative colitis or Crohn's disease additional hospital notes, x ray films, and histological slides were requested from the consultant responsible for the patient's care.

To qualify for a diagnosis of ulcerative colitis the inflammation had to be confined to the colon, be present in the rectum, and spread from the rectum in continuity. The histological features of ulcerative colitis had to be present and those suggestive of Crohn's disease absent. There were sufficient data in our records to confirm the diagnosis of ulcerative colitis in all cases. For patients with Crohn's disease segmental disease associated with characteristic radiological and histological features had to be present; x ray films were used to confirm the diagnosis in six cases and histological slides in 10. One patient was re-diagnosed as suffering from ulcerative colitis, and a further patient was excluded from the study as the x ray films and

Department of Community Medicine and General Practice, Radcliffe Infirmary, Oxford OX2 6HE

MARTIN VESSEY, MD, FRCPED, professor
ALISON SMITH, BSC, research assistant
DAVID YEATES, PHD, computer scientist
KLIM McPHERSON, PHD, university lecturer

Gastroenterology Unit, Radcliffe Infirmary, Oxford OX2 6HE
DEREK JEWELL, DPHIL, FRCP, consultant physician

Correspondence to: Professor Vessey.

histological slides provided no evidence of inflammation. These assessments were made in the absence of information about use of tobacco and contraceptives.

We believe that as a result of this procedure we identified all the adequately diagnosed cases of ulcerative colitis and Crohn's disease in the study cohort. From information collected routinely during the investigation we calculated the incidences of the two diseases in relation to age, social class, cigarette smoking habits, and use of oral contraceptives. Details of the statistical methods used are reported elsewhere.¹²

Results

Altogether we identified 31 cases of ulcerative colitis and 18 of Crohn's disease. The overall incidence of ulcerative colitis (0.15/1000 woman years) was thus almost twice that of Crohn's disease (0.09/1000 woman years). Both diseases were more common in the third and fourth decades of life than in the fifth. There was little indication of any association between social class and the incidence of ulcerative colitis; Crohn's disease was more common in women of lower social class, but this difference did not reach significance.

Table I shows the relation between cigarette smoking and chronic inflammatory bowel disease. The smoking histories were obtained when women entered the study so there may have been some misclassification, which would be expected to blur relations. None the less, the associations were in the expected direction: ulcerative colitis was less common among current smokers than among those who had never smoked, and the reverse was true for Crohn's disease. For both diseases the incidences in ex-smokers were close to those in women who had never smoked. When the incidences in those smoking on entry to the study were compared with the incidences in those not doing so the difference was significant for Crohn's disease but not for ulcerative colitis.

Table II shows the relation between use of oral contraceptives and chronic inflammatory bowel disease. There was no misclassification here because accurate histories of contraceptive use are recorded regularly throughout the study. The incidences of both ulcerative colitis and Crohn's disease were higher in women currently using oral contraceptives than in those who had never used them. In addition, the incidences of both conditions were similar in ex-users and those who had never used oral contraceptives. Comparison of

the incidences in current users and non-users gave a significant difference for ulcerative colitis but not for Crohn's disease. We also examined the incidences in women currently taking oral contraceptives in relation to duration of use. There was some suggestion of a positive relation for Crohn's disease. The data were too few to allow us to investigate different brands of oral contraceptives.

Because of the suggestion that colonic Crohn's disease is particularly likely to occur in users of oral contraceptives¹⁰ we classified the 18 cases of Crohn's disease according to the part of the bowel affected. In seven only the colon was affected, in seven only the ileum, and in four both areas were diseased. The number of current users of oral contraceptives in each of the three groups was four, two, and two respectively. These data are not inconsistent with the hypothesis that the colon is particularly likely to be the site of Crohn's disease in those using the pill, but the numbers are too small for firm conclusions to be drawn.

The analyses in tables I and II do not take account of the inter-relationship between variables. For example, women of low social class and women who use oral contraceptives are more likely to smoke cigarettes than women of high social class and women who use non-steroidal contraception. Accordingly, we recalculated the incidences in relation to smoking and use of oral contraceptives, adjusting the figures by indirect standardisation to allow for the effects of the other variables.¹² Table III summarises the results. Differences were slightly reduced, but the previous conclusions were unaltered.

TABLE I—Incidences of ulcerative colitis and Crohn's disease related to smoking habit on entry to study

Cigarette smoking habits	Woman years of observation	Ulcerative colitis		Crohn's disease	
		No of cases	Incidence/1000 woman years	No of cases	Incidence/1000 woman years
Never smoked:	115 162	19	0.16	6	0.05
Ex-smoker	24 444	5	0.20	1	0.04
Current smoker:					
1-14/day	37 081	6	0.16	6	0.16
≥15/day	27 698	1	0.04	5	0.18
Total	204 385	31	0.15	18	0.09

* Difference in incidence between those smoking on entry to the study and those not doing so: $\chi^2_1 = 0.81, 0.50 > p > 0.30$.
 † Difference in incidence between those smoking on entry to the study and those not doing so: $\chi^2_1 = 5.89, 0.02 > p > 0.01$.

TABLE II—Incidences of ulcerative colitis and Crohn's disease related to use of oral contraceptives

Use of oral contraceptives	Woman years of observation	Ulcerative colitis		Crohn's disease	
		No of cases	Incidence/1000 woman years	No of cases	Incidence/1000 woman years
Never used	75 950	8	0.11	6	0.08
Ex-user	67 319	7	0.10	4	0.06
Current user‡:					
≤24 months' use	18 326	5	0.27	1	0.05
≥25 months' use	42 790	11	0.26	7	0.16
Total	204 385	31	0.15	18	0.09

* Difference in incidence between those currently using pill and those not doing so: $\chi^2_1 = 4.09, 0.05 > p > 0.01$.
 † Difference in incidence between those currently using pill and those not doing so: $\chi^2_1 = 0.62, 0.50 > p > 0.30$.
 ‡ Defined as those using pill within the six months preceding onset of disease.

TABLE III—Crude and adjusted incidences of ulcerative colitis and Crohn's disease per 1000 woman years related to cigarette smoking and use of oral contraceptives

Classification variable	Incidence of ulcerative colitis*		Incidence of Crohn's disease	
	Crude	Adjusted	Crude	Adjusted
Cigarette smoking (on entry to study)‡:				
Never smoked	0.16	0.16	0.05	0.06
Ex-smoker	0.20	0.20	0.04	0.04
Current smoker	0.11	0.11	0.17	0.15
Use of oral contraceptives§:				
Never used	0.11	0.11	0.08	0.09
Ex-user	0.10	0.11	0.06	0.06
Current user	0.26	0.23	0.13	0.12

* Difference in adjusted incidence between those currently using pill and those not doing so: $\chi^2_1 = 3.46, 0.10 > p > 0.05$.
 † Difference in adjusted incidence between those currently smoking and those not doing so: $\chi^2_1 = 3.88, 0.05 > p > 0.02$.
 ‡ Cigarette smoking: adjusted incidence standardised for age, social class, use of pill.
 § Oral contraceptive use: adjusted incidence standardised for age, social class, smoking.

Discussion

The incidences of ulcerative colitis (0.15/1000 woman years) and of Crohn's disease (0.09/1000 woman years) in our study are consistent with those recorded elsewhere,^{13,17} bearing in mind that our investigation was limited to women of childbearing age and that the use of oral contraceptives was thus much greater than that in the general population. Our findings on cigarette smoking are similar to those reported by others,^{1,7} with ulcerative colitis being less common and Crohn's disease more common in current smokers than in those who had never smoked. Incidences in ex-smokers were similar to those in women who had never smoked. Because smoking histories were recorded when women were first recruited to the investigation some misclassification may have arisen, but this would have tended to obscure true relations rather than bring out spurious ones. Perhaps more importantly, the smoking histories were taken when the women who went on to develop chronic inflammatory bowel disease were, so far as can be established, well. It is thus extremely unlikely that the development of bowel disease influenced the women's smoking habits rather than the reverse.

The association between cigarette smoking and chronic inflammatory bowel disease (negative for ulcerative colitis, positive for Crohn's disease) must now be regarded as established, but the mechanism underlying the association remains obscure. Somerville *et al*, though stating that "we can offer no explanation why Crohn's disease might tend to occur more commonly in smokers and ulcerative colitis in non-smokers," suggested that there might be a genetic predisposition to chronic inflammatory bowel disease and

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that smoking habit might determine which of the two diseases develops.⁷ They also observed that cigarette smoking is associated with increased consumption of refined sugar and that such consumption has consistently been associated with Crohn's disease. Studies of diet have not, however, shown any association between consumption of refined sugar and ulcerative colitis. Furthermore, Thornton *et al* recently provided evidence that smoking and a high consumption of refined sugar show independent positive associations with the development of Crohn's disease.⁶

With regard to use of oral contraceptives our data on Crohn's disease, indicating a possible increased risk of the disease in those taking the pill, are consistent with the findings of others.^{8,10,11} In our study the use of oral contraceptives was, however, more strongly associated with ulcerative colitis than with Crohn's disease, though even this association fell just short of conventional levels of significance in the adjusted analysis (see table III). The only other studies of the relation between the use of oral contraceptives and ulcerative colitis have been performed by the Royal College of General Practitioners, which found a positive association,⁹ and by Rhodes *et al*, who did not.¹⁰

It might be argued that women developing such a disabling condition as chronic inflammatory bowel disease would want to avoid pregnancy at all costs and might, therefore, switch to oral contraception, thus producing a spurious positive association between the pill and disease. This argument does not, however, explain our observations. Firstly, as far as was possible, we identified the date of onset of disease in each woman and related use of contraceptives to that date. Secondly, the association between use of the pill and disease was stronger in those who had been using oral contraceptives for a long time than in those who had recently started this method of birth control.

If oral contraceptives do have an aetiological role in chronic inflammatory bowel disease (and this cannot yet be regarded as established) the mechanism of their action is obscure. The suggestion, however, that colonic Crohn's disease is particularly associated with use of the pill points towards a possible vascular basis for the lesion, as there have been several cases of acute

segmental colitis associated with the oral contraceptive pill that have been interpreted as having an ischaemic aetiology.^{18,19}

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Increase in bronchopulmonary infection due to *Branhamella catarrhalis*

D T McLEOD, F AHMAD, S CAPEWELL, M J CROUGHAN, MARGARET A CALDER, A SEATON

Abstract

In a six month prospective study during the winter *Branhamella catarrhalis* was isolated from the sputum of 63 patients with symptoms of bronchopulmonary infection: 49 isolates were in pure culture and 14 were with another pathogen, *Haemophilus influenzae* being the commonest (found with 10 of the 14 *B catarrhalis* isolates). Of 36 patients infected in the community, 26 required admission to hospital. The remaining 27 patients

were infected while in hospital. Forty four of the 63 isolates produced β lactamase; 26 of these had been acquired in the community. As a result 29 patients were treated inappropriately with ampicillin and did not respond to this treatment. β Lactamase produced by *B catarrhalis* may also protect other pathogens normally susceptible to β lactam antibiotics. Most patients had chronic lung diseases or lung cancer, but three otherwise healthy patients who did not smoke developed bronchitis. *B catarrhalis* contributed to the death of five patients.

A survey of the antibiotic prescribing habits of the referring general practitioners together with the sensitivity results of *B catarrhalis* suggest that changes in antibiotic prescribing habits in the community may be responsible for the increase in *B catarrhalis* infection.

Introduction

Branhamella catarrhalis, previously considered to be a harmless oropharyngeal commensal, is being recognised increasingly as an important pathogen. Its presence in the oropharynx lends itself to

Chest Unit and Department of Bacteriology, City Hospital, Edinburgh E10 5SB

D T McLEOD, MRCP, medical registrar, chest unit
F AHMAD, MB, MIBiol, registrar in bacteriology
S CAPEWELL, MRCP, medical registrar, chest unit
M J CROUGHAN, FIMLS, senior chief medical laboratory scientific officer
MARGARET A CALDER, MD, consultant bacteriologist
A SEATON, MD, FRCP, consultant physician, chest unit

Correspondence to: Dr D T McLeod, North Tees General Hospital, Stockton on Tees, Cleveland TS19 8PE.