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Acknowledgements—We thank our data coordination team, Alwynne Tidy, Clare Jacobs and Gill Murrells for management of this trial.

Eur J Cancer, Vol. 26, No. 6, pp. 684–690, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00

Case-control Study of Risk Factors for Cervical Intraepithelial Neoplasia in Young Women

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A case-control study of 497 women under age 40 diagnosed with cervical intraepithelial neoplasia (CIN) and 833 controls was done in the London area between 1984 and 1988 to examine whether known risk factors for invasive cervical cancer produced similar risks for CIN of different grades in young women. Cases of CIN III had a risk profile similar to that seen for invasive disease whereas CIN I cases were similar to the controls in all risk factors examined except a history of genital warts. Cases of CIN II were intermediate between the two. Among several indicators of sexual and reproductive behaviour, age at first childbirth and a history of multiple sexual partners were the strongest risk factors for CIN II and CIN III. Smoking had a strong and independent effect on the risk of CIN II and CIN III, but had only a limited effect for CIN I. Use of oral contraceptives was widespread in cases and controls, but length of use of oral contraceptives was not found to be a risk factor. A small protective effect of barrier contraception was observed.
Eur J Cancer, Vol. 26, No. 6, pp. 684—690, 1990.

INTRODUCTION

SEXUAL and reproductive factors are well established features of risk for invasive cervical cancer [1–5]. Cigarette smoking is also a well documented, albeit less well understood, factor [6–10], while the risk associated with oral contraceptive usage remains controversial [11–15]. Less is known about the relation of these factors to different grades of cervical intraepithelial neoplasia (CIN), especially the mild lesion CIN I [3, 11, 16–19]. The frequency of both invasive cancer and CIN is rising rapidly in young British women [20, 21] and, to see which factors are most related, we have done a case-control study of CIN in women under the age of 40.

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SUBJECTS AND METHODS

Subjects

We studied 497 cases of CIN and 833 controls between 1984 and 1988. The mean age of the cases was 28 (range 18–39). Cases

were unselected routine referrals from local general practitioners (GPs) to the Royal Northern Hospital, London, of women with an abnormal cervical smear. They were all diagnosed within 2 years of interview, 53% within 6 months. The patients were classified histologically from biopsy material as CIN I, II and III [22]. The most severe disease indication was used, i.e. patients coded CIN I/II were classified as CIN II. Patients with invasive or micro-invasive disease were excluded, as were patients found to be normal, to have only inflammatory disease or other minor abnormalities not amounting to CIN.

The controls were patients of local GPs or Family Planning Clinics (FPCs) in the catchment area from which cases were drawn. 54% came from one general practice, which was felt to represent broadly the population that would routinely be referred to the Royal Northern Hospital, 9% came from other GPs and 37% came from FPCs. All controls were randomly selected from either the practice list of patients 16–40 years old or from women in the same age group who were attending FPCs. Women who had had a hysterectomy or a long-standing serious illness, or had never experienced sexual relations were not eligible for the study either as cases or controls. GP controls drawn were invited to participate by letter. If no reply was received a second letter was sent followed by telephone calls. To overcome the difficulty of locating potential controls in an inner city area and to obtain consent to participate, we selected most of the GP controls from one practice which was situated only 2 miles from the hospital. Of all selected GP controls, 55% were successfully interviewed, 15% refused to participate, 19% did not reply and could not be contacted by phone, 8% had changed address and 3% failed to attend the interview although they had agreed to participate.

To assess potential biases associated with the use of one practice for selecting controls, we took another set of controls from the three major FPCs in the district. Of the 209 women who were contacted at FPCs, 206 (99%) were successfully interviewed.

All subjects were interviewed between September 1984 and December 1988 by two experienced interviewers at the hospital clinic (for the cases) or at the GP's surgery or FPCs (for the controls). Information was collected on personal, sexual, reproductive and contraceptive factors. Details of previous sexually transmitted diseases (STDs) and the date of the last negative smear (if within the previous 5 years) were also recorded.

Statistics

Univariate and multivariate logistic regression analyses were used. Odds ratios (ORs) were obtained separately for the three CIN categories and for all cases combined. All estimates were adjusted for age and social class (by father's occupation). The analyses were also done separately with each of the two control groups. After adjusting for education and social class the results were similar (data not shown), and results are presented for the combined control group only. Trend tests for factors on an ordinal scale were computed by testing their significance in the logistic model when treated as continuous variables. Confounding variables were adjusted for by fitting multivariate models containing the variables of interest and the confounders. A forward stepwise technique was applied to identify the most important risk factors.

Table 1. Percentage distribution by selected sociodemographic factors

Variable	Controls (n = 833)	Cases: All (n = 497)	CIN I (n = 110)	CIN II (n = 103)	CIN III (n = 284)
Age					
≤20	4	6	10	10	3
21–23	13	14	22	19	9
24–26	20	21	23	24	19
27–29	22	21	16	24	22
30–32	20	22	20	13	26
33–35	13	14	8	10	18
36–40	9	3	1	0	4
Social class					
I	13	13	11	16	13
II	35	30	34	33	27
III NM*	7	10	6	9	11
III M	22	26	26	21	28
IV	8	10	10	6	11
V	5	6	4	8	6
Unknown	11	6	10	8	5
Education					
None or CSE	17	31	25	21	37
O levels	26	25	30	27	23
A levels	23	18	14	22	18
Degree	34	23	29	29	19
Unknown	1	3	3	0	4

*Including armed forces.

RESULTS

Sociodemographic characteristics

CIN I and CIN II cases were younger than CIN III cases and controls (Table 1). There were no substantial differences in social class. No significant differences were found in race, place of birth and religion: most women were white (93% of cases and 94% of controls), were born in the U.K. (84% and 87%) and were Church of England (39% and 37%) or Catholic (22% of cases and controls). A larger proportion of cases had limited

Table 2. Odd ratios and 95% confidence intervals for education*

Education	CIN I	CIN II	CIN III	All cases
None and CSE†	1	1	1	1
O levels	0.76 (0.42–1.35)	0.79 (0.42–1.46)	0.40 (0.27–0.60)	0.52 (0.38–0.73)
A levels	0.37 (0.18–0.76)	0.73 (0.37–1.43)	0.35 (0.22–0.54)	0.41 (0.28–0.58)
Degree	0.62 (0.34–1.16)	0.68 (0.35–1.32)	0.22 (0.14–0.35)	0.35 (0.25–0.51)
χ^2_1 for trend	3.3	1.2	46.7***	34.7***

*Adjusted for age and social class excluding 'not known'.
†Reference group.
***$P < 0.001$.

Table 3. Percentage distribution of cases and controls by sexual and reproductive factors

Variable	Controls	Cases			
		All	CIN I	CIN II	CIN III
Age at menarche					
≤12	37	36	35	41	38
13–14	49	47	52	43	46
>16	15	17	13	17	16
Age at 1st intercourse					
≤16	26	39	28	43	41
17–19	51	45	46	45	44
≥20	23	17	26	13	15
No. of partners					
1	19	9	9	7	9
2	12	8	14	8	6
3–5	25	27	28	29	25
6–19	36	46	42	48	46
≥20	8	11	7	9	14
Parity					
0	68	65	83	73	55
1	15	15	11	15	16
2	13	12	4	6	18
≥3	4	8	3	6	11
Age at 1st birth*					
<20	18	38	16	57	38
20–29	65	58	84	39	59
≥30	17	3	0	4	4

*Percentages are computed for n'= 267, 174, 19, 28 and 128 respectively.

education, especially in CIN III cases where the ORs showed a highly significant trend (Table 2).

Sexual and reproductive characteristics

Many variables relating to sexual behaviour were examined (Table 3). Age at menarche had no significant relation with risk of CIN I, CIN II or CIN III (χ^2 for trend: 0.3, P = 0.58, = 0.01, P = 0.92, and 0.1, P = 0.75, respectively). The ORs for age at first intercourse, adjusted for age and social class, showed significant trends in the CIN II and CIN III groups but not for CIN I (Table 4). The lifetime number of sexual partners was significantly increased in all three disease categories and the risks were similar. Increasing parity was associated with a significantly elevated risk for CIN III only, but a protective association was found for CIN I. An early age at childbirth was found to increase significantly the risk of both CIN II and CIN III, but appeared to be protective for CIN I, although this was only marginally significant.

Because these variables were correlated, their effects were re-examined after adjustment was made for all the others (Table 4). Only number of partners and age at first birth retained significance, with parity significant if age at first birth was not included.

Several other sexual and reproductive variables were considered. Number of sexual partners in the past 2 years and number of abortions were found to be less informative than total number of partners and parity, respectively. Similarly the period of sexual activity before age 20 and interval between age at menarche and age at first intercourse were found to be less powerful than age at first intercourse.

Table 4. Odds ratios for sexual and reproductive factors (reference group is defined by lowest category for each variable)

Variable	CIN I		CIN II		CIN III		All cases	
	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2
Age at 1st intercourse								
≤16	1	1	1	1	1	1	1	1
17–19	0.89	0.89	0.54*	0.68	0.51*	0.69*	0.58*	0.74*
≥20	1.30	1.76	0.41*	0.78	0.35*	0.78	0.50*	0.96
χ^2_1 for trend	0.6	2.1	9.6**	1.2	29.1***	2.1	20.7***	0.5
No. of partners								
1	1	1	1	1	1	1	1	1
2	2.29	2.72*	1.77	1.78	1.07	1.20	1.48	1.68
3–5	2.48*	2.91*	3.35*	3.41*	2.36*	2.68*	2.52*	2.83*
6–19	2.72*	3.30*	3.89*	3.67*	2.97*	3.43*	3.05*	3.44*
≥20	2.58	3.18*	4.10*	3.50*	4.15*	4.79*	3.76*	4.17*
χ^2_1 for trend	6.1*	6.8**	14.0***	8.6**	36.6***	32.3***	32.3***	38.0***
Parity								
0	1	1	1	1	1	1	1	1
1	0.70	0.66	1.23	3.70*	1.31	2.73*	1.10	2.29*
2	0.26*	0.27	0.75	1.90	1.58*	3.07*	1.07	2.11*
≥3	0.57	0.57	2.09	4.22*	2.76*	4.45*	2.01*	3.43*
χ^2_1 for trend	6.8**	0.6	0.4	0.0	14.0***	1.8	4.5*	1.1
		(3.0)		(0.9)		(19.0***)		(9.5**)
Age at 1st childbirth								
<20	1	1	1	1	1	1	1	1
20–29	1.75	1.65	0.21*	0.25*	0.43*	0.59	0.44*	0.57*
≥30	0	0	0.10*	0.11*	0.10*	0.14*	0.10*	0.12*
Null	2.65	†	0.32*	†	0.31*	†	0.42*	†
χ^2_1 for trend	4.9*	1.4	1.8	10.9***	17.5***	13.5***	7.1**	19.3***

OR_1 adjusted for age and social class; OR_2 adjusted in addition for all other variables in table. †Confounded. χ^2 trend: *P < 0.05, **P < 0.01 and ***P < 0.001 (value in parentheses is not adjusted for age at first birth). Null = nulliparous.

Table 5. Odds ratios for contraceptive methods (reference group is defined by lowest category for each variable)

	CIN I		CIN II		CIN III		All cases	
Variable	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2	OR_1	OR_2
Years on OCs								
0	1	1	1	1	1	1	1	1
0.01–2	4.48	4.78*	2.23	1.70	1.10	0.84	1.63	1.48
2.01–4	2.07	1.68	2.09	1.71	1.08	0.89	1.17	1.01
4.01–9	2.23	1.84	3.47	2.46	1.04	0.78	1.35	1.08
>9	2.10	1.78	3.61	2.46	1.80	1.34	1.91	1.54
χ^2_1 for trend	0.9	2.1	4.9*	2.4	2.2	0.5	1.4	0.1
Years on barrier method								
0	1	1	1	1	1	1	1	1
0.01–2	0.70	0.70	0.58*	0.60	0.81	0.84	0.74*	0.76
2.01–4	0.46*	0.43*	0.86	0.79	0.76	0.75	0.71	0.69
>4	0.71	0.72	0.42*	0.40*	0.66	0.63	0.62*	0.60*
χ^2_1 for trend	3.2	3.2	3.8*	4.5*	4.1*	4.3*	8.0**	8.1**
Years on IUD								
0	1	1	1	1	1	1	1	1
0.01–2	0.39	0.42	1.65	1.42	1.11	0.87	1.03	0.85
2.01–4	1.17	1.55	0.71	0.58	1.16	0.84	1.07	0.87
>4	0.77	0.73	1.70	1.27	1.16	0.74	1.15	0.82
χ^2_1 for trend	0.4	0.2	1.3	0.1	0.6	1.6	0.5	1.1

OR_1 adjusted for age and social class; OR_2 adjusted in addition for sexual and reproductive factors (age at first intercourse, number of partners, parity and age at first childbirth).
Years on OCs additionally adjusted for years since last negative smear.
χ^2 trend: $^*P < 0.05$, and $^{**}P < 0.01$.
IUD = intra-uterine device.

Contraceptive methods

Few cases and controls (5%) had never used oral contraceptives (OCs) and duration of use of OCs was not related to risk (Table 6). However, long-term OC users (10 or more years) were more frequent among CIN III cases (24%) than controls (16%) and had an elevated relative risk for CIN III which did not reach the conventional level of significance (OR = 1.80, 95% CI 0.85–3.82). When ORs were adjusted for sexual and reproductive variables, they were all closer to unity and not significant (Table 5) and were not further modified by additional adjustment for education.

Duration of use of barrier methods showed some protective effect for CIN II and CIN III, which was partly reduced by adjustment for sexual and reproductive variables (Table 5). The correlation between this variable and education, however, explained most of the protective effect, as the additional adjustment for education reduced all ORs to near unity and the χ^2 trend tests were not significant (1.4, $P = 0.24$; 2.3, $P = 0.13$; and 1.2, $P = 0.27$, for CIN I, II and III, respectively).

History of sexually transmitted diseases

A history of genital warts (before diagnosis of CIN in cases) was significantly associated with risk of CIN lesions of all grades (ORs: 8.37, 7.07 and 3.40, respectively, for CIN I, II and III, all with CI excluding unity; Table 6). The risks of CIN I and CIN II were particularly elevated, possibly because of the similar cytological and histological features of these lesions to those shown by human papilloma virus infection [23, 24]. A history of herpes virus infection had a weaker relation, which was similar in the three groups and not significant (Table 6).

Table 6. Percentages and odds ratios for history of sexually transmitted diseases†

	Controls	CIN I		CIN II		CIN III	
Variable	%	%	OR	%	OR	%	OR
Genital warts							
No	95	67	1	72	1	84	1
Yes	5	33	8.37*	28	7.07*	16	3.40*
Herpes virus							
No	98	97	1	96	1	96	1
Yes	2	3	1.77	4	1.94	4	1.83

ORs adjusted for age, social class, and sexual and reproductive factors. Reference group is the 'No' category.
†Excluding 'not known': percentages refer to totals of 832, 110, 101 and 281 for genital warts and to 828, 109, 103 and 280 for herpes virus, respectively.
$^*P < 0.05$.

Table 7. Percentages of cases and controls in smoking categories

Variable		Controls	Cases All	CIN I	CIN II	CIN III
Smoking						
Never		45	31	42	32	27
Ex		17	13	10	12	14
Current		39	56	48	56	59
Age started*						
Ex-smoker	≤16	33	40	27	50	40
	17–20	55	52	64	50	50
	≥21	12	8	9	0	10
Current smoker	≤16	37	46	42	44	47
	17–20	49	48	46	53	46
	≥21	14	7	12	4	7
Pack-years†						
Ex-smoker	0.01–2	39	31	27	67	21
	2.01–4	11	12	18	0	13
	4.01–8	26	30	36	8	34
	8.01–12	14	15	18	8	16
	>12	11	13	0	17	16
Current smoker	0.01–2	21	12	18	13	10
	2.01–4	21	15	22	18	12
	4.01–8	25	24	28	32	19
	8.01–12	15	20	10	20	23
	>12	18	30	22	18	36

*Excluding 'not known' and 'never' smokers; percentages refer to totals of 139, 63, 11, 12 and 40 ex-smokers and 321, 273, 52, 57 and 167 current smokers.

†Percentages refer to 137, 61, 11, 12 and 38 ex-smokers and 310, 272, 50, 56 and 166 current smokers.

Smoking history

The distribution of selected smoking indicators is shown in Table 7. Current smoking had a limited effect on the risk of CIN I and a large effect on the risk of CIN III; the results for CIN II were intermediate (Table 8). Age of first smoking was important for the risk of CIN III in current smokers but not in ex-smokers. Similarly pack-years, computed as the product of daily consumption of packets of 20 cigarettes and the total number of years of smoking, showed highly significant trends for current smokers in the CIN III group (χ^2 trend = 56.4, $P < 0.001$). The effect of current smoking on the risk of CIN III was much reduced, but still significant, after adjustment for sexual and reproductive variables (Table 8). Additional adjustment for education did not alter these results.

Multivariate analysis

Multiple sexual partners, early age at first childbirth, history of genital warts and current smoking appeared to be associated with an elevated risk of CIN II and CIN III. For CIN I these factors showed weaker or no effects, except for a history of genital warts. To identify the most important independent factors for each grade of disease, stepwise multivariate logistic regression analyses were performed. The variables entering the model at the 5% significance levels are shown in Table 9.

The only significant risk factor for CIN I was a history of genital warts. This was also the most significant factor for risk of CIN II, followed by age at first birth, and pack-years for current smokers. No other variables were significant nor were any interactions.

A different picture emerged for CIN III. The most significant variable was education, followed (in order of entry) by number

Table 8. Odds ratios for smoking variables (reference group is defined by lowest category for each variable)

Variable	CIN I OR_1	CIN I OR_2	CIN II OR_1	CIN II OR_2	CIN III OR_1	CIN III OR_2	All cases OR_1	All cases OR_2
Smoking								
Never	1	1	1	1	1	1	1	1
Ex	0.76	0.79	1.16	1.02	1.30	1.11	1.12	1.02
Current	1.30	1.21	2.03*	1.52	2.44*	1.72*	2.02*	1.52*
χ^2_1 for trend	1.4	0.7	15.0***	3.0	34.0***	10.6***	32.3***	9.8***
Age started smoking (current smoker)								
Never	1	1	1	1	1	1	1	1
≥20	1.31	1.00	0.77	0.60	1.08	0.81	1.09	0.82
17–19	1.20	1.07	2.17*	1.79*	2.32*	1.87*	1.96*	1.61*
≤16	1.43	1.56	2.34*	1.57	3.22*	1.94*	2.47*	1.72*
χ^2_1 for trend	1.6	1.5	11.0***	3.2	41.2***	12.2***	37.8***	12.1***
Pack-years (current smoker)								
Never	1	1	1	1	1	1	1	1
0.01–2	0.83	0.67	0.96	0.73	1.27	0.92	1.07	0.82
2.01–4	1.24	1.14	1.52	1.26	1.23	1.01	1.28	1.08
4.01–8	1.48	1.51	2.71*	2.14	2.00*	1.55	1.95*	1.56*
8.01–12	1.07	1.08	2.98*	2.25	3.85*	2.72*	2.87*	2.21*
>12	2.23*	2.49	2.97*	1.77	4.91*	3.14*	3.86*	2.72*
χ^2_1 for trend	3.3	3.1	15.0***	5.8*	56.4***	23.6***	54.4***	23.6***

OR_1 adjusted for age and social class; OR_2 adjusted in addition for sexual and reproductive factors.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 9. Multivariate analyses (OR and 95% CI)*

Variable	CIN I	CIN II	CIN III	All cases
Genital warts: yes	8.15	7.64	3.17	5.10
	(4.80–13.84)	(4.26–13.70)	(1.91–5.26)	(3.37–7.70)
χ^2_1 to delete	56.3***	43.4***	20.3***	69.2***
Pack-years (current smokers)				
0.01–2		0.89	0.84	0.72
		(0.35–2.24)	(0.43–1.63)	(0.43–1.22)
2.01–4		1.73	0.96	1.10
		(0.82–3.62)	(0.54–1.74)	(0.71–1.72)
4.01–8		2.72	1.44	1.49
		(1.41–5.24)	(0.86–2.40)	(0.98–2.25)
>8		2.14	2.37	2.10
		(1.11–4.11)	(1.58–3.56)	(1.47–3.01)
χ^2_4 to delete		13.0***	20.3***	21.8***
Age at first birth				
20–29		0.23	0.70	0.71
		(0.09–0.58)	(0.40–1.25)	(0.43–1.19)
≥30		0.10	0.19	0.16
		(0.01–0.85)	(0.06–0.57)	(0.06–0.44)
Nulliparous		0.33	0.56	0.66
		(0.15 0.69)	(0.32–0.99)	(0.40–1.09)
χ^2_3 to delete		12.7***	11.9***	16.2***
No. of partners				
2			0.96	1.41
			(0.47–1.97)	(0.82–2.42)
3–5			2.17	2.34
			(1.25–3.75)	(1.50–3.63)
6–19			2.71	2.67
			(1.60–4.57)	(1.74–4.08)
≥20			3.12	2.51
			(1.57–6.19)	(1.40–4.50)
χ^2_4 to delete			25.2***	27.2***
Education				
O levels			0.53	0.62
			(0.34–0.82)	(0.42–0.90)
A levels			0.46	0.48
			(0.28–0.76)	(0.32–0.74)
Degree			0.30	0.41
			(0.18–0.49)	(0.27–0.63)
χ^2_3 to delete			23.0***	18.9***

*All analyses were adjusted for age and social class. Reference group is defined by lowest category for all variables. (i.e. no genital warts, non-smoker and ex-smokers, age at first child <20, 1 partner, no or CSE education). Subjects with 'not known' answers in any variable were excluded.
***$P < 0.001$.

of partners, history of genital warts, pack-years for current smokers and age at first birth. The inclusion of history of genital wart infections partly reduced the initial significance of number of partners, whilst the entry of pack-years and age at first birth did not substantially affect risks associated with the other variables. Education and number of partners were partly confounded, with the protective effect of education being reduced when the number of reported partners was 20 or more (result not shown).

DISCUSSION

The choice of appropriate controls was the major difficulty in this study. An ideal approach would have been to select controls at random from the lists of the GP of each individual case. This had severe logistic problems in an inner city area since lists are inaccurate and out of date because of the mobile population. Also, even when contacted, consent from controls to be interviewed is likely to be low. To overcome this problem we decided to collect most of the GP controls from one representative practice with up-to-date lists and an enthusiastic GP who would encourage women to take part. To cover outlying areas a few controls were taken from other GP lists. We feel the resulting inclusion rate of 55% is acceptable for this type of study. As a check on the possible biases that might have been introduced, a second control group was taken from FPCs. We chose the three largest clinics in the catchment area of the hospital. These clinics are used by most sexually active young women and sampling from them gives a broad spectrum of the population at risk.

Before analysing our data, we checked whether the main GP's patients had different characteristics from the rest of the GP controls and whether the GP and FPC controls differed from each other. We found that the main GP's patients were slightly older than the other GP controls and were more educated. This was reflected by the distribution of their fathers' occupations and the higher percentage of nulliparous women. However, there were no significant differences in the other factors. In particular, no significant differences were found in the use of OCs, barrier methods or the IUD. Thus an analysis adjusted for education and social class, as in Table 9, is valid.

The results identified differences between risk factors for CIN I and CIN III in young women. Women with CIN I were similar to the controls in sexual and reproductive histories, use of contraceptives and smoking habits. The only important difference was a history of genital warts, which was strongly associated with CIN I and only weakly related to CIN III. Since the histological appearance of CIN I is similar to that for human papilloma virus infection it is possible that most of these lesions have low malignant potential.

For CIN III the risk factors were similar to those found for invasive disease. In particular the most important sexual factors were age at first childbirth and number of partners. The former appeared to be more important than parity by itself and to carry most of the effect of early age at first intercourse, in general agreement with the findings of Jussawalla *et al.* [25] who suggested that multiparity at early age might be an independent factor for invasive cervical cancer. Also Parazzini *et al.* [26] found that number of births, and early age at first child, had an independent effect on risk of invasive cervical cancer, after adjustment was made for sociodemographic and sexual variables. However, in contrast with our results, they did not find this for CIN, possibly because the three grades were combined in their analysis. Compared with women with a single sexual partner, 3–5 partners doubled the risk of CIN III and 5 or more partners increased risk about threefold in our study. These figures are consistent with other studies of the risk of invasive cervical cancer and CIN [3–5] although higher values were found in a Canadian study of cervical dysplasia [18].

A history of genital warts explained much of the risk associated with number of partners for CIN III. Other studies have found a history of genital warts more frequently among cases than controls [4, 27], but none have found such strong effects, possibly because of the low total reported frequency.

Age at first intercourse had some effect independent of number of partners, in agreement with some studies [3, 5, 14] but in contrast to Harris *et al.* [11]. In most of the other studies and in our work, population controls were used, whilst Harris *et al.* used hospital contols. This could explain some of the discrepancy. The relation of age at first intercourse and parity to risk remains unclear. Our data suggest parity is the more important factor and the related variable, age at first childbirth, appeared to be more predictive than either of these.

Our results did not show a significant relation with duration of OC use but more than 10 years of use yielded slightly elevated risks, in agreement with Brinton *et al.* [5] and others [11, 12]. The estimated ORs were corrected for interval since last negative smear because this could act as a negative confounder of the OC effect [13, 14, 28]. Also exclusion of the FPC controls, which might have biased the results, did not modify these values. Lifetime use of barrier methods showed some protective effect which was highly correlated with education. We did not have data on use of contraceptive foams, creams or jellies so we could not verify the protective effect of these found by Peters *et al.* [4] and Celentano *et al.* [14].

Smoking had an independent effect on risk of CIN II and CIN III with a monotonic dose–response curve and consumption of 4 or more pack-years in current smokers being associated with a doubling of risk. Dose–response relations have been shown in most other studies [4, 9, 29] but not in all [7]. Nischan *et al.* [10] found significant interactions between smoking and number of partners and smoking and number of pregnancies, neither of which occurred in our data. Winkelstein *et al.* [8] first suggested smoking might be a real risk factor for invasive cervical cancer, as opposed to being a correlate of some other variable such as unmeasured sexual behaviour. Biological studies have strengthened this belief: nicotine has been found in cervical mucus of smokers [6] and the cervical epithelium of smokers has been found to contain smaller numbers of Langerhans' cells than that of non-smokers, suggesting that local immunity is impaired [30]. This could be an important cofactor in the natural history of human papilloma virus infections.

After adjusting for all other variables, education was still an important risk factor for CIN III. This might be due to the choice of the controls, but it is a consistent finding in other studies [4, 18, 31] and suggests that either some additional aetiological factor, correlated with education, is yet to be identified and/or that some of the factors known to influence risk are poorly measured and the measurement error is correlated with education.

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Acknowledgements—We thank our interviewers, Jane Webster and Judith Young, for their efforts, the doctors who provided access to patients and the subjects for their time and information about themselves.