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PARITY AS A RISK FACTOR FOR CERVICAL CANCER

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In a case-control study of 759 invasive cervical cancer patients and 1,430 controls in Colombia, Costa Rica, Mexico, and Panama conducted during 1986–1987, an association with number of pregnancies persisted after adjustment for sexual and socioeconomic variables. Risks rose steadily to 5.1 (95% confidence interval 2.7–9.7) for those with 14 or more pregnancies and a relation of risk to multiparity was observed in all four study countries. Pregnancy associations appeared to relate to the number of live births rather than to miscarriages or abortions, with multiparity relations most pronounced among premenopausal women and oral contraceptive users. Human papillomaviruses types 16 and 18, as measured by filter in situ hybridization, were not significantly associated with number of births and did not explain the strong relation of parity to risk. Our results indicate the need for further consideration of reproductive factors on cervical cancer risk, with attention given to possible mechanisms of action, including hormonal factors and cervical trauma.

cervix neoplasms; cesarean section; hormones; infection; reproduction

Studies have suggested that poorly managed parturition may increase the risk of cervical cancer (1); however, an independent effect of pregnancy as a risk factor has generally been dismissed because of the assumed correlation with sexual activity, an established risk factor for this disease (2). Among a few studies that have been able to adequately control for the separate effects of reproductive and sexual behaviors, a persistent relation of multiparity has been found (3–5). This has been particularly true in populations where a large proportion of the women had multiple pregnancies (3, 4); but even in a recent US study, a 2.2-fold excess risk was associated with five or more births after adjustment for other identified risk factors (5). Further

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support for an adverse effect of pregnancy on cervical cancer risk is the high rate of detection of cervical abnormalities among pregnant women (6, 7), possibly due to the migration of the endocervix during pregnancy (8), although the effect may only represent more intensive screening. In addition, recent investigations have demonstrated that pregnant women have high detection rates of human papillomaviruses (9, 10), strong etiologic candidates for cervical cancer (11).

A large four country Latin American case-control study of invasive cervical cancer with many multiparous women provided a unique opportunity to evaluate the relation of reproductive factors to risk of disease. Information on maternal ages, numbers and outcomes of each pregnancy, as well as methods of delivery and pregnancy complications, enabled a variety of specific reproductive hypotheses to be examined. In addition, deoxyribonucleic acid (DNA) hybridization assays for type-specific human papillomaviruses allowed us to assess the possibility that pregnancy may exert an effect through enhanced susceptibility to viral infection.

Materials and methods

This case-control study included four study sites in Latin America—Panama; Costa Rica; Bogota, Colombia; and Mexico City, Mexico. Cases consisted of women newly diagnosed with invasive cervical cancer during the period January 1, 1986 to June 30, 1987 at the participating study hospitals. Cases were restricted to women who had not received prior treatment for cervical cancer, who were younger than 70 years of age, and who had been residents of the defined study areas for at least six months. Gynecologic oncologists detected and staged the cases in the study hospitals. These included: 1) the Ministry of Health cancer referral center in Bogota, which treats most lower and lower-middle class cancer patients in that city; 2) three Social Security Oncology Hospitals in San Jose, Costa Rica, the major referral centers for all neoplastic diseases in that country; 3) the Social Security's Oncology Hospital in Mexico City, which provides care for the majority of salaried employees in the area; and 4) the National Oncology Institute in Panama City, which is the major referral center for oncology patients, treating at least 90 per cent of cervical cancers diagnosed in Panama (12).

For each case, two age-matched (by five-year age groups) female controls were randomly selected. In Panama and Costa Rica, one community and one hospital control were selected, while in Bogota and Mexico City both controls were from hospitals.

Hospital controls were selected in Panama and Costa Rica from inpatient services of the patient's referral hospital; in Bogota from eight tertiary level government hospitals; and in Mexico City from three social security hospitals serving the population from which cases derived. Hospital controls were randomly selected from women admitted with nongynecologic conditions. Women who had a previous diagnosis of cancer (including cervical cancer), had undergone hysterectomy, or were admitted with endocrine or smoking-related diseases were not eligible as controls.

Community controls from Panama and Costa Rica were randomly selected from computerized census listings, which are updated every several years. An age-matched control was selected from a random censal segment in the same district of residence as each case. A short questionnaire was administered to all selected subjects, and those found to have had a hysterectomy were replaced with other randomly selected women.

Of the 766 patients and 1,532 controls eligible for study, 759 (99.1 per cent) and 1,467 (95.8 per cent) agreed to be interviewed. Nonresponse was accounted for by refusal (0 cases vs. 41 controls), death (3 cases vs. 0 controls), language or hearing problems (2 cases vs. 10 controls), mental illness (1 case vs. 8 controls), and inability to locate (1 case vs. 6 controls).

Interviews were conducted by standardly

trained personnel in private settings, either in the hospital or at the subject's home. Interviews ascertained information on sociodemographic factors, residential patterns, living conditions, pregnancy history, hygiene and menstrual factors, sexual behavior, contraceptive and medical history, smoking, diet, marital and occupational factors, and family history. Interviews lasted an average of 60 minutes.

Material for human papillomavirus DNA assays was collected using a cotton-tipped swab to gently scrape the surface of the cervical lesion of cases or the endocervix of controls. Swabs were suspended in phosphate buffered saline and stored at −20 C until tested. Assays were conducted by the filter in situ hybridization method (11, 13). Cells from each sample were filtered onto three separate nitrocellulose filters. DNA-DNA hybridization was carried out at 42 C in 50 per cent formamide (Tm −17 C) using pBR322 plasmid alone, or with inserts of human papillomavirus types 16 and 18 or human papillomavirus types 6 and 11 DNA. The probes were labeled with ^{32}P dCTP to a specific activity of greater than 1×10^8 cpm/g using a commercial nick translation system. After hybridization, the filters were washed four times for one hour at 65 C (Tm −15 C) and then exposed at −70 C for one to three days to x-ray film using a Kodak intensifying screen. All autoradiographs were examined independently by three observers, and those specimens recorded as positive by at least two observers were considered positive. Specimens that reacted positively in the pBR322 assay (3 per cent of cases, 5 per cent of controls) were considered as a separate category in the analyses.

To estimate the risk of cervical cancer associated with selected exposures, odds ratios, as approximations of relative risks (RR), were calculated. Unconditional logistic regression was used to adjust for potential confounding variables (included as categorical variables, with separate levels for missing data) (14), deriving maximum likelihood estimates of combined relative risks and 95 per cent confidence intervals (CI). Conditional logistic regression (15), also performed, found that the matching achieved little in terms of controlling for confounding and actually resulted in some loss of power, partially because of elimination of unmatched elements. Tests for trend in the logistic analyses were obtained by categorizing the exposure variables and then entering the scored variables as continuous. Multiplicative terms were entered in the logistic regression models to test the statistical significance of interactions.

In order to adjust simultaneously for effects of number of sexual partners and age at first intercourse, virgins were eliminated from the analyses, resulting in a final data set of 759 cases and 1,430 controls. Cases versus controls from each study area consisted of 214 versus 416 from Bogota, 192 versus 372 from Costa Rica, 155 versus 294 from Mexico City, and 198 versus 348 from Panama.

Results

The mean ages of the cases and controls were both 46.5 years. Major nonreproductive risk factors identified were early ages at first sexual intercourse (RR = 2.0 for < 16 vs. ≥ 20 years), multiple sexual partners (RR = 2.0 for ≥ 6 vs. 1 partner), absence of prior Papanicolaou smear screening (RR = 2.8 for no prior Papanicolaou smear vs. one in the 24 months preceding diagnosis), and limited education (RR = 2.8 for < 4 vs. ≥ 10 years). These factors were thus considered as potential confounders in subsequent analyses. Smoking and oral contraceptive use, related to cervical cancer in some studies, were not significant risk factors in this population.

A total of 745 cases (98.2 per cent) and 1,377 controls (96.3 per cent) reported ever having been pregnant (crude RR = 2.0) (table 1). Adjustment for potential confounders only slightly altered this relation (RR = 2.0, 95 per cent CI 1.0–3.7). The mean number of pregnancies was 6.8 among cases compared with 5.5 among controls, and risk increased linearly with number of

TABLE 1

Relative risks of invasive cervical cancer associated with pregnancy history, Latin American Cervical Cancer Study, 1986–1987

Pregnancy history	Cases	Controls	Crude RR†	Adjusted*	
				RR†	95% CI‡
Ever pregnant					
No	14	53	1.00	1.00	
Yes	745	1,377	2.05	1.96	1.0–3.7
No. of pregnancies					
0 or 1	33	148	1.00	1.00	
2 or 3	117	332	1.59	1.84	1.2–2.9
4 or 5	162	330	2.27	2.54	1.6–4.0
6 or 7	160	224	3.53	3.44	2.1–5.5
8 or 9	107	166	3.38	3.37	2.0–5.5
10 or 11	80	118	3.69	3.48	2.1–5.9
12 or 13	60	72	4.58	3.68	2.1–6.4
≥14	40	39	5.83	5.10	2.7–9.7
Unknown	0	1			
Age (years) at first pregnancy§					
≥23	123	380	1.00	1.00‖	
21–22	98	193	1.56	1.25	0.8–1.7
19–20	158	292	1.67	1.04	0.7–1.5
17–18	167	301	1.71	0.95	0.6–1.4
<17	197	202	3.01	1.51	0.9–2.4
Unknown	2	9	0.69	0.34	0.1–2.0
Difficulty becoming pregnant					
No	724	1,321	1.00	1.00	
Yes	29	95	0.55	0.83	0.5–1.3
Unknown	6	14	0.78	1.67	0.6–5.0

* Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, and years of education.

† RR, relative risk.

‡ CI, confidence interval.

§ Limited to ever pregnant women.

‖ Adjusted further for number of pregnancies.

pregnancies. Although subjects with multiple pregnancies were at high risk by virtue of having earlier ages at first sexual intercourse, they were at low risk because of more recent Papanicolaou smear screening histories (data not shown). Thus, adjustment for these two factors as well as number of sexual partners and years of education (which were marginally related to occurrence of pregnancies) only slightly diminished the relation of number of pregnancies to cervical cancer risk. Notably, a significant linear trend of risk with number of pregnancies persisted ($p < 0.001$) and women with 14 or more pregnancies had a relative risk of 5.1 (95 per cent CI 2.7–9.7) compared with those with zero or one pregnancy. These risks were even higher when the small number of women without prior pregnancies were excluded, and pregnancy associations were apparent in all four study sites, with the strongest relation seen in Mexico City (RR = 5.0, 95 per cent CI 1.5–16.8 for ≥ 10 pregnancies) and the weakest in Bogota (RR = 3.0, 95 per cent CI 1.3–7.3). In addition, in Panama and Costa Rica cases continued to show an excess number of pregnancies regardless of whether the comparison was with hospital or community controls.

Although age at first pregnancy appeared initially to be inversely related to risk, after adjustment for number of pregnancies and other risk factors the association disappeared. Further inquiry regarding a history of difficulty becoming pregnant (encom-

passing a wide range of possible causes) also revealed no relation to risk.

The relations of varied pregnancy outcomes are shown in table 2. A strong linear relation of risk with number of live births was observed, with the associations persisting after adjustment for other pregnancy outcomes. Thus, women who reported 12 or more live births had an adjusted risk of 4.0 (95 per cent CI 2.3–7.0) compared with those with zero or one live birth. In contrast, there was no relation of risk to number of stillbirths, miscarriages, or induced abortions regardless of whether crude or adjusted associations were considered.

Risk associated with prenatal attributes are shown in table 3. Ever having had a prenatal checkup was associated with reduced risk (RR = 0.8, 95 per cent CI 0.7–1.0). Use of vitamin supplements or folk medicines during any pregnancy did not appear to relate to risk. A marginally significant reduction in risk (RR = 0.8, 95 per cent CI 0.6–1.0) was associated with complications during pregnancy (which included such varied conditions as precipitous labor, threatened abortion, asthma, nervous problems, and cramps), with the relation persisting after adjustment for ever having had a prenatal checkup.

Examination of a variety of delivery and postnatal characteristics (table 4) revealed no relation of risk to complications during delivery, use of forceps, or complications after delivery. However, a marginally significant relation was associated with ever

TABLE 2

Relative risks of invasive cervical cancer among ever pregnant women associated with varied pregnancy outcomes, Latin American Cervical Cancer Study, 1986–1987

Pregnancy outcome	Cases	Controls	Age adjusted RR†	Adjusted*	
				RR†	95% CI‡
No. of live births					
0 or 1	39	146	1.00	1.00§	
2 or 3	152	387	1.45	1.75	1.1–2.7
4 or 5	180	334	2.08	2.17	1.4–3.3
6 or 7	148	211	2.94	2.81	1.8–4.4
8 or 9	99	145	3.02	2.80	1.7–4.5
10 or 11	70	101	3.15	2.52	1.5–4.2
≥12	57	53	5.02	3.99	2.3–7.0
No. of stillbirths					
0	672	1,257	1.00	1.00‖	
1	64	101	1.19	1.13	0.8–1.6
≥2	9	19	0.90	0.69	0.3–1.6
No. of miscarriages					
0	456	896	1.00	1.00¶	
1	159	284	1.10	1.19	0.9–1.5
2	77	116	1.31	1.34	0.9–1.9
≥3	53	81	1.30	1.27	0.8–1.9
No. of abortions					
0	704	1,306	1.00	1.00**	
1	22	47	0.87	0.89	0.5–1.5
≥2	19	24	1.47	1.51	0.8–2.9

* Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, and years of education.

† RR, relative risk.

‡ CI, confidence interval.

§ Adjusted additionally for number of stillbirths, miscarriages, and abortions.

‖ Adjusted additionally for number of live births, miscarriages, and abortions.

¶ Adjusted additionally for number of live births, stillbirths, and abortions.

** Adjusted additionally for number of live births, stillbirths, and miscarriages.

TABLE 3

Relative risks of cervical cancer among ever pregnant women associated with selected prenatal characteristics, Latin American Cervical Cancer Study, 1986–1987

Pregnancy characteristic	Cases	Controls	RR*	95% CI†
Ever had a prenatal checkup				
No	284	398	1.00	
Yes	461	979	0.83	0.7–1.0
Ever use of vitamin supplements during pregnancy				
No	335	572	1.00	
Yes	410	805	1.01	0.8–1.2
Ever use of folk medicines during pregnancy				
No	613	1,197	1.00	
Yes	132	180	1.11	0.8–1.4
Complications during pregnancy‡				
No	596	1,032	1.00	
Yes	145	325	0.83	0.6–1.0
Unknown	1	6	0.26	0.0–2.3

* RR, relative risk. Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, years of education, and number of live births.

† CI, confidence interval.

‡ Limited to parous women.

TABLE 4

Relative risks of cervical cancer among parous women associated with selected delivery and postnatal characteristics, Latin American Cervical Cancer Study, 1986–1987

Characteristic	Cases	Controls	RR*	95% CI†
Complications during delivery				
No	650	1,166	1.00	
Yes	90	186	0.91	0.7–1.2
Unknown	2	11	0.41	0.1–1.9
Cesarean section ever				
No	668	1,164	1.00	
Yes	74	197	0.75	0.6–1.0
Unknown	0	2		
Use of forceps ever				
No	643	1,149	1.00	
Yes	87	173	1.03	0.8–1.4
Unknown	12	41	0.61	0.3–1.2
Complications after delivery				
No	629	1,147	1.00	
Yes	113	214	1.02	0.8–1.3
Unknown	0	2		
Usual location of deliveries				
Hospital	428	908	1.00	
Doctor's office	10	21	1.10	0.5–2.5
Home	304	434	1.10	0.9–1.4
Usual days bed rest after delivery				
0–1	129	259	1.00	
2–3	213	374	1.03	0.8–1.4
4–7	92	204	0.93	0.6–1.3
8–14	140	257	1.04	0.8–1.4
≥15	167	261	1.34	0.9–1.8
Unknown	1	8	0.29	0.0–2.4

* RR, relative risk. Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, years of education, and number of live births.

† CI, confidence interval.

having had a cesarean section (RR = 0.8, 95 per cent CI 0.6–1.0). Although information on number of cesarean sections was not available, it was noted that among women with only one full-term pregnancy (18 cases, 86 controls) no cases had delivered by cesarean section as compared with 23 controls (27 per cent) who had delivered by this method. The reduced risks associated with cesarean section, prenatal care, and complications during pregnancy all persisted after adjustment for each other. There was no evidence that place of usual delivery or days of usual bed rest following deliveries significantly affected risk.

To assess whether sexual activity might interact with the observed pregnancy relations, we examined the association of risk with patterns of sexual intercourse during pregnancy and resumption after delivery (table 5). This analysis showed no indication that the continuation of intercourse into the final trimester of pregnancy or resumption within the first month or two after delivery had an unusual effect on risk.

The relations of a variety of hormonal factors to the parity association were also assessed (table 6). Parity associations appeared to vary little by age at menarche or regularity of menstrual cycles. However, there was some indication that number of births was a stronger risk factor among premenopausal than postmenopausal women (RR for ≥ 10 births = 4.0 and 2.3, respectively). The relation of number of births was especially pronounced among women reporting prior usage of oral contraceptives. Oral contraceptive users who had 10 or more births had a nine-fold excess risk compared with those with zero or one birth, while the comparable excess among non-oral contraceptive users was only 2.9-fold. Although the interaction between menopausal status and number of live births was statistically significant (p = 0.006), that with oral contraceptive use and number of births was not (p = 0.20).

Although detection of human papillomavirus types 16 and 18 DNA was a risk factor in these data (adjusted RR = 5.0, 95 per cent CI 3.9–6.3), there was no evidence that the prevalence of detection increased with number of births (table 7). Thus, a linear relation of risk ($p < 0.001$) with number of births persisted after adjustment for viral DNA status, and there was evi-

TABLE 5

Relative risks of cervical cancer among parous women associated with sexual behavior in relation to pregnancy, Latin American Cervical Cancer Study, 1986–1987

Sexual behavior	Cases	Controls	RR*	95% CI†
Discontinuation of sexual activity during pregnancy				
First trimester	92	172	1.00	
Second trimester	139	318	0.84	0.6–1.2
7th month	112	223	0.94	0.6–1.4
8th month	152	294	0.99	0.7–1.4
9th month	241	324	1.28	0.9–1.8
Unknown	6	32	0.35	0.1–0.9
Resumption of sexual activity after delivery (weeks)				
1–4	150	243	1.00	
5–8	261	445	1.09	0.8–1.4
9–12	138	257	1.03	0.7–1.4
≥13	193	402	0.89	0.7–1.2
Unknown	0	16		

* RR, relative risk. Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, years of education, and number of live births.

† CI, confidence interval.

TABLE 6

Relative risks of cervical cancer associated with number of live births by other hormonally related factors, Latin American Cervical Cancer Study, 1986–1987*

	Number of live births					
	0 or 1	2 or 3	4 or 5	6 or 7	8 or 9	≥10
Age (years) at menarche						
<13	1.00 (14)†	1.72 (49)	1.91 (47)	1.81 (33)	2.63 (24)	3.05 (38)
13	1.00 (9)	2.19 (34)	3.04 (48)	3.78 (40)	3.27 (30)	3.91 (28)
14	1.00 (9)	1.32 (29)	3.02 (49)	2.22 (27)	3.35 (24)	3.38 (38)
≥15	1.00 (6)	2.86 (40)	2.52 (35)	5.93 (47)	3.56 (21)	3.80 (22)
Regularity of menstrual cycles						
Regular	1.00 (31)	1.94 (129)	2.27 (152)	2.85 (132)	2.74 (80)	3.28 (116)
Irregular	1.00 (8)	1.27 (23)	2.58 (27)	3.62 (16)	3.88 (19)	2.75 (10)
Menopause status						
Premenopausal	1.00 (27)	1.87 (115)	2.13 (125)	3.28 (87)	3.94 (47)	3.98 (43)
Menopausal	1.00 (12)	1.35 (36)	2.36 (54)	1.94 (60)	1.88 (51)	2.31 (83)
Oral contraceptive use						
Yes	1.00 (9)	2.57 (59)	2.23 (53)	3.86 (33)	6.50 (16)	9.01 (17)
No	1.00 (30)	1.65 (92)	2.56 (127)	2.86 (114)	2.65 (83)	2.91 (110)

* Adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, and years of education. Unknowns are excluded from analysis.

† Numbers of relevant cases are shown in parentheses.

TABLE 7

Relative risks of cervical cancer associated with number of live births by detection with human papillomavirus (HPV) types 16 and 18, Latin American Cervical Cancer Study, 1986–1987*

	Number of live births					
	0 or 1	2 or 3	4 or 5	6 or 7	8 or 9	≥10
Per cent of controls with detectable HPV 16/18	17.1	12.1	13.5	15.2	17.9	22.1
Relative risks by HPV detection status						
HPV −	1.00 (16)†	1.50 (58)	1.78 (64)	2.96 (54)	2.90 (34)	3.20 (44)
HPV +	1.00 (13)	3.89 (66)	4.13 (74)	5.73 (71)	4.72 (48)	3.93 (58)
Unknown	1.00 (10)	1.08 (28)	1.75 (42)	1.08 (23)	1.51 (17)	3.14 (25)
Relative risks adjusted for HPV detection status	1.00 (39)	1.86 (152)	2.27 (180)	2.86 (148)	2.74 (99)	2.97 (127)

* Relative risks are adjusted for age, age at first intercourse, number of sexual partners, interval since last Papanicolaou smear, and years of education.

† Numbers of relevant cases are shown in parentheses.

dence of a trend of risk among both those with and without detectable human papillomavirus DNA.

DISCUSSION

Although previously dismissed as a risk factor for cervical cancer, a strong linear relation of risk to number of births was found in this study, with women reporting 12 or more live births being at a four-fold excess risk compared with women with one or no births. Pregnancy associations seemed to relate exclusively to number of live births, with no strong evidence that stillbirths, miscarriages, or abortions were involved.

It is surprising that limited attention has been given to the effects of pregnancy on cervical cancer risk, especially given the biologic plausibility of an association. An

effect of mismanaged parturition on cervical cancer risk was well accepted in the 1930s (1), but subsequent studies found that the relation of parity disappeared after adjustment for age at marriage (16–19) leading investigators to focus on other risk factors, especially sexual behavior. Given that multiple investigations have now demonstrated strong associations of early ages at first sexual intercourse and multiple sexual partners with cervical cancer risk, it is noteworthy that studies have not considered the interrelations of these variables with reproductive factors. Furthermore, previous studies have not examined confounding effects of Papanicolaou smear screening history, which was a negative confounder in the present study and counteracted the positive confounding effects exerted by early initiation of sexual activity. Thus, consideration of multiple sources of confounding, as done in a previous US study (5) as well as in the present study, suggests that multiple births may substantially increase the risk of cervical cancer. The power to detect associations is obviously enhanced in populations with higher numbers of births, such as in Latin America (mean number of pregnancies among controls in this study was 5.5); thus, the failure of recent studies to detect increases in risk may be due to limitations in the number of women with multiple pregnancies (20).

In addition, previous investigations have not examined related variables, such as prenatal factors, complications of delivery, or postpartum recovery factors. Although we attempted to examine relations with a number of variables, the interpretation was difficult because of their likely correlation with socioeconomic factors which might not have been measured in this study. Although ever having had prenatal care was associated with a reduction in risk, the reasons for the relation were unclear. The possibility of more extensive prior screening among these women cannot be excluded, although the association persisted after adjustment for the interval since last Papanicolaou smear. Surprisingly, reported complications during pregnancy were associated with a reduction in risk, a relation independent of prenatal care. These complications were extremely varied, and may reflect a reporting bias by social class.

A reduction in risk associated with cesarean section could also represent a social class effect. We did not collect information on number of cesarean sections, but the striking reduction in risk association with this procedure among women with one delivery indicates that the cervical trauma of delivery may in part explain the strong relations with number of deliveries. The predilection of neoplasia for the anterior cervical lip has been attributed to obstetric trauma to this area (21), and in some support of this hypothesis was the finding in our study that early pregnancy terminations (miscarriages and abortions) were unrelated to risk, although it is enigmatic why stillbirths did not increase risk.

Alternatively, pregnancy could exert an adverse effect on cervical cancer risk through its well recognized immunosuppressive effect (7), which might increase susceptibility to infectious agents. In view of evidence that pregnant women have high detection rates of human papillomaviruses (9, 10), we examined the relation of pregnancy to detection of types 16 and 18, suspected etiologic agents for invasive cervical cancer. There was no evidence that rates of positivity increased with number of births, and the presence of human papillomavirus DNA did not explain the observed relations with parity. Our data, however, do not exclude a synergistic effect between persisting viral DNA and pregnancy, since women were not pregnant when sampled. Enhanced expression of human papillomavirus genome appears to occur during the last trimester of pregnancy (10), and such expression could facilitate cervical neoplasia.

Yet another explanation for our findings is that pregnancy may exert an adverse effect through an hormonal mechanism. Although not generally recognized as an hor-

monally related tumor, hormone receptors have been found in normal as well as cancerous cervical tissue (22, 23). Further supporting an hormonal etiology are several recent reports linking extended use of oral contraceptives to increased cervical cancer risk (24–26). It was thus noteworthy that interactions of number of live births were found with both menopausal status and oral contraceptive use, with the menopause interaction being statistically significant.

Finally, although this study failed to find an association of risk with use of vitamins during pregnancy, further consideration should be given to the effect on cervical cancer of nutritional factors, especially folacin deficiency that occurs during each pregnancy (27). Megaloblastic features in cervical epithelial cells as well as low serum and red blood cell levels of folacin have been noted among oral contraceptive users, and folate supplementation has led to a decrease in the severity of cervical dysplasia (28, 29); however, the relation of folacin deficiency to cervical neoplasia in the absence of oral contraceptive use remains unclear.

Although this study has demonstrated a clear association of parity with cervical cancer risk, the reasons for the relation remain unclear. Trauma to the cervix during delivery is one possible explanation, but alternative mechanisms that warrant exploration include increased susceptibility to infection through immunosuppression, hormonal influences, and dietary deficiencies. The strong influences demonstrated in this study support the need for a reexamination of the effects of reproductive factors on cervical cancer risk, especially in populations where multiple births are common and other standardly accepted risk factors fail to explain observed incidence patterns.

References

1. Smith FR. Etiologic factors in carcinoma of the cervix. Am J Obstet Gynecol 1931;21:18–25.
2. Brinton LA, Fraumeni JF Jr. Epidemiology of uterine cervical cancer. J Chronic Dis 1986; 39:1051–65.
3. Jussawalla DJ, Deshpande VA, Standfast SJ. Assessment of risk patterns in cancer of the cervix: a comparison between greater Bombay and western countries. Int J Cancer 1971;7:259–68.
4. Kessler II, Kulcar Z, Zimolo A, et al. Cervical cancer in Yugoslavia. II. Epidemiologic factors of possible etiologic significance. JNCI 1974;53:51–60.
5. Brinton LA, Hamman RF, Huggins GR, et al. Sexual and reproductive risk factors for invasive squamous cell cervical cancer. JNCI 1987;79:23–30.
6. MacGregor JE, Teper S. Uterine cervical cytology and young women. Lancet 1978;1:1029–31.
7. Orr JW, Shingleton HM. Cancer in pregnancy. Chicago: Year Book Medical Publishers, Inc., 1983.
8. Ostergard DR. The effect of pregnancy on the cervical squamocolumnar junction in patients with abnormal cervical cytology. Am J Obstet Gynecol 1979;134:759–60.
9. Garry R, Jones R. Relationship between cervical condylomata, pregnancy and subclinical papillomavirus infection. J Reprod Med 1985;5:393–9.
10. Schneider A, Hotz M, Gissmann L. Increased prevalence of human papillomaviruses in the lower genital tract of pregnant women. Int J Cancer 1987;40:198–201.
11. Reeves WC, Caussy D, Brinton LA, et al. Case-control study of human papillomaviruses and cervical cancer in Latin America. Int J Cancer 1987;40:450–4.
12. Reeves WC, Brenes MM, de Britton RC, et al. Cervical cancer in the Republic of Panama. Am J Epidemiol 1984;119:714–24.
13. Caussy D, Orr W, Daya A, et al. Evaluation of methods for detecting human papillomavirus deoxyribonucleotide sequences in clinical specimens. J Clin Microbiol 1988;26:236–43.
14. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. Lyon, France: IARC Scientific Publications, 1980. (Publication no. 32).
15. Lubin JH. A computer program for the analysis of matched case-control studies. Comput Biomed Res 1981;14:138–43.
16. Boyd JT, Doll R. A study of the aetiology of carcinoma of the cervix uteri. Br J Cancer 1964;18:419–34.
17. Lombard HL, Potter EA. Epidemiological aspects of cancer of cervix. Cancer 1950;3:960–8.
18. Stocks P. Cancer of the uterine cervix and social conditions. Br J Cancer 1955;9:487–94.
19. Wynder EL, Cornfield J, Schroff PD, et al. A study of environmental factors in carcinoma of the cervix. Am J Obstet Gynecol 1954;68:1016–52.
20. Peters RK, Thomas D, Hagan DG, et al. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. JNCI 1986;77:1063–77.
21. Richart RM. Natural history of cervical intraepithelial neoplasia. Clin Obstet Gynecol 1967; 10:748–84.
22. Hunter RE, Longcope C, Keough P. Steroid hormone receptors in carcinoma of the cervix. Cancer 1987;60:392–6.
23. Twiggs LB, Potish RA, Leung BS, et al. Cytosolic

estrogen and progesterone receptors as prognostic parameters in stage IB cervical carcinoma. Gynecol Oncol 1987;28:156–60.
24. Brinton LA, Huggins GR, Lehman HF, et al. Long-term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 1986; 38:339–44.
25. Vessey MP, Lawless M, McPherson K, et al. Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. Lancet 1983; 2:930–4.
26. World Health Organisation Collaborative Study of Neoplasia and Steroid Contraceptives. Invasive cervical cancer and combined oral contraceptives. Brit Med J 1985;290:961–5.
27. King JC, Bronstein MN, Fitch WL, et al. Nutrient utilization during pregnancy. World Rev Nutr Diet 1987;52:71–142.
28. Whitehead N, Reyner F, Lindenbaum J. Megaloblastic changes in the cervical epithelium: association with oral contraceptive therapy and reversal with folic acid. JAMA 1973;226:1421–4.
29. Butterworth CE Jr, Hatch KD, Gore H, et al. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. Am J Clin Nutr 1982;35:73–82.