Risk Factors for Cervical Intraepithelial Neoplasia in Taiwan

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A population-based case–control study was conducted in Taiwan between July 1991 and June 1994 to evaluate the significance between risk factors for cervical intraepithelial neoplasia (CIN) among Taiwanese women. Personal interviews were compiled with 288 histologically confirmed CIN who were matched by age to 576 randomly selected controls with normal cervical smears. Using logistic regression models to simultaneously evaluate the effects of multiple factors as predictors of CIN, we found that the strongest risk was associate with HPV infection (OR = 5.02). Other significant risks included husband's visiting prostitutes (OR = 2.56), four or more vaginal deliveries (OR = 2.01), two or more induced abortions (OR = 1.96), and multiple sex partners (OR = 1.87). A protective effect was also noted with the use of condoms (OR = 0.38). These data support the hypothesis that CIN is sexually transmitted in Taiwan's population and may have a viral etiology. Furthermore the results indicate the important role of the husband's visiting prostitutes and the nonuse of condoms as contributing factors in the high incidence rate for CIN in a population. © 1996 Academic Press, Inc.

INTRODUCTION

Although the rate of cervical cancer has declined significantly in Western countries during the past three decades, it remains as one of the most common female forms of cancer in developing countries [1, 2]. In Taiwan, cervical cancer is now the leading cancer incidence and the third leading cancer death among females, with cumulative incidence and mortality rates to age 85 of 4.2 and 1.25%, respectively [3].

Although there remain many puzzling aspects in the epidemiology of cervical cancer, its correlation with sexual activity has been well documented [4, 5]. At least in part, the relation between cervical cancer to some sexually transmitted and probably infectious agent appears inescapable [6]. Three recent epidemiologic studies from different geographical areas, including Brazil, China, Spain, and Colombia, using polymerase chain reaction techniques have demonstrated high risks of cervical cancer associated with human papillomavirus [7–9]. However, concentration on female sexual activity fails to explain the high incidence of cervical cancer in Taiwan, since they traditionally have few sex partners. Attention might therefore be directed to the importance of a ''husband factor.''

The sexual behavior of Taiwanese men and women differs from contemporary Western practices. There is a convectional double standard for sexual behavior in Taiwan's population. While female virginity prior to marriage and fidelity subsequent to marriage are highly valued, many husbands frequently visit prostitutes—a practice which is tolerated within society. Given this pattern of sexual behavior, prostitutes may act as an infectious reservoir, and the husband's sexual behavior may be a major determinant of risk factors for cervical cancer in wives. The theory is that husband access to prostitutes may explain in part the high incidence of cervical cancer in Taiwan where female sexual behavior is generally conservative [10, 11].

In addition, other factors including the possible role of cigarette smoking [12, 13], oral contraceptive use [14, 15], parity [16, 17], venereal infections other than human papillomavirus (HPV) [18, 19], dietary factors [20], hygienic practices [21], socioeconomic status [22], tumor suppressor gene of host [23, 24], and histocompatibility types [1] have been suggested as putative causes of cervical cancer. However, available studies yielded largely contradictory results.

To investigate whether the higher incidence of this disease in Taiwan may be due to risk factors which differ from those typically occurring in Western populations, or to effects of a different magnitude for known risk factors in the causation of cervical intraepithelial neoplasia (CIN), we performed a population-based case–control study in Taiwan during the period 1991–1994. This study focused on how promiscuity in husbands, condom use, vaginal deliveries, induced abortions, and HPV infections are related as risk factors to the development of CIN.

SUBJECTS AND METHODS

The Interview and the Questionnaire

Since 1989, we have been conducting a cervical cancer screening program in Taiwan. The methodological details

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of this study have been reported elsewhere [25]. Briefly, questionnaires were administered to all participants during a period from 1991 to 1994 at 12 district health centers by standardly trained public health nurses. The mean interview time was 20 min. Information was obtained concerning health issues related to the etiology of CIN, including questions related to sociodemographic data, contraceptive and reproductive history, personal habits (tobacco, hygiene), sexual behavior (women and their husband), as well as Pap smear history. Medical records were examined to validate responses about the self-reported frequency of Pap smear screening at 12 health centers. With regard to sexual behavior, women were asked their age at the time of their first sexual intercourse and the number of sex partners they had had. One of the interviewers (Shu-Lian Kao), a well-trained nurse who was unaware of the case or control status, interviewed the husbands of all subjects by telephone and asked whether they had visited a prostitute, and, if so, how often, and whether they had been circumcised. She had the general impression that husbands actually were embarrassed to give answers, since the theme of visiting prostitutes and perhaps even circumcision is very private for some husbands.

Definition of Cases and Controls

Patients were recruited to participate in the educational and cervical cancer screening programs at the 12 public health centers during the study period. In this program the importance of routine cervical cancer screening was explained to the patient, and the patient then received a pelvic examination and a Pap smear was administered with a plastic exocervic brush by the program physicians. Specimens were mixed on one side of a glass slide and fixed with a spray fixative. Upon arriving at the cytopathology laboratory at the Taipei pathological center, the smears were stained by the standard Papanicolaou method. Smears were classified using standard criteria as normal, benign atypia, or dysplastic atypia. If the results of the Pap smear test were abnormal (dysplastic atypia), the women were referred to municipal hospitals for a coloposcopically directed biopsy. All women for whom biopsy was recommended were tracked by program nurses to ensure that the biopsy was actually conducted.

A total number of 386 cases were diagnosed as having CIN at the 12 district health centers during the study period. The eligibility criterion is the case with histologically confirmed diagnosis of CIN. Ninty-three patients were excluded by the criterion. Incident cases were included in the study; however, they did not include the interval (time between two screenings) cases.

Approximately 98.3% of eligible cases (288/293) were interviewed and included in these analyses. Participation by eligible controls in the study was also excellent: 98.3% (576/

586). Reasons for nonparticipation were refusal (three cases, seven controls) and inability to locate (two cases, three controls).

Two hundred and eighty-eight women with histologically confirmed diagnosis of cervical intraepithelial neoplasia incident cases were studied. Among intraneoplasia, 45.9% were classified as CIN 1, (mild dysplasia), 41.2% as CIN 2 (moderate dysplasia), and 12.9% CIN 3 (severe dysplasia or carcinoma *in situ*).

Of the total number of 1,030,461 women in the 12 districts, 39,194 were screened during the study period. Two controls per case were drawn at random from a list of patients who had normal cervical smears at 12 health centers. Controls were matched to CIN cases within a 5-year age group and within the same month as when the case was diagnosed. Women who had undergone total hysterectomy were not included. A total of 576 control subjects were included in the study.

Studies on Microorganisms

In addition to screening for cervical cancer, all smears were examined for the presence of infections and organisms. These included *Candida* (defined as hyphae identified in the stained smear), *trichomonas* (defined as an intact organism of appropriate size and configuration with an identifiable characteristic nucleus), and specific morphologic changes caused by such agents as human papillomavirus (defined as the presence of either koilocytosis or any two of the following features: nuclear wrinking, multinucleation, dyskeratosis, or the presence of epithelial spikes). Since vaginal cytologic screening is a routine procedure in Taiwan, the prevalence of koilocytosis can be estimated. When polymerase chain reaction (PCR) tests were repeated, the prevalence of HPV DNA was higher than that of koilocytosis from stained smears in similar populations. However, a stained smear is easily accomplished and can be a valuable by-product of cytologic screening for cervical cancer.

Statistical Methods

Initially, to estimate the risk of CIN with associated selected variables, the effects of individual factors and the presence of a trend for ordered variables were assessed by Mantel–Haenszel extension methods and the odds ratio, their 95% confidence interval, and the χ^2 for trends were calculated. Subsequently, however, in our final prediction model variables were selected because of biological plausibility or because they were statistically significant in univariate analyses. A conditional logistic regression model was then used to adjust for potential confounding variables, deriving maximum likelihood estimates of relative risk and 95% confidence interval.

TABLE 1
Risk of Cervical Intraepithelial Neoplasia in Relation to Selected Sociodemographic
Characteristics among Taiwanese Women, 1991–1994

Characteristic	Cases ($n = 288$)	Controls ($n = 576$)	Odds ratio	95% CI
Education				
>12	52	122	1.0	
9–12	104	235	1.04	0.67–2.0
<9	132	219	1.41	0.79–2.65
	Trend test, $P = 0.11$			
Ethnicity				
Taiwanese	243	485	1.0	
Mainlander	45	91	0.99	0.62–3.45
Frequency of Pap smear				
Once a year	26	51	1.0	
Once every 2 years	65	136	0.94	0.60–2.57
Once every 3 to 5 years	66	133	0.97	0.62–2.60
None	131	256	1.0	0.67–2.31
	Trend test, $P = 0.47$			
Cigarette smoking				
Never	277	556	1.0	
Ever	11	20	1.10	0.72–6.91
Husband circumcision				
Yes	84	208	1.0	
No	204	368	1.37	1.0–2.78
Genital washes after coitus				
Frequently or always	114	261	1.0	
Never or rarely	174	315	1.31	1.0–2.80

RESULTS

Comparative analyses of characteristics in the case and control population were performed to identify risk factors for the presence of CIN. There were no missing data in the results (Tables 1–6). Sociodemographic relationships with risk factors using univariate analysis are shown in Table 1. A trend of increasing risk with less education was observed, although it was not statistically significant. Ethnicity was not found to be related to risk. The absence of regular prior Pap smear did not appear to increase risk. Among subjects, a large number of women reported never having had a Pap smear, which was not associated with an elevation in risk.

No clear relationship was observed for cigarette smoking, although very few women in this population reported smoking. However, both the husband's circumcision and genital washing following coitus were associated with reduced risks, although the effects were only marginally significant.

Table 2 presents information on CIN risks associated with selected sexual behavior. The husband's intercourse with prostitutes was found to be a major risk factor for CIN in this study. Those who visited prostitutes >5 times per year represented a 2.5-fold excess risk compared with those who had reported never visiting prostitutes while those visiting prostitutes 1–5 times per year yielded a 53% increased risk. The trend of increasing risk with increased frequency of

visiting prostitutes was statistically significant ($P < 0.01$). In addition, a significant trend of increased risk was observed in wives with numerous of sex partners. Those with four or more sex partners represented a 1.94-fold excess risk compared with women reporting only one partner. However, the younger a women starts having sexual relations the greater her risk of CIN, with those <20 years old at first coitus showing a significant 82% increase in risk.

The risks of CIN associated with selected reproductive factors are presented in Table 3. A significant trend in risk was observed in those reporting 2 to 3 vaginal deliveries having a OR = 1.3, while ≥4 vaginal deliveries resulted in a OR = 2.0 (for trend, $P < 0.01$). In addition, the number of induced abortions was also related to increased risk (for trend, $P < 0.01$). Women reporting induced abortions more than two times had a 1.98-fold risk compared to those who had reported never having an induced abortion. Other reproductive measures investigated including stillbirths and spontaneous abortions were not significantly identified as risks.

Because sexual activity represents a strong risk factor for CIN, it is possible that certain methods of contraception may afford some degree of protection against the disease. As Table 4 shows, a protective trend was observed for the duration of condom use. Those using condoms for ≤5 years showed a significant 59% reduction in risk (OR = 0.41) and for >5 years 62% reduction in risk (OR = 0.38). In contrast,

TABLE 2
Risk of Cervical Intraepithelial Neoplasia in Relation to Indicators of Sexual Activity among Taiwanese Women, 1991–1994

Characteristic	Cases ($n = 288$)	Controls ($n = 576$)	Odds ratio	95% CI
Number of sexual partners				
1	214	470	1.0	
2–3	59	89	1.46	1.16–3.50
≥4	15	17	1.94	1.20–4.37
	Trend test, $P < 0.01$			
Age at first coitus				
≥20	266	551	1.0	
15–19	22	25	1.82	1.18–4.22
Number of husband's visiting to prostitutes per year (based on her husband's report)				
Never	81	240	1.0	
1–5	91	176	1.53	1.25–3.10
≥5	116	160	2.15	1.56–3.97
	Trend test, $P < 0.01$			

the years of oral contraceptive use were related to increased risk, with those having used the oral contraceptive for >5 years having a 1.46-fold elevation in risk compared with those who had never been users, although no significant trend in risk was observed. No consistently increased risk was observed in women who either used intrauterine devices or had had tubal ligation.

The relationship between various infections and CIN was also investigated (Table 5). A strong risk factor was found for the HPV infection. Compared with women without HPV infection, the odds ratio of CIN was 9.10 among those with HPV infection. In contrast, for CIN 2,3, the HPV infection associated with elevation in odds ratio (OR = 6.26) tended to be slightly weaker than that seen with CIN. In addition, for CIN, neither candidial nor trichomonal infection was significantly related to risk. Odds ratio for CIN 2,3 varied little with candidial or trichomonal infection and remained close to the odds ratio of those who had never been infected.

To further evaluate the relative importance of variables found to be associated with CIN, we performed multivariate logistic regression analysis (Table 6). To determine which factors were independently associated with likelihood of CIN, we created models incorporating number of sex partners, age at first coitus, husband's frequency of visiting prostitutes, HPV infection, oral contraceptive use, condom use, vaginal deliveries ≥4, and induced abortion ≥2. Using this model, we found HPV infection (OR = 5.02), husband's frequency of visiting prostitutes (OR = 2.56), vaginal deliveries (OR = 2.01), induced abortions ≥2 (OR = 1.96), and multiple sex partners (OR = 1.87) as factors associated with a significantly elevated risk of CIN, while use of condoms

was associated with a diminished risk (OR = 0.38). Notably, although earlier age at first coitus was an important predictor of risk in univariate analysis, it was not statistically significant after adjustment for other risk factors in this regression model. In addition, no measure of oral contraceptive use was found to be related to the risk of CIN after simultaneous adjustment for potentially confounding factors.

It is believed that most CIN 1 are caused by HPV infection and that an epidemiological study on the HPV infection of CIN should exclude women with CIN 1. We also analyzed the data including women with CIN 2 and CIN 3 (Table 6). The HPV infection was associated a 4.38-fold elevation in the odds ratio of CIN 2,3, but this increase was weaker than that seen for CIN analysis (OR = 5.02). In contrast, observed associations with other risk factors (sex partner, age at first coitus, husband's ever visiting prostitutes, etc.) changed little for CIN 2,3.

DISCUSSION

This study utilized case–control methodology to investigate risk factors for the development of CIN in a population of cytologically screened women. Cases had histopathologically confirmed CIN and controls had normal cervical cytologies. HPV infection was diagnosed using cytomorphology. Many risk factors which have been consistently linked with invasive cervical cancer were found to be associated with CIN in our study. As in several previous studies, CIN increased directly with number of sex partners [16, 26, 27],

TABLE 3
Risk of Cervical Intraepithelial Neoplasia in Relation to Selected Reproductive Factors among Taiwanese Women, 1991–1994

Characteristic	Cases ($n = 288$)	Controls ($n = 576$)	Odds ratio	95% CI
Number of vaginal deliveries				
0–1	31	92	1.0	
2–3	128	293	1.30	1.01–2.96
≥4	129	191	2.0	1.16–3.27
	Trend test, $P < 0.01$			
Number of stillbirths				
0	275	551	1.0	
≥1	13	25	1.04	0.71–4.76
Number of spontaneous abortions				
0	254	506	1.0	
≥1	34	70	0.97	0.70–3.57
Number of induced abortions				
0	138	356	1.0	
1	91	143	1.65	1.23–3.14
≥2	59	77	1.98	1.45–3.72
	Trend test, $P < 0.01$			

TABLE 4

Risk of Cervical Intraepithelial Neoplasia in Relation to Selected Contraceptive Methods among Taiwanese Women, 1991–1994

Characteristic	Cases ($n = 288$)	Controls ($n = 576$)	Odds ratio	95% CI
Years of use of oral contraceptive				
Nonuser	258	526	1.0	
⩽5	20	36	1.13	0.83–3.87
>5	10	14	1.46	0.95–4.42
	Trend test, $P = 0.07$			
Years of use of condoms				
Nonuser	264	469	1.0	
⩾5	14	60	0.41	0.16–0.98
>5	10	47	0.38	0.12–0.98
	Trend test, $P = 0.01$			
Years of use of intrauterine device				
Nonuser	132	266	1.0	
⩾5	60	115	1.05	0.60–2.95
>5	96	195	0.99	0.62–2.74
	Trend test, $P = 0.53$			
Years of tubal ligation				
No	270	545	1.0	
⩾10	5	10	1.0	0.47–4.89
>10	13	21	1.25	0.63–4.57
	Trend test, $P = 0.75$			

supporting a hypothesized infectious etiology. However, Taiwan has a double standard of sexual morality resulting in a prevalence in prostitution. A woman's risk of CIN will depend less on her own behavior than on that of her husband. In agreement with a British study by Buckley *et al.* [28], we noted that among subjects in our study there was strong correlation between husband's visiting prostitutes and CIN, with 71.9% of husbands of cases reporting having visited prostitutes compared with 58.3% of husbands of controls reporting having visited prostitutes. These figures are relatively high, compared to a U.S. study of 6.7% [29] and a Denmark study of 7.7% [30]. Therefore, the sexual background of the husband in the genesis of CIN may be of much more importance in the Taiwanese population than in Western cultures. It is of interest to note that age at first coitus does not persist as a significant risk factor of CIN in the multiple regression model, although the relationship was observed in univariate analysis. While this finding fails to support Coppleson's hypotheses that adolescence is a period when the cervex is most vulnerable to the effects of sexual behavior [31], it is in agreement with the results of the study of CIN by Harris *et al.* [32]. Nevertheless, it is in contrast to some case–control studies of invasive cancer which have shown independent effects after adjustment for other potential confounding factors [33, 34]. It is possible that exposure of the cervix at a younger age is more predictive of invasive

TABLE 5

Risk of Cervical Intraepithelial Neoplasia in Relation to Selected Infection among Taiwanese Women, 1991–1994

Characteristic	CIN			CIN 2, 3			
	No. of cases	Odds ratio	95% CI	No. of cases	Odds ratio	95% CI	No. of controls
HPV infection							
Negative	217	1.0		120	1.0		556
Positive	71	9.10	2.67–15.73	27	6.26	1.98–13.60	20
Candidial infection							
Negative	280	1.0		142	1.0		557
Positive	8	0.84	0.51–5.64	5	1.03	0.60–5.95	19
Trichomonal infection							
Negative	282	1.0		144	1.0		565
Positive	6	1.09	0.53–5.73	3	1.07	0.52–5.70	11

TABLE 6
Adjusted Odds Ratio for Cervical Intraepithelial Neoplasia According to Various Risk Factors
among Taiwanese Women, 1991–1994

Risk factor	CIN		CIN 2, 3	
	Adjusted odds ratio	95% CI	Adjusted odds ratio	95% CI
>1 sex partner	1.87	1.13–2.46	2.01	1.26–2.57
First coitus <20 years	1.08	0.77–1.86	1.09	0.80–1.95
Husband's ever visiting prostitutes	2.56	1.68–3.82	2.33	1.59–3.74
HPV infection	5.02	2.54–8.01	4.38	2.26–7.80
Oral contraceptive use	1.20	0.81–4.50	1.31	0.93–4.87
Condom use	0.38	0.16–0.95	0.34	0.14–0.91
≥4 vaginal deliveries	2.01	1.50–3.84	1.93	1.42–3.69
≥2 induced abortions	1.96	1.45–3.77	2.05	1.58–3.94

cervical cancer, and this idea is supported by Terris *et al.* [35], who addressed the progression of invasive cancer involving a period of increased vulnerability of the cervix at earlier ages.

Slattery *et al.* [36] postulated that the regular use of condoms may protect the cervix from opportunistic transmission by an infectious agent. Consistent with this hypothesis and with findings from other studies [37, 38], we found condom use to be associated with a reduction in risk in which prolonged use correlated with risk reduction. It is clear that high-risk husband behavior is characterized by intercourse with prostitutes without condoms who constitute a reservoir of infection. If he contracts viral agents he may subsequently pass the agents to his wife. This may account, at least in part, for the high risk of CIN in their wives. However, only 8.3% of cases and 18.5% of controls in the present study reported ever having used a condom during any part of their sexually active period compared with some 40% of the general population in Denmark [30]. Therefore, it should be useful for public health workers to emphasize that, in addition to birth control and reducing sexually transmitted diseases (including AIDS), frequent condom use may help to protect women against cervical neoplasia.

The causal role of oral contraceptive in CIN, however, remains more equivocal [39]. Since the use of oral contraceptives is highly correlated with number of sexual partners and age at first intercourse, residual confounding was likely in many previous studies [39]. Recently, a metaanalysis based on the pooled statistical analysis of 21 studies resulted in a slightly increased risk for ever users compared to nonusers, particularly among long-term users [40]. In contrast to this report, however, Coker *et al.* showed a protective effect for OC use and high-grade dysplasia in North Carolina women, although the relationship was not statistically significant after adjustment for multiple factors [13]. Some studies have found a positive association between OC and cervical cancer and others a negative association. However, in our study OC

use was found to be unrelated to risk of CIN. Simultaneous adjustment for potentially confounding factors changed the risk estimates very little, strengthening the impression that CIN was unrelated to OC use. When other contraceptive measures were analyzed, we were unable to demonstrate either a protective or adverse effect for the use of intrauterine devices or tubal ligation, as reported by Williams *et al.* [16].

Increasing evidence suggests that HPV plays a major role in the etiology of cervical cancer [7–9]. Our findings, as previously reported for invasive cancer [41], found HPV infection to be the strongest risk factor associated with CIN, with a >5-fold excess risk in women with HPV infection compared to those without HPV infection, supporting a more primary etiologic role for HPV in CIN. In the present study, husbands of cases were more likely to have visited prostitutes compared to the husbands of controls. These data support previous studies which have addressed the existence of an infectious agent and possibly reflect viral transmission from the husbands to their wives [42]. In addition, our previous study of contraceptive use among Taiwanese women showed that 19% of women had never used any contraception [43]. This figure is relatively high compared to those in Denmark (3.5%) [30]. In all probability some difference may be explained by a higher prevalence of infertility caused by multiple genital infections in this population, in line with the high-incidence area of cervical cancer (Taiwan) containing a higher proportion of women who have never used contraception [30].

When the relation of infection with HPV to occurrence of CIN was assessed from all Pap smears, we observed that the presence of HPV infection was related to an increased adjusted odds ratio of CIN (OR = 5.02, 95% CI = 2.54–8.01) but to a weaker increase in adjusted odds ratio of CIN 2,3 (OR = 4.38, 95% CI = 2.26–7.80). At present, it is believed that the virus may infect an epithelial cell and be incorporated into the DNA, which then produces viral proteins resulting in the morphologic changes of koilocytosis,

dyskeratosis, multinucleation, nuclear wrinking, and/or epithelial spikes. If the cellular atypic condition progresses with the development of the morphologic changes of dysplasia, the characteristics of the koilocyte are lost. Thus, koilocytosis is found more frequently in CIN 1 with CIN 2 and CIN 3.

Many earlier studies failed to document an association between reproductive factors and invasive cancer risk [44, 45]. However, more recent studies among Hispanic women in the United States and in Latin America [46, 47], in which multiple births are more common, indicate that the number of births has an independent and relevant role in invasive disease. We observed a linear relationship between CIN risk and number of vaginal deliveries, with women reporting four or more vaginal deliveries being at a twofold excess risk compared with women with one or no vaginal deliveries, even when adjusting for potential confounding factors. Hypotheses related to the development of CIN resulting from trauma of the cervix during childbirth were supported by our data, as we observed a relationship between the number of vaginal deliveries and CIN. From a mechanistic perspective, in support of this hypothesis was the finding in our study that the number of induced abortions (including mechanical process of dilatation and curretage) was related to risk. In contrast, spontaneous abortion and stillbirth did not exhibit a similar association with CIN.

Most published studies which have examined the role of socioeconomic indicators in cervical neoplasm have concluded that educational status is also a risk factor for invasive disease [48]. In contrast to these reports, however, we found that educational status did not affect CIN risk, as reported by Harris *et al.* [32] and Jones *et al.* [22].

Although Winkelstin found that 15 of 18 studies since 1966 have noted an association of smoking with the increased risk of invasive disease [49], the present study did not find a similar association with CIN. It is possible that too few study subjects (11 cases and 20 controls) were smoking to allow a meaningful analysis of effects of smoking as a risk factor for CIN (because only a 3.2% prevalence of Taiwanese women ever smoked cigarettes), indicating a cigarette smoking-mediated effect on one of the latter stages of the process of carcinogenesis.

CIN is usually asymptomatic and is discovered only as a result of Pap smear screening. Screening tends to increase diagnosis of CIN while reducing the incidence of invasive disease. Thus, frequency of Pap smear exerted positive confounding on CIN risk, while exerting negative confounding on the risk of invasive cancer. Although La Vecchia found that longer Pap screening intervals were associated with invasive disease [50], our data were not consistent with this Pap smear effect, partly because of only a 14% coverage rate of Pap smear among Taiwanese women.

The risk factors identified for CIN in our study are quite similar to those of the other studies on the etiology of invasive cancer [35]. Thus, we suggest that CIN and invasive cancer should be considered to be stages in a continuum of one single disease.

In summary, the incidence of cervical cancer, as of any other sexually transmitted diseases, can be expected to be highest in Taiwan, where many men, not using condoms, have intercourse with a small number of prostitutes who constitute a reservoir of infection. It is clear that ''common source transmission from prostitutes'' in Taiwanese population differs in transmission mode from ''propagate transmission from extramarital sex partners'' in Western populations. This theory may explain, at least in part, a high incidence of cervical cancer in Taiwan in which females have had few sex partners. Surprisingly, however, we found some 58% of husbands reported having visited prostitutes, but only 8.3% of cases and 18.5% of controls reported ever having used a condom during sexual intercourse. From our data, we also estimated some 60% of the CIN in women can be attributed to the nonuse of a condom in this population. There is no question that unsafe prostitution without condom use has been a prominent epidemiological feature of cervical neoplasia in Taiwan.

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