

# Prostitution, Condom Use, and Invasive Squamous Cell Cervical Cancer in Thailand

David B. Thomas,<sup>1</sup> Roberta M. Ray,<sup>1</sup> Tieng Pardthaisong,<sup>2</sup> Supawat Chutivongse,<sup>3</sup> Suporn Koetsawang,<sup>4</sup> Suporn Silpisornkosol,<sup>2</sup> Pramuan Virutamasen,<sup>3</sup> William M. Christopherson,<sup>5</sup> Joseph L. Melnick,<sup>6</sup> Olav Meirik,<sup>7</sup> Timothy M. M. Farley,<sup>7</sup> and Gustave Riotton<sup>8</sup>

Cervical cancer is probably caused by a sexually transmitted agent. A case-control study was conducted in three hospitals in Thailand to investigate further the role of male sexual behavior, particularly regarding sexual contacts with prostitutes, in the development of this disease. Data were obtained from interviews with 225 married women with invasive squamous cell cervical carcinoma and 791 hospitalized controls, all of whom reported having only one sexual partner, and from interviews with their husbands. Risk of cervical cancer was strongly related to the women's husbands having visited prostitutes without using a condom when the husbands were less than 30 years old. A strong increasing trend in risk in relation to decreasing frequency of the husbands' condom use with prostitutes was observed, and a weaker increasing trend in risk with husbands' estimated lifetime total number of visits to prostitutes was found. The average latent period between the women's likely initial exposure to a sexually transmitted oncogenic agent and her diagnosis of invasive cervical cancer was about a quarter of a century. Regular use of condoms by customers of prostitutes could reduce the number of invasive cervical cancer cases in the general population of Thailand by at least one fourth. *Am J Epidemiol* 1996;143:779–86.

cervix neoplasms; condoms; prostitution

It has been well documented that sexual behavior conducive to the acquisition of sexually transmitted diseases increases a woman's risk of developing cancer of the uterine cervix (1). Evidence has also accumulated implicating male sexual practices in the etiology of this disease. Some of the highest rates of cervical cancer occur in regions such as portions of Latin America where social pressures and tradition result in most women being chaste before marriage and monogamous afterward but most men having multiple pre- and postnuptial partners, including prostitutes (2). Also, correlations have been documented between incidence rates of cancers of the cervix and penis (3) and between mortality rates of these two neoplasms (4); and increased incidence (5) and mortality (6) rates of cervical cancer have been observed in women whose husbands had cancer of the penis. In addition, cervical cancer mortality rates were shown to be particularly high in women whose husbands had occupations associated with travel away from home (7). Increased incidence rates of cervical cancer were also observed in the subsequent wives of men previously married to a woman with cervical cancer (8).

Case-control studies involving interviews with the husbands of study subjects have provided additional information on the role of men in the etiology of cervical cancer. Studies involving women with noninvasive disease have shown increased risks associated with multiple partners of the husband (9-13), as have studies of women with invasive disease (14, 15). Risk of cervical cancer in the wife was associated with a history of one or more sexually transmitted diseases in the husband in some of these studies (9, 10, 12, 13),

Received for publication June 29, 1995, and in final form January 25, 1996.

Abbreviation: HSV-2, herpes simplex virus type 2.

<sup>&</sup>lt;sup>1</sup> Fred Hutchinson Cancer Research Center, Program in Epidemiology, Seattle, WA.

<sup>&</sup>lt;sup>2</sup> Chiang Mai University, Faculty of Medicine, Chiang Mai, Thailand.

<sup>&</sup>lt;sup>3</sup> Chulalongkom University, Faculty of Medicine, Department of Obstetrics and Gynecology, World Health Organization Collaborating Center for Research in Human Reproduction, Bangkok, Thailand.

<sup>&</sup>lt;sup>4</sup> Mahidol University, Faculty of Medicine, Siriraj Hospital, Department of Obstetrics and Gynecology, Siriraj Family Planning Research Center, Bangkok, Thailand.

<sup>&</sup>lt;sup>5</sup> University of Louisville, School of Medicine, Louisville, KY.

<sup>&</sup>lt;sup>6</sup> Baylor College of Medicine, World Health Organization Collaborating Center for Virus Reference and Research, Department of Virology and Epidemiology, Houston, TX.

<sup>&</sup>lt;sup>7</sup> World Health Organization, Geneva, Switzerland.

<sup>&</sup>lt;sup>8</sup> University of Geneva Medical School, Department of Pathology, Geneva, Switzerland.

Reprint requests to David B. Thomas, Program in Epidemiology, MP474 Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

although the associations were not strong or consistent among investigations; and in the largest and most comprehensive study (15), no such associations were observed except for a nonsignificant relation to penile ulcers. Similarly, visits to prostitutes by husbands was significantly associated with increased risk of cervical cancer in their wives in one study (10) and weakly so in two others (12, 13), but not in the larger study of Brinton et al. (15). Although circumcision status of the husband has not consistently been shown to be related to cervical cancer in the wife, associations have been reported with poor penile hygiene as evidenced by the presence of smegma (15) or infrequent washing of the genitals (12).

Women who have used a diaphragm, or whose husbands have used a condom during intercourse with them, have long been known to be at reduced risk of cervical cancer (1, 16). However, the extent to which this is due to the confounding effect of women's sexual behavior, rather than the protective effect of the devices used, has not been adequately evaluated. If a man's extramarital sexual experiences are of importance in the transmission of an infectious agent responsible for the development of cervical cancer in his wife, then his use of condoms with women other than his wife may be of equal or even greater importance than use with his wife. A reduced risk of cervical cancer associated with such use was observed by Kjaer et al. (12). Brinton et al. (15) also found a weak apparent protective effect of such condom use, especially when condoms were always or frequently used; however, the proportion of subjects who reported regular use was low. Conversely, a small increase in risk of cervical cancer was associated with condom use by the husband in another investigation (10), although this may be explainable by the observation that such use was sporadic and mainly when there was exposure to sexually transmitted diseases.

Data for this report were collected from three centers in Thailand, a country where rates of invasive cervical cancer are high, a large proportion of women have a single sexual partner, prostitution is widespread, and condom use is encouraged. These circumstances provided an opportunity to evaluate further the role of male sexual behavior and prostitution in the development of cervical cancer and the possible protective effect of condom use against this disease.

# MATERIALS AND METHODS

The data utilized for this report were collected as part of the World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives (17). This multinational, hospital-based, case-control study was conducted primarily to determine whether oral or injectable steroid contraceptives alter risks of cancers of the breast, liver, gallbladder, ovary, endometrium, and uterine cervix. Interviews were conducted with the husbands of selected cervical cancer cases and controls in three collaborating hospitals in Thailand to determine whether male sexual behavior confounded possible associations between steroid contraceptives and this disease. Analyses of data from these interviews plus data from the corresponding wives serve as the basis for this report.

Cases in Thailand were accrued from October 1979 to September 1988 in Siriraj and Chulalongkorn hospitals in Bangkok and at Maharaj Nakorn Chiang Mai Hospital in Chiang Mai. Cases were detected by monitoring all new admissions to wards where cervical cancer is treated, outpatient gynecologic or tumor clinic records, and pathology reports. Cases were restricted to those women born after 1930 in Bangkok and after 1925 in Chiang Mai who had resided for at least the previous year in a defined geographic area served by each hospital. Such women were provisionally included in the study if diagnosed by a local pathologist as having severe dysplasia, carcinoma in situ, or invasive cervical carcinoma.

Details of the control selection procedures have been described previously (17). Briefly, controls were selected from among women hospitalized for conditions generally not considered to be associated with steroid contraceptive use who met the same year of birth and residential criteria as the cases. Approximately two controls were selected for each case; however, they were not matched to individual cases. Because this was a study of multiple neoplasms, there were more than two controls for each case of cervical cancer.

A standardized questionnaire was administered to all women while they were hospitalized to obtain information on the known and suspected risk factors for the neoplasms being studied. Blood samples from a subset of these women were assayed for herpes simplex virus type 2 (HSV-2) antibodies (17). Histologic slides of the cervical lesions from all cases were sent to a single reference laboratory for uniform histologic classification according to the World Health Organization International Histological Classification of Tumours (18).

Beginning in 1986, attempts were made to interview the husbands of all newly recruited currently married cervical cancer cases. The controls chosen at each hospital for provisional inclusion in this portion of the study were the next two selected for the main study whose ages were within 5 years of the corresponding previously identified cervical cancer case, and attempts were likewise made to interview the husbands of those who were currently married. Male interviewers used a standardized questionnaire based on that developed by Brinton et al. (15) to elicit information on the man's sexual history, including frequency of intercourse, annual number of visits to prostitutes, number of sexual partners other than prostitutes, and frequency of condom use, during each decade of life after initiation of sexual activity. If the number of visits to prostitutes per year varied within a specific decade, the maximum number was recorded. Frequency categories of condom use were defined as always (100 percent), frequently (50-75 percent), sometimes (10-49 percent), rarely (1-9 percent), and never (0 percent). Visits to prostitutes were recorded as numbers of times per week, month, or year. Total visits to prostitutes were estimated separately for each decade and summed to estimate total lifetime visits. Lifetime frequency of condom use was considered to be "always or frequently" only if reported as either always or frequently during each decade of use, and it was similarly considered to be "rarely or never" only if reported as either rarely or never at all ages of use; otherwise, lifetime frequency was considered to be "sometimes." Information was also obtained on history of various sexually transmitted diseases, use of alcohol and tobacco, genital hygiene, and circumcision status.

All data were sent to a coordinating center for quality control monitoring, processing, and analysis. For this report, the unconditional logistic model for large strata (19) was used to calculate odds ratios as estimates of relative risks in relation to various aspects of the husbands' sexual history, adjusted for multiple potentially confounding variables. Such variables were entered into regression models as categorical variables, one at a time, and retained if the resulting estimate of the relative risk of interest was altered by more than 5 percent. When assessing the joint effects of frequency of condom use and lifetime number of visits to prostitutes, or when controlling simultaneously for their potential confounding effect, a composite categorical variable was utilized consisting of women whose husbands never visited prostitutes as the reference group and nine other combinations of frequency of condom use and total visits to prostitutes. All relative risk estimates were also controlled for age and center.

## RESULTS

A total of 929 women with cervical neoplasia were provisionally identified as eligible for inclusion in the investigation during the period when husbands were being studied. Of these, 907 (97.6 percent) were interviewed, 517 of whom were considered by the reference pathologist to have invasive squamous cell carcinoma. Of these latter cases, 394 were currently married, and interviews were completed on 322 (81.7 percent) of their husbands.

Of the 2,768 controls recruited during the period when husbands were being studied, 2,673 (96.6 percent) were interviewed. Of these, 111 had had a hysterectomy and were eliminated because they were not at risk of cervical cancer; and 72 less than 21 years old were eliminated because no cases included in the analyses on which this report is based were younger than 21. Of the remaining 2,490 controls, 1,477 had been provisionally selected for inclusion in the male partner study, and 1,072 were found to be currently married. The husbands of 951 (88.7 percent) of these women were interviewed.

The data analyses for this report were further restricted to the 225 cases and 791 controls who had been married only once, who claimed to have had sexual intercourse only with their husband, and whose husband was interviewed. Of these cases, 112, 72, and 41 came from Chiang Mai, Siriraj, and Chulalongkorn hospitals, respectively, as did 420, 245, and 126 of the controls. Because the major findings reported below were observed in all three centers, only findings from all centers combined are presented.

As shown in table 1, compared with the husbands of the controls, the husbands of cases tended to be slightly older; and a higher proportion of them ever smoked cigarettes or drank alcoholic beverages regularly. Also, fewer husbands of cases had completed 12 years of schooling, and fewer had a history of vasectomy or circumcision. However, after controlling for

TABLE 1. Selected characteristics of the husbands of invasive squamous cell cervical cancer cases and controls in Thailand, 1986–1988

Husband's		inds of ses	Husbands of controls		
characteristics	No.	%	No.	%	
Age (years)					
<34	22	9.8	140	17.7	
35-44	57	25.3	210	26.5	
45-54	89	39.6	244	30.8	
≥55	57	25.3	197	24.9	
Education (years)					
None	10	4.4	41	5.2	
1–3	17	7.6	51	6.5	
4	121	53.8	389	49.2	
5–12	49	21.8	174	22.0	
≥13	22	9.8	118	14.9	
Unknown	6	2.7	18	2.3	
Ever smoked					
cigarettes	182	80.9	599	75.7	
Ever drank alcohol	172	76.4	576	72.8	
Vasectomy	16	7.1	60	7.5	
Circumcised	74	32.9	295	37.3	

.

the woman's age and center, risk of cervical cancer was not associated with any of these factors.

In exploratory analyses, controlling only for woman's age and center, risk of cervical cancer was found to be directly associated with the husband's total number of visits to prostitutes, his total number of sexual partners of any kind, and his history of a variety of sexually transmitted diseases; and risk was inversely related to the husband's frequency of condom use with prostitutes, his age at first sexual relationship, and his age at first visit to a prostitute. As shown in table 2, after controlling also for number of sexual partners of the husband and number of episodes of sexually transmitted diseases reported by the husband, there is a significant trend (p = 0.004) of increasing risk with decreasing frequency of husband's condom use with prostitutes and a weaker trend in risk (p = 0.12) with his estimated lifetime total number of visits to prostitutes; however, there is little or no trend with his age at first visit to a prostitute. As shown in the upper portion of table 3, the relative risks in women married to men with more than 280 estimated visits to prostitutes are greater in women whose husbands only sometimes or rarely or never used condoms with prostitutes than in women whose husbands reported always or frequently using them with prostitutes. However, this possible interaction could readily have occurred by chance (p value of test for interaction excluding women whose husbands never visited prostitutes = 0.40). The lower portion of table 3 shows no consistent trend in risk with age of husbands' first visit to a

prostitute, regardless of his history of condom use with prostitutes (p value of test for interaction = 0.42). However, a trend of increasing risk with decreasing frequency of husbands' condom use with prostitutes is generally seen in most strata irrespective of his total visits to prostitutes or his age at first visit to a prostitute.

Relative risks also declined with total frequency of condom use with all female partners (not shown); however, this trend was weaker than that for condom use with a prostitute, and total frequency of condom use and frequency of condom use with a prostitute were highly correlated. After controlling for husband's total visits to prostitutes and frequency of condom use with prostitutes, risk was not associated with husband's total number of sexual partners, number of preor extramarital partners other than prostitutes, or age at first intercourse with any woman or with a woman other than his wife or a prostitute.

Relative risks of cervical cancer in relation to husbands' visits to prostitutes were significantly increased only in women whose husbands visited prostitutes during their teens or twenties (table 4). After controlling for such visits, the husbands' experiences with prostitutes at a later age were not associated with an increased risk of cervical cancer in their wives. Relative risks do not increase with the annual number of visits that the husbands made to prostitutes when the husbands were in their teens and early twenties; however, the risk in these women is significantly elevated

TABLE 2. Relative risks of invasive squamous cell cervical cancer in monogamous Thai women in relation to their husbands' number of lifetime visits to prostitutes, use of condoms when visiting prostitutes, and age at first visit to prostitutes, 1986–1988

Husband's experience	No. of	subjects	Relative	95% confidence	
with prostitutes	Cases	Controls	risk*	interval	
No visits to prostitutes	42	267	1.00	Reference	
Number of lifetime visits					
1–80	66	217	1.68†	0.91-3.09	
81–280	37	107	2.06	0.96-4.44	
>280	76	194	2.52	1.16-5.48	
Frequency of condom use					
Always or frequently	10	56	0.96‡	0.39-2.33	
Sometimes	35	140	1.24	0.60-2.56	
Rarely or never	134	322	2.05	1.12-3.78	
Age at first visit (years)					
≥30	15	34	1.81§	0.80-4.10	
20–29	69	202	1.56	0.82-2.96	
≲19	95	282	2.11	1.09-4.09	

\* All estimates are adjusted for woman's age, center, number of sexual partners of husband, and husband's number of episodes of sexually transmitted diseases. Excluded were four cases and six controls with no information on one or more of husband's experience with prostitutes.

+ p value of test for trend = 0.116 (excluding women whose husbands never visited prostitutes).

‡ p value of test for trend = 0.004 (excluding women whose husbands never visited prostitutes).

§ p value of test for trend = 0.173 (excluding women whose husbands never visited prostitutes).

	Frequency of condom use											
	Always or frequently				Sometimes			Rarely or never				
	No. of cases	No. of controls	RR	95% CI†	No. of cases	No. of controls	RR	95% CI	No. of cases	No. of controls	RR	95% CI
Total visits												
180	4	32	0.85	0.26-2.81	4	40	0.55	0.16-1.82	58	145	2.10	1.12-3.91
81-280	2	6	2.14	0.37-12.5	11	34	1.83	0.68-4.92	24	67	2.06	0.91-4.67
>280	4	18	1.15	0.31-4.22	20	66	1.96	0.7 <del>9</del> –4.87	52	110	2.97	1.31-6.71
Age at first visit (years)												
≥30	2	6	1.40	0.25-7.65	2	4	1.95	0.32-12.0	11	24	1.89	0.76-4.69
20-29	5	27	0.88	0.28-2.73	15	43	1.62	0.67-3.88	49	132	1.65	0.85-3.19
≤19	3	23	1.02	0.26-4.04	18	93	1.11	0.48-2.56	74	166	2.67	1.36-5.23

TABLE 3. Relative risks (RRs)\* of invasive squamous cell cervical cancer in monogamous Thai women whose husbands used condoms with prostitutes with varying frequencies, by the husband's total lifetime visits to prostitutes, and by the husband's age at first visit to a prostitute, 1986–1988

\* All risk estimates are relative to women whose husbands never visited prostitutes (42 cases, 267 controls) and are adjusted for woman's age, center, number of sexual partners of husband, and husband's number of episodes of sexually transmitted diseases. Excluded were four cases and six controls with no information on one or more relevant variables.

† CI, confidence interval.

TABLE 4. Relative risks\* of invasive squamous cell cervical cancer in monogamous Thai women in relation to frequency of visits to prostitutes and frequency of use of condoms with prostitutes by their husbands at various ages, 1986–1988

Features of visits	Husband's age at time of visits to prostitutes (years)						
to prostitutes	≤19	20-29	30-39†	40-49‡			
No visits at age shown (reference)	1.00	1.00	1.00	1.00			
Any visits at age shown	1.58§	1.75§	1.00	0.96			
Visits per year							
1–2	1.23	1.8 <del>9</del> §	0.84	1.35			
36	1.12	1.16	1.47	0.74			
7–12	1.71	1.99§	1.16	0.98			
13–36	2.18§	2.26§	0.76	0.57			
37–104	2.41§	1.76	0.75	0.70			
≥105	1.88	1.52	0.72	3.08			
Frequency of condom use							
Always or frequently	0.94	0.88	0.37	0.58			
Sometimes	0.50	1.69	0.79	0.39			
Rarely or never	1.72§	1.90§	1.34	1.39			

\* Separate relative risk estimates were calculated for each of the four decades of the husband's life and for each of the three features of his visits to prostitutes. All estimates are adjusted for woman's age, center, husband ever having other sexual partners outside marriage at any age, and husband ever visiting prostitutes at the other ages shown in the table.

† Six cases and 47 controls with husband under age 30 excluded.

‡ Forty-seven cases and 206 controls with husbands under age 40 excluded.

§ Lower limit of 95% confidence interval greater than 1.0.

if the husbands rarely or never used condoms with prostitutes at those ages.

As shown in table 5, after controlling only for age and center, associations with cervical cancer risk were observed in relation to the husband's history of most sexually transmitted diseases, or to symptoms of such diseases, that were considered. However, after also controlling for three additional variables (husband's total number of sexual partners and total visits to prostitutes and his frequency of condom use with prostitutes), risk was not significantly increased in women whose husbands gave a history of most of the reported sexually transmitted conditions. Two exceptions are gonorrhea and chancre, but the relative risk estimates associated with these conditions were also reduced by controlling for the three additional sexual behavioral variables. Similarly, initially observed significant trends of increasing cervical cancer risk with husband's number of different types of sexually transmitted diseases, and with his number of different episodes of such diseases, were attenuated by controlling for these same three variables (not shown).

	History*		No history*		Crude†		Adjusted‡	
	Cases	Controls	Cases	Controls	RR	95% CI§	RR	95% CI
Genital warts	21	68	203	721	1.17	0.69-1.98	0.75	0.45-1.23
Pubic lice	59	156	165	634	1.49	1.05-2.12	1.07	0.76-1.50
Lymphadenopathy	25	70	199	721	1.29	0.7 <del>9–</del> 2.10	0.82	0.52-1.30
Gonorrhea	104	250	120	541	2.18	1.58-3.00	1.57	1.14-2.17
Genital herpes	10	32	212	755	1.13	0.54-2.38	0.77	0.38-1.54
Syphilis	5	14	217	773	1.20	0.42-3.42	0.65	0.23-1.84
Penile discharge	54	144	170	647	1.83	1.24-2.70	1.18	0.80-1.72
Dysuria	56	149	168	640	1.77	1.21-2.58	1.20	0.83-1.73
Penile ulcer	35	94	189	697	1.52	0.98-2.37	1.24	0.84-1.82
Chancre	22	33	202	758	3.03	1.68-5.44	2.22	1.24-3.99
Any of the above	200	468	121	483	2.26	1.62-3.13	1.49	0.98-2.28

TABLE 5. Relative risks (RRs) of invasive squamous cell cervical cancer in monogamous Thai women in relation to history of sexually transmitted diseases and genital symptoms in their husbands, 1986–1988

\* Cases and controls with unknown history excluded.

† Adjusted for woman's age and center.

‡Adjusted for woman's age, center, husband's total numbers of sexual partners and visits to prostitutes, and husband's frequency of condom use with prostitutes.

§ Cl, confidence interval.

Risk of cervical cancer in relation to various aspects of the husband's genital hygiene was also considered. No significant associations were observed between cervical cancer and the husband's frequency of bathing or washing his genitals. An age- and centeradjusted relative risk of 1.63 (95 percent confidence interval 0.76-3.50) was estimated in women whose husband gave a history of anal intercourse with a man (based on 10 cases and 25 controls with such a history). No association of risk with the husband having reported anal intercourse with a woman was observed, but the husbands of only four cases and 11 controls reported such practice. Only one case and one control were married to men who had a previous wife who died of cervical cancer.

The observed associations between risk of cervical cancer and husband's total visits to prostitutes, and with his frequency of condom use with prostitutes, were not appreciably altered by controlling for any of the other characteristics of the husbands that have been mentioned. They were also not significantly influenced by controlling for the woman's HSV-2 antibody status or by the following factors ascertained from interviews of the women: numbers of pregnancies, induced abortions, and prior cervical smears; age at first sexual intercourse; use of alcohol or tobacco; history of various sexually transmitted diseases; number of years she attended school; contraception with oral or injectable steroidal agents or an intrauterine device; or a history of abdominal surgery or chest x-rays.

There were 126 cases whose husbands were in their teens or twenties when they visited prostitutes before marriage and rarely or never used condoms during such visits. Because female premarital sexual relations were rare in Thailand at the time these women were married, the earliest opportunity for them to contract the sexually transmitted agent that may have caused their cervical cancer was the date of their marriage. The time between that date and the date of their diagnosis thus provides an estimate of the latent period from initial infection to diagnosis of invasive cervical cancer. This period ranged from 6 to 45 years (standard deviation 9 years), and the mean and median periods were both 24 years.

# DISCUSSION

In this study, women whose husbands were teenagers or in their twenties at the time of their early visits to prostitutes were found to be at higher risk of cervical cancer than women whose husbands never visited prostitutes. Also, among women whose husbands visited prostitutes, a major predictor of risk was whether he used condoms during such visits. The husband's total number of visits to prostitutes, or the frequency of these visits, appeared to be less strongly predictive of cervical cancer risk than lack of condom use with prostitutes.

Although the husband's history of a number of specific sexually transmitted diseases, and symptoms related to such diseases, were associated with risk of cervical cancer after controlling only for age and center, all of the relative risk estimates were markedly reduced after controlling also for husband's total visits to prostitutes and his use of condoms with prostitutes. It is not unexpected that the specific sexually transmitted diseases considered were generally not found to be highly associated with cervical cancer in the men's wives because, with the possible exception of HSV-2, none are likely causes of cervical carcinoma. These findings regarding sexually transmitted diseases, and the observed relations between cervical cancer and the husband's experiences with prostitutes, suggest that husbands transmit some infectious carcinogenic entity that was not considered in this study from prostitutes to their wives and that use of condoms reduces the likelihood of this transmission. Various types of human papilloma viruses have been strongly implicated as causes of cervical cancer (20). These viruses are sexually transmitted (21, 22), and it is therefore reasonable to assume that, like other sexually transmitted agents, they probably occur with unusually high frequency in prostitutes. It is also likely that sexual transmission of genital human papilloma virus can be diminished by use of condoms, although this has not been adequately substantiated (22).

The average time between a woman's likely first exposure to the sexually transmitted oncogenic agent and her diagnosis of invasive cervical cancer was estimated to be 24 years. This estimate of the mean latent period is subject to two sources of error. If transmission of the agent from the husband occurred sometime after the date of marriage, this would result in an overestimate of the latent period. Conversely, women in Bangkok and Chiang Mai who were born before 1930 and 1925, respectively, were excluded from the study, and this would tend to result in a low estimate of the latent period. On balance, however, it seems reasonable to conclude that the average latent period for invasive cervical cancer is approximately one quarter of a century. Also, the range of values for the latent period was wide, which suggests that some invasive cervical carcinomas develop at a much faster rate than others. The possible roles of various types of human papilloma viruses, and of various cofactors, in this variability in latent period should be the subjects of additional studies.

Our observations are not likely to have resulted from differential recall of past sexual experiences by the husbands of cases and controls. All were husbands of hospitalized women, were interviewed by the same individuals in the same manner, and were not made aware of the specific hypotheses being investigated.

The findings are also not likely to be due to confounding by other risk factors for cervical cancer. Only cases and controls who gave a history of a single sexual partner were included in the analyses for this report, thus minimizing the potential for confounding by the sexual behavior of the women. In addition, the results were not altered by controlling for other recognized and suspected risk factors for cervical cancer as ascertained from interviews with the women or by controlling for HSV-2 antibodies in the women.

The internal consistency of the findings, their biologic plausibility, the strengths of the observed associations, and the trends in risk with frequency of condom use with prostitutes and possibly with lifetime numbers of visits to prostitutes, all tend to also rule out chance as a likely explanation for the findings and to support a causal interpretation. Furthermore, our results are broadly consistent with those from other studies showing associations between risk of cervical neoplasia and the woman's husband having had multiple sexual partners (9-15) and experiences with prostitutes (10, 12, 13), although in one large study in Latin America (15), no association with husband's visits to prostitutes was observed. Use of condoms by the husband during extramarital intercourse has likewise been associated with a reduced risk of cervical cancer in previous studies (12, 15).

Of the 517 women with invasive cervical cancer who were interviewed for this study, 366 (71 percent) claimed to have had a single sexual partner. Also, only 42 (19 percent) of the 225 interviewed husbands of cases who had a single sexual partner claimed to have never visited prostitutes. It is therefore reasonable to conclude that prostitution plays an important role in the development of cervical cancer in the general population of Thailand. Use of condoms by the customers of prostitutes could have an appreciable impact on this disease. Based on the relative risk estimates of 2.05 and 1.24 for women whose husbands rarely or never, and sometimes, used condoms with prostitutes (table 2), and the proportions of controls whose husbands used condoms with prostitutes at these frequencies (41 and 18 percent, respectively), we estimated, using the method of Levin (23), that 29 percent of the cases in this study could be attributed to being married to men who rarely or never used condoms with prostitutes. Similarly, 4 percent could be attributed to being married to men who only sometimes used condoms with prostitutes. Thus, approximately one third (29 percent + 4 percent = 33 percent) of the cases with a single sexual partner could have been prevented by more consistent use of condoms by their husbands during intercourse with prostitutes. Because 71 percent of the cases had only one sexual partner, and if we assume that the remaining cases developed cervical cancer as a result of contact with sexual partners other than their husbands, then about one fourth (71 percent  $\times$  33 percent = 23 percent) of all cases in the general population of Thailand may be attributed to lack of condom use by the customers of prostitutes. This is probably a conservative estimate of the impact that universal use of condoms with prostitutes could have

on the rates of cervical cancer in Thailand both because some of the cases with multiple partners may have developed their disease as a result of their husband's sexual behavior and because we have little information on risk of cervical cancer in women whose husbands used condoms with prostitutes 100 percent of the time.

The government of Thailand is currently actively promoting use of condoms to prevent transmission of the human immunodeficiency virus, with some success (24). Incidence rates of invasive cervical cancer in Thailand are among the highest in the world (25); and if this condom use program is successful, an added long-term benefit will be the prevention of many cases of cervical cancer.

Women at risk of exposure to partners who have had unprotected intercourse with prostitutes, like other women at high risk of cervical cancer, should have periodic cervical smears.

## ACKNOWLEDGMENTS

This study received primary financial support from the Special Program of Research, Development and Research Training in Human Reproduction, World Health Organization, and supplemental support from contract NIH-CE-84-16 from the US National Institute of Child Health and Human Development.

The authors acknowledge the support and collaboration of the following individuals: Viruch Charoeniam and Choti Theetranont (Chiang Mai University); Banpot Boonsiri, Chansuda Wongsrichanalai, and Sermsri Sindhavananda (Chulalongkorn University); Duangdao Rachawat and Amorn Koetsawang (Mahidol University); Ervin Adam (Baylor College of Medicine); and Susan Holck (World Health Organization).

#### REFERENCES

- 1. Brinton LA, Fraumeni JF Jr. Epidemiology of uterine cervical cancer. J Chron Dis 1986;39:1051-65.
- Skegg DCG, Corwin PA, Paul C, et al. Importance of the male factor in cancer of the cervix. Lancet 1982;2:581–3.
- Bosch FX, Cardis E. Cancer incidence correlations: genital, urinary and some tobacco-related cancers. Int J Cancer 1990; 46:178-84.
- Li J-Y, Li FP, Blot WJ, et al. Correlation between cancers of the uterine cervix and penis in China. J Natl Cancer Inst 1982;69:1063-5.

- 5. Graham S, Priore R, Graham MA, et al. Genital cancer in wives of penile cancer patients. Cancer 1979;44:1870-4.
- 6. Smith PG, Kinlen LJ, White GC, et al. Carcinoma of penis and cervix. Lancet 1980;2:417.
- Beral V. Cancer of the cervix: a sexually transmitted infection? Lancet 1972;1:1037-40.
- Kessler II. Venereal factors in human cervical cancer. Cancer 1977;39:1912–19.
- 9. Buckley JD, Harris RWC, Doll R, et al. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2:1010-15.
- Zunzunegui MV, King MC, Coria CF, et al. Male influences on cervical cancer risk. Am J Epidemiol 1986;123:302-7.
- Donnan SPB, Wong FWS, Ho SC, et al. Reproductive and sexual risk factors and human papilloma virus infection in cervical cancer among Hong Kong Chinese. Int J Epidemiol 1989;18:32-6.
- 12. Kjaer SK, de Villiers E-M, Dahl C, et al. Case-control study of risk factors for cervical neoplasia in Denmark. I. Role of the "male factor" in women with one lifetime sexual partner. Int J Cancer 1991;48:39-44.
- Agarwal SS, Sehgal A, Sardona S, et al. Role of male behavior in cervical carcinogenesis among women with one lifetime sexual partner. Cancer 1993;72:1666-9.
- Zhang Z-F, Parkin DM, Yu S-Z, et al. Risk factors for cancer of the cervix in a rural Chinese population. Int J Cancer 1989;43:762-7.
- Brinton LA, Reeves WC, Brenes MM, et al. The male factor in the etiology of cervical cancer among sexually monogamous women. Int J Cancer 1989;44:199-203.
- Parazzini F, Negri E, LaVecchia C, et al. Barrier methods of contraception and the risk of cervical neoplasia. Contraception 1989;40:519-30.
- WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. Contraception 1992;45:299-312.
- World Health Organization. Histological typing of female genital tract tumours. International Histological Classification of Tumours. Geneva: World Health Organization, 1975.
- Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. (IARC scientific publication no. 32). Lyon: International Agency for Research on Cancer, 1980.
- Schiffman MH. Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. J Natl Cancer Inst 1992;84:394-8.
- Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev 1988; 10:122-63.
- Kataja V, Syrjanen S, Yliskoski M, et al. Risk factors associated with cervical human papillomavirus infections: a casecontrol study. Am J Epidemiol 1993;138:735–45.
- Levin M. The occurrence of lung cancer in man. ACTA Int Union Against Cancer 1953;9:531-41.
- Hanenberg RS, Rojanapithayakorn W, Kunasol P, et al. Impact of Thailand's HIV-control programme as indicated by the decline of sexually transmitted diseases. Lancet 1994;344: 243-5.
- Martin NC, Lorvidhaya V, Changwaiwit W, et al. Cancer incidence and mortality 1983–1987 in Chiang Mai Province. Chiang Mai, Thailand: Faculty of Medicine, 1989.