Research Article

Cancer Epidemiology, Biomarkers & Prevention

Smoking and Passive Smoking in Cervical Cancer Risk: Pooled Analysis of Couples from the IARC Multicentric Case–Control Studies

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Abstract

Background: The independent role of tobacco smoking in invasive cervical cancer (ICC) has been established. We evaluated the potential impact of passive smoking (PS).

Methods: A pooled analysis of 1,919 couples enrolled in one of seven case–control studies involving cervical carcinoma *in situ* (CIS) or ICC was investigated. Information on smoking and sexual behavior was collected from interviews. Specimens were taken from the cervix and penis for human papillomavirus (HPV) DNA testing. Three PS risk models were constructed with all couples, couples with monogamous women, and couples with lifetime nonsmoking monogamous women. For the third model, the analysis considered potential misclassification of smoking status and was restricted to the risk period for which the woman was exposed to both HPV, a necessary cause of ICC, and PS. Multivariable unconditional logistic regression was used to estimate associations between CIS or ICC and PS.

Results: An increased risk was found among couples with both ever smoking men and women (OR = 2.26; 95% CI: 1.40–3.64). No statistically increased risk of CIS was found with PS in the models analyzed. Similar significant increased risks of ICC with PS was found among all couples (OR = 1.57; 95% CI: 1.15–2.15) and couples with monogamous women (OR = 1.55; 95% CI: 1.07–2.23) but not among lifetime nonsmoking monogamous women married to ever smoking men.

Conclusion: PS could not be detected as an independent risk factor of ICC in the absence of active smoking.

Impact: The combined effects of exposure to active and PS suggest its potential adverse role in cervical carcinogenesis. *Cancer Epidemiol Biomarkers Prev; 20(7); 1379–90. ©2011 AACR.*

Introduction

Men play an important role in the transmission of human papillomavirus (HPV), the etiologic factor for invasive cervical cancer (ICC). As HPVs involved in cervical carcinogenesis are sexually transmitted, it is central to understand patterns of sexual behavior in HPV transmission including the behaviors of both men and women. It has been debated that the cervical cancer risk for a woman will depend more on the full sexual

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history of the male partner than on her own behavior (1). This is particularly relevant in societies where women tend to be virgins at marriage and monogamous thereafter. Epidemiologic studies have tried to characterize the male role and the consequent female partner risk of HPV acquisition and of cervical cancer (2–5). Although a number of studies mostly involving monogamous women have observed an association between the number of sexual partners of the husband and his wife's risk for cervical cancer (6–8), other studies have not (9–12). Other inconclusive associations with prostitution have been identified (9–12).

Besides sexual behavior, other male factors, such as tobacco smoking has been less explored despite it being a well-established risk factor for cervical precancer and cancer (13, 14). Several reviews have summarized the epidemiologic and biological association of passive smoking (PS) on the risk of cervical cancer (15–17), however, the evidence has been suggestive rather than sufficient to implicate the role of PS in the etiology of cervical cancer among lifetime nonsmoking women. Among the studies identified, the recognized limitations include small sample sizes of nonsmoker controls and cases of cervical cancer, lack of specific information on HPV and sexual behavior and most studies obtained spousal history of smoking through questioning of the women rather than the men. Furthermore, most of the studies involved cervical intraepithelial neoplasia grade 3 (CIN-3)/carcionoma *in situ* (CIS) rather than invasive disease, which is a relevant distinction since evidence suggests that smoking acts in the stages of progression from CIS to invasive cancer (14).

To evaluate the male role in the etiology of cervical cancer, specifically the risk related to PS, we carried out a pooled analysis of five case–control studies involving ICC and two case–control studies involving CIS, of couples in which husbands or stable partners of ICC and CIS case and control women participated. The studies were conducted in three continents, mainly in developing countries, and were coordinated by the International Agency for Research on Cancer (IARC) in Lyon, France, and the Catalan Institute of Oncology (ICO) in Barcelona, Spain. The IARC/ICO series of case–control studies remain the largest dataset of sexual couples on etiologic investigations of ICC that fully addresses the role of HPV DNA and of independent cofactors. Some of the associations with risk factors (i.e., penile HPV infection and male circumcision) have been assessed in subsets of the subjects in this analysis (9, 11, 14, 18–20). For this study, we characterize in depth the role of PS with the full dataset on HPV and risk factors of the men and their associations with ICC.

Materials and Methods

The IARC/ICO case–control program included a series of studies on ICC and CIS from eleven countries with a broad range of cervical cancer incidence rates. Among these, seven studies conducted in five countries, enrolled husbands or stable partners of women with CIS or cervical cancer and control women were pooled for these analyses. Methods of each study and primary results related to women have been published previously. Countries included Brazil (21) and Colombia (9, 11, 22), Philippines (23), Thailand (24), and Spain (9, 25). Briefly, women with histologically confirmed incident cervical CIS, invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous-cell carcinoma were recruited from reference hospitals before treatment. Control women were recruited from the general population in two of the studies of ICC in Spain and Colombia and from the same hospitals as the cases for the other studies. Control women were frequency matched to case patients by 5-year age groups.

Current husbands or stable partners (herein referred to as husbands) of enrolled women were defined as men who reported having had regular sexual intercourse with the women for at least 6 months, irrespective of whether or not they were married or lived together.

Informed consent was obtained from both men and women who agreed to participate.

Questionnaire

A standardized questionnaire was administered to participants by a trained interviewer that included questions about socio-demographic factors, sexual behavior, hygienic practices, and history of sexually transmitted infections (STI). For specific questions on smoking habits, subjects were first asked to classify themselves as lifetime never smoker, ex-smoker (defined as a former smoker who stopped smoking at least one year prior to the interview) or current smoker. Ever smokers were also asked at what age they started smoking regularly, the duration and how many cigarettes per day they smoked. Additional questions were asked on the type of tobacco (blond, black, or other) and type of filter (filter, no filter, or both) used. Ex-smokers were asked the age at which they stopped smoking.

Penile and cervical HPV DNA sampling

Two samples of exfoliated cells were obtained from the penis: one from the distal urethra with the use of a very thin, wet, cotton-tipped swab, and one from the external surface of the glans and coronal sulcus with the use of a standard-sized wet, cotton-tipped swab.

Two samples of cervical exfoliated cells were collected with wooden spatulae and endocervical brushes. After preparation of one Papanicolaou smear, the remaining cells were eluted in saline, centrifuged and frozen at −70°C until shipment to the central laboratory for HPV DNA testing. A tumor-biopsy sample was obtained from cases and frozen at −70°C. Cytology and histology diagnosis were reviewed and confirmed by a panel of expert pathologists that agreed on a diagnosis by consensus or majority.

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Detection of HPV DNA

Detailed descriptions of the PCR assays used in these studies have been described elsewhere. HPV DNA was detected by PCR amplification of a small fragment of the *L1* gene by using MY09 and MY11 consensus primers for the studies in Spain and Colombia (26) and $GP5^+/6^+$ general primer system for the other studies (27–29). β-Globin primers were used to amplify the β-globin gene to assess the quality of the DNA in the specimen. HPV DNA in PCR products was analyzed with the use of a cocktail of HPV-specific probes and genotyped by hybridization with type-specific probes for 33 HPV types in the case of cervical samples and for at least 6 HPV types (6, 11, 16, 18, 31, and 33) in the case of the penile samples. Samples that tested positive for HPV DNA but did not hybridize with any of the type-specific probes were labeled as HPV X.

Statistical analyses

To evaluate the association between smoking habits, and risk of CIS or ICC, we first used age- and country-adjusted univariate logistic regression analyses to determine the effects of each of the following potential male factors by using an α-level of 0.05: age, history of smoking (nonsmoker, current smoker, or ex-smoker, lifetime pack-years, and use of tobacco and filter type), education, sexual history (age at first sexual intercourse, lifetime number of sexual partners, history of contact with sex workers, history of STIs, and history of anal sex), hygienic practices (i.e., pay attention to uncover penis and to wash the region, able to fully uncover spontaneously or by pulling the penis from the skin prepuce, and wash before and after sexual intercourse), male circumcision status, and to control for potential confounding of PS characteristics and risk of cervical cancer, final models were adjusted for male factors that contributed change to any of the estimated OR and 95% CI. To control for additional potential confounding by characteristics of the women, female risk factors (education, age at first sexual intercourse, lifetime number of sexual partners, history of pap smear 12 months prior to study enrolment, use of oral contraceptives, parity, and smoking) for cervical cancer were fitted into the final multivariate models (i) for the CIS adjusted models if they contributed to any change to the OR estimates for male characteristics; and (ii) for the final ICC adjusted models as they are well-established risk factors known to be associated with ICC. However, when we adjusted the OR estimates with all female risk factors in the CIS model, the estimates did not significantly differ (data not shown). We identified lifetime number of sexual partners (a significant risk factor of exposure to HPV) to be heterogeneous across study countries (Supplementary Table S1) and an interaction term combining lifetime number of sexual partners and country were included in the fully adjusted multivariate models.

In addition, we found a statistically significant interaction between some male risk factors (e.g., age at first sexual intercourse, lifetime number of sexual partners, history of sexual intercourse with a sex worker, and HPV-positivity status) and case status (i.e., ICC vs. CIS), which justified the use of 2 separate models for each disease stage. This is in agreement with our current understanding of the natural history of CIS, as it has been estimated that about 31% of CIS cases will develop cancer within 30 years, leaving a proportion of CIS cases that will not advance to invasive disease (30). Thus, some of the risk factors associated with CIS incidence may differ from those associated with progression from CIS to ICC.

Furthermore, to better clarify the relationship between PS characteristics and cervical cancer in their female partners, we removed the potential effect of previous male partners the woman may have had by calculating and comparing 3 different statistical models for CIS and ICC: one included all study couples, the second model included only couples with monogamous women, and the third model included couples with lifetime nonsmoking monogamous women. For the third model restricted to 765 couples with lifetime nonsmoking monogamous women, we further reclassified the husband's smoking history according to the risk period for which the woman would have been exposed to HPV infection (a necessary factor in cervical carcinogenesis), PS and risk of progression to cervical cancer (Fig. 1). Ninety male ex-smokers ($n = 44$ cases and $n = 43$ controls) of couples with monogamous women were reclassified as nonsmokers, and the duration of exposure to passive smoke and smoking pack-years were recalculated (Supplementary Table S2).

Results

Patient characteristics

Table 1 describes selected characteristics of the male and female subjects. Of the 291 CIS and 692 ICC cases and 936 control women, 59.8%, 70.9%, and 81.2%, were monogamous, respectively. In general, husbands were older than their wives, and husbands and wives of CIS cases and controls were younger than those of ICC.

Table 2 shows penile HPV prevalence among husbands of cases and controls of CIS and ICC by history of smoking and country. Penile HPV detection was doubled in husbands of cases than controls of CIS and was higher among cases than controls of ex-smokers (2.4% vs. 0%) and current smokers (13.9% vs. 3.8%). Similar penile HPV detection was found in husbands of cases and controls of ICC (17.6% vs. 16.2%), which was also similar among cases and controls of ex-smokers and current smokers. However, penile HPV was more prevalent among husbands of cases than controls of ICC (9.7% vs. 6.6%), respectively.

Table 3 presents selected male risk factors and their univariate associations with risk of CIS and ICC, stratified by all couples and couples with monogamous women. In

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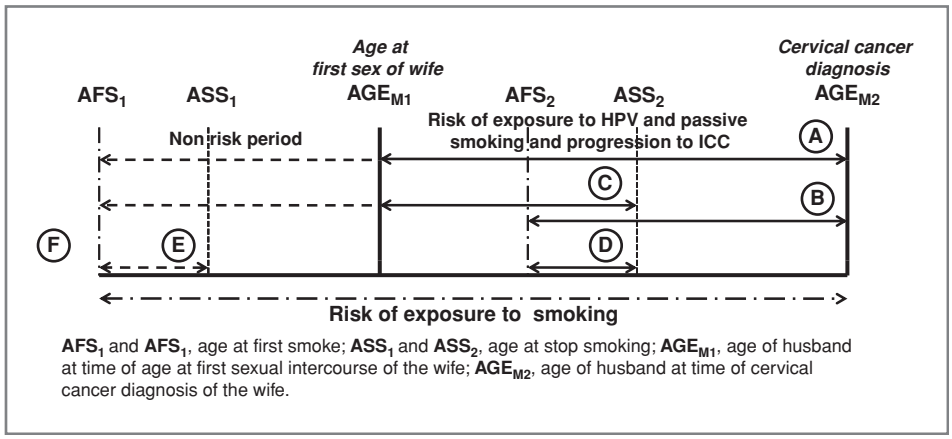

Figure 1. Model of risk of exposure to HPV and PS and progression to ICC among nonsmoking monogamous women according to the husband's history of husband. Period of risk is defined between age at first sexual intercourse of the wife and cervical cancer diagnosis. Duration of exposure to PS is defined as: (A) current smoker = (AGE_{M2}–AFP) if AFS_1; (B) current smoker = (AGE_{M2}–AFS_2); (C) ex-smoker = (ASS_2–AGE_{M1}) if $AFSI_1$; (D) ex-smoker = (ASS_2–AFS_2). Women are not at risk for HPV and PS if (E) ex-smoker = (ASS_1–AFS_1) or their husband is a (F) nonsmoker. Smoking status of the husband is classified as follows: current smokers = A + B; ex-smokers = C + D; and nonsmokers = E + F.

general, similar associations were observed in all couples and couples with monogamous women models, except for associations of CIS with education and smoking status. Hygienic practices (able to fully uncover spontaneously or by pulling the penis from the prepuce and washing before and after sexual intercourse) and history of anal sex were not associated with CIS or ICC in univariate analyses (data not shown). The following risk factors of husbands were found to be associated with an increased risk of CIS or ICC early age at first sexual intercourse, history of sexual intercourse with a sex worker (ever and while with current wife), history of gonorrhea, increasing number of STIs, being a current smoker and increasing lifetime smoking pack-years. Lack of education was associated with an increased risk of ICC but not CIS, whereas being uncircumcised and HPV positive were associated with an increased risk of CIS but not ICC. An inverse relation between use of "black" tobacco type, as compared with "blond" tobacco type among smokers, and the risk of CIS was observed, as well as some hygienic practices such as lack of attention to uncover the penis to wash the region and the risk of ICC.

Table 4 shows the association between selected male smoking characteristics and cervical CIS and ICC in multivariate analyses. Generally, similar associations were identified in the 2 analyses of all couples and only couples with monogamous women, therefore, we will describe our findings herein forward according to the all couples model. No statistically significant increased risk

Table 1. Characteristics of both corresponding husbands of women with and without (a) CIN-3/CIS or (b) ICC

	Total no. of husbands		Age of husbands[a]		Age of wives[a]	
	Cases	Controls	Cases	Controls	Cases	Controls
a. CIN-3/CIS						
Colombia	127	164	40	41.5	36	35
Spain	164	184	38	37	34	35
Pooled	291	348	38	39	34	35
b. ICC						
Brazil	72	76	52	53.5	46	48
Colombia	91	89	47	52	43	44
Philippines	155	111	46	46	46	44
Spain	146	139	50	50	50	52
Thailand	228	173	46	46	46	47
Pooled	692	588	50	50	45	46

[a]Median.

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Table 2. Penile HPV prevalence among husbands of cases and controls of CIS and ICC by history of smoking and country

	HPV tested[a]		HPV positive		HPV positive among those tested					
					Nonsmokers		Ex-smokers		Current smokers	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
CIS	165	186	35 (21.2)	14 (7.5)	8 (4.8)	7 (3.8)	4 (2.4)	0 (0.0)	23 (13.9)	7 (3.8)
Spain	102	106	22 (21.6)	4 (3.8)	2 (2.0)	0 (0.0)	4 (3.9)	0 (0.0)	16 (15.7)	4 (3.8)
Colombia	63	80	13 (20.6)	10 (12.5)	6 (9.5)	7 (8.8)	0 (0.0)	0 (0.0)	7 (11.1)	3 (3.8)
ICC	444	346	78 (17.6)	56 (16.2)	16 (3.6)	18 (5.2)	19 (4.3)	15 (4.3)	43 (9.7)	23 (6.6)
Brazil	53	56	19 (35.8)	22 (39.3)	4 (7.5)	5 (8.9)	7 (13.2)	8 (14.3)	8 (15.1)	9 (16.1)
Colombia	49	48	16 (32.7)	14 (29.2)	6 (12.2)	10 (20.8)	2 (4.1)	1 (2.1)	8 (16.3)	3 (6.3)
Philippines	149	106	9 (6.0)	5 (4.7)	2 (1.3)	1 (0.9)	0 (0.0)	2 (1.9)	7 (4.7)	2 (1.9)
Spain	84	62	10 (11.9)	2 (3.2)	0 (0.0)	0 (0.0)	3 (3.6)	1 (1.6)	7 (8.3)	1 (1.6)
Thailand	109	74	24 (22.0)	13 (17.6)	4 (3.7)	2 (2.7)	7 (6.4)	3 (4.1)	13 (11.9)	8 (10.8)

[a]HPV testing of adequate specimens that were β-globin positive.

of CIS was observed for women whose partners had a history of smoking. An increasing risk of ICC was observed with decreasing time since smoking cessation with current smokers having the highest risk (OR = 1.61; 95% CI: 1.16–2.24), suggesting PS as a potential risk factor for cervical cancer. No increased risk of ICC was observed for women with male partners who used a specific tobacco type or filter. An increased risk of ICC was observed for women with partners who smoked at least a low number of smoking pack-years (OR = 1.62; 95% CI: 1.14–2.29).

Table 5 shows the association between passive and active smoking history and risk of ICC after reclassifying smoking status of men according to Figure 1. As compared with the active smoking model, we did not observe an association between male smoking habits and risk of cervical cancer among couples with lifetime nonsmoking monogamous women. Although PS was not independently associated with risk of ICC, there was an increased OR from 1.23 to 2.26 when women were exposed to PS alone or to both active and PS. The interaction term was, however, not statistically significant ($P = 0.77$; Table 6).

Discussion

This study shows no independent association of PS and risk of cervical cancer in the absence of active smoking. In the first 2 models of all couples and couples with monogamous women, the lack of association with CIS and the significant association with ICC suggests that passive cigarette smoking could potentially acts as a late carcinogen in the transition from persistent infection/preinvasive lesions to invasion. These findings are not new and are consistent with previous findings (15–17, 31–33). However, when we considered the possibility of misclassification bias in our third model of couples with lifetime nonsmoking monogamous women and reclassified the smoking status of men according to the risk period for which the woman would be exposed to both HPV infection and PS, no independent association could be found. The greatest risk estimate was more than 2-fold for couples who were both ever smokers.

The contradicting results as shown in the different models highlight the distortion of estimates probably resulting from misclassification of smoking status. This suggests that a model considering only the time period of exposure to HPV and PS should be used to determine susceptibility to carcinogenesis. The timing of exposure to tobacco smoke relative to cervical cancer development is important in defining exposure. Because we had detailed information on smoking and sexual history, we were able to define and calculate exposure based on a series of responses. The strict definitions of exposure to tobacco smoke in our analyses showed associations with risk of cervical cancer that were obscured by using simpler definitions. Nonsmoking monogamous women with men classified as ex-smokers who have quit smoking before initiating a sexual relationship may not be as susceptible to PS. In addition, the man's lifetime duration of smoking does not necessarily include the whole period of the couple's if he stops smoking during the relationship or he starts and stops smoking during the relationship. Although the possibility of misclassification of the woman's smoking status cannot be excluded, we do not believe inclusion of nonsmokers who were actually true smokers would cause substantial bias because female smoking prevalence in these study countries is low (34). In epidemiologic studies of cervical cancer etiology, the definitions of exposure should reflect a model of risk to HPV infection and cervical carcinogenesis.

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Table 3. Male characteristics and their univariate association with a risk of woman of CIN-3/CIS or ICC

	CIN-3/CIS				ICC			
	All couples		Husbands with monogamous women		All couples		Husbands with monogamous women	
	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]
	No.		No.		No.		No.	
Education								
≥Secondary	120/157	1.00	61/123	1.00	226/236	1.00	165/197	1.00
Primary school	148/167	1.21 (0.86–1.68)	100/129	**1.58 (1.04–2.38)**	374/299	**1.62 (1.24–2.12)**	260/250	**1.52 (1.12–2.07)**
No school	21/23	1.36 (0.70–2.64)	12/17	1.49 (0.65–3.41)	92/53	**2.81 (1.83–4.33)**	66/44	**2.71 (1.66–4.42)**
Age at first sexual intercourse								
≥21	31/78	1.00	17/68	1.00	175/190	1.00	132/173	1.00
17–20	105/129	**2.36 (1.43–3.89)**	68/103	**3.02 (1.62–5.64)**	317/25	**1.49 (1.14–1.96)**	222/213	**1.51 (1.12–2.04)**
≤16	154/141	**4.48 (2.58–7.81)**	89/98	**5.79 (2.91–11.55)**	199/143	**1.89 (1.36–2.64)**	136/104	**2.14 (1.47–3.12)**
History of sexual intercourse with a sex worker								
Never	81/131	1.00	43/109	1.00	216/236	1.00	155/213	1.00
Ever	210/217	**1.72 (1.21–2.45)**	131/160	**2.22 (1.42–3.45)**	473/349	**1.58 (1.25–2.01)**	333/277	**1.78 (1.36–2.34)**
History of sexual intercourse with a sex worker while with current wife								
Never	81/131	1.00	43/109	1.00	216/236	1.00	155/213	1.00
Never sexual intercourse while with wife	113/142	1.41 (0.96–2.08)	63/101	**1.68 (1.03–2.74)**	197/187	1.28 (0.96–1.71)	115/142	1.23 (0.87–1.72)
Ever sexual intercourse while with wife	97/75	**2.32 (1.52–3.56)**	68/59	**3.21 (1.90–5.39)**	245/162	**1.87 (1.42–2.46)**	218/135	**2.29 (1.69–3.11)**
History of STIs								
Never	153/208	1.00	89/168	1.00	393/394	1.00	284/347	1.00
Syphilis only	4/4	1.37 (0.33–5.62)	3/2	2.71 (0.44–16.59)	12/13	0.96 (0.42–2.14)	9/10	1.19 (0.47–2.99)
Gonorrhea only	48/40	**1.82 (1.12–2.95)**	23/27	1.81 (0.95–3.43)	154/77	**1.96 (1.43–2.69)**	105/57	**2.26 (1.57–3.27)**
Herpes only	2/7	0.43 (0.09–2.13)	2/5	0.85 (0.16–4.54)	5/3	1.59 (0.37–6.76)	4/3	1.55 (0.34–7.08)
Condyloma only	7/5	1.88 (0.58–6.06)	4/3	2.47 (0.54–11.36)	12/6	2.07 (0.76–5.62)	9/5	2.39 (0.78–7.30)
Other venereal disease only	32/44	1.06 (0.64–1.77)	24/34	1.44 (0.79–2.61)	51/28	**2.01 (1.23–3.28)**	35/19	**2.52 (1.39–4.55)**
≥2 STIs	45/40	**1.83 (1.10–3.04)**	29/30	**2.12 (1.14–3.94)**	65/67	1.07 (0.72–1.58)	45/50	1.21 (0.76–1.92)
Number of STIs								
Never	153/208	1.00	89/168	1.00	393/394	1.00	2/347	1.00
1	93/100	1.37 (0.95–1.96)	56/71	**1.63 (1.04–2.56)**	234/127	**1.87 (1.44–2.42)**	162/94	**2.18 (1.61–2.96)**
≥2	45/40	**1.81 (1.09–3.00)**	29/30	**2.13 (1.15–3.97)**	65/67	1.04 (0.70–1.55)	45/50	1.20 (0.75–1.90)
Circumcision								
Yes	15/36	1.00	8/26	1.00	179/139	1.00	138/130	1.00
No	271/311	**2.33 (1.23–4.43)**	163/242	**2.29 (1.00–5.24)**	511/449	1.15 (0.76–1.73)	352/361	1.33 (0.84–2.10)

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Table 3. Male characteristics and their univariate association with a risk of woman of CIN-3/CIS or ICC (Cont'd)

	CIN-3/CIS				ICC			
	All couples		Husbands with monogamous women		All couples		Husbands with monogamous women	
	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]	Cases/controls	OR (95% CI)[a]
Pay attention to uncover your penis and to wash the region								
Yes	220/256	1.00	130/191	1.00	621/507	1.00	438/471	1.00
No	71/92	0.79 (0.53–1.18)	44/78	0.75 (0.46–1.21)	62/80	**0.60 (0.39–0.91)**	49/73	**0.61 (0.38–0.97)**
Time since smoking cessation								
Nonsmoker	83/137	1.00	56/105	1.00	149/183	1.00	98/148	1.00
Ex-smoker >11 years	11/8	2.34 (0.90–6.10)	5/7	1.35 (0.41–4.45)	45/50	1.21 (0.76–1.93)	32/47	1.08 (0.64–1.84)
Ex-smoker ≤10 years	24/29	1.41 (0.76–2.60)	7/20	1.67 (0.27–1.69)	83/79	1.31 (0.89–1.92)	68/66	**1.56 (1.01–2.40)**
Current smoker	171/172	**1.67 (1.15–2.43)**	104/136	1.48 (0.95–2.31)	414/274	**1.85 (1.41–2.43)**	293/229	**1.94 (1.41–2.66)**
Use of tobacco type by smokers								
Blond	37/25	1.00	20/19	1.00	299/222	1.00	216/179	1.00
Black	68/84	**0.46 (0.24–0.90)**	41/67	**0.42 (0.19–0.97)**	80/62	1.13 (0.56–2.28)	59/56	0.89 (0.41–1.91)
Both	82/84	0.60 (0.33–1.11)	47/63	0.59 (0.27–1.28)	74/42	1.49 (0.72–3.07)	55/35	1.39 (0.62–3.11)
Others	4/2	1.10 (0.18–6.74)	3/1	1.82 (0.16–20.50)	69/54	0.98 (0.63–1.51)	49/51	0.82 (0.50–1.34)
Use of smoking filter type by smokers								
Filter	89/84	1.00	56/66	1.00	277/205	1.00	205/165	1.00
No filter	15/19	0.80 (0.37–1.73)	7/15	0.51 (0.19–1.42)	42/42	0.86 (0.51–1.45)	25/36	0.63 (0.35–1.15)
Both	94/99	0.91 (0.58–1.43)	50/76	0.72 (0.41–1.25)	154/99	1.32 (0.89–1.97)	114/87	1.15 (0.74–1.78)
Others	4/2	1.86 (0.32–10.69)	3/1	3.09 (0.30–31.96)	69/54	0.98 (0.63–1.53)	49/51	0.79 (0.48–1.30)
Smoking lifetime pack-years[b]								
Nonsmoker	83/137	1.00	56/105	1.00	149/183	1.00	98/148	1.00
Low no. of pack-years	96/112	1.41 (0.94–2.10)	49/89	1.05 (0.64–1.71)	272/202	**1.58 (1.18–2.11)**	196/174	**1.65 (1.18–2.30)**
Medium/high no. of pack-years	106/95	**2.00 (1.30–3.06)**	65/72	**1.79 (1.08–2.97)**	263/198	**1.75 (1.30–2.36)**	190/164	**1.82 (1.29–2.57)**
HPV status								
Negative	130/172	1.00	77/140	1.00	366/290	1.00	266/253	1.00
Positive	35/14	**3.25 (1.67–6.32)**	18/9	**3.68 (1.57–8.62)**	78/56	1.22 (0.82–1.81)	50/41	1.27 (0.80–2.03)
No HPV result/inadequate	126/162	1.04 (0.75–1.44)	79/120	1.21 (0.81–1.81)	248/242	0.83 (0.64–1.08)	175/197	0.91 (0.67–1.22)

NOTE: Bolded ORs (95% CI) were statistically significant associations ($P < 0.05$).

[a]Adjusted for age and study country.

[b]CIN-3/CIS model: Smoking lifetime pack-years for the all husbands model is defined as low (36.5–6,022.5 pack-years) and medium/high (6,132–56,611.5 pack-years); and for the husbands with monogamous women model, low (36.5–6,716 pack-years) and medium/high (6,825.5–38,963.8 pack-years); ICC: Smoking lifetime pack-years for the all husbands model is defined as: low (36.5–7,300 pack-years) and medium/high (7,354.8–43,435 pack-years); and for the husbands with monogamous women model, low (36.5–7,665 pack-years) and medium/high (7,829.3–43,435 pack-years).

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Overall, more than three-quarters of couples were with monogamous women, allowing us to explore the male PS factors in depth and to limit any potential residual confounding that may exist if women were largely not monogamous. Our results may predominantly represent societies in which women report lifetime monogamy and multiple partnerships are more common among men, which is a pattern that is generally more common in developing countries rather than in developed countries (35).

This study strengthens the current evidence for several reasons. First, this study has the largest dataset of couples with nonsmoking women to measure PS. Because our study obtained direct information from interviews with both the husband and wife, our results are considered reliable as previous studies have found good agreement in responses concerning spousal smoking status to range from 90 to 100 percent (17) and previous cotinine studies of never smokers have validated the use of spousal history as a marker of exposure to tobacco smoke and people who live with smokers tend to mix with smokers outside the home (15). In contrast, previous studies had small sample sizes with small numbers of nonsmokers.

Table 4. Multivariate associations between selected male smoking characteristics and risk of CIN-3/CIS or ICC

Male smoking characteristics	OR (95% CI)	
	All couples	Couples with monogamous women
CIN-3/CIS[a]		
Time since smoking cessation		
Nonsmoker	1.00	1.00
Ever smoker	1.33 (0.89–1.99)	1.16 (0.71–1.88)
Ex-smoker >11 years	1.51 (0.53–4.31)	0.84 (0.22–3.19)
Ex-smoker ≤10 years	1.17 (0.58–2.34)	0.67 (0.24–1.87)
Current smoker	1.36 (0.88–2.07)	1.26 (0.76–2.09)
Use of tobacco type by smokers		
Blond	1.00	1.00
Black	0.49 (0.23–1.06)	0.33 (0.12–0.88)
Both	0.49 (0.24–0.99)	0.36 (0.14–0.91)
Others	0.89 (0.12–6.39)	1.03 (0.07–15.53)
Use of smoking filter type by smokers		
Filter	1.00	1.00
No filter	0.76 (0.29–1.96)	0.49 (0.14–1.68)
Both	0.78 (0.45–1.32)	0.61 (0.31–1.18)
Others	1.63 (0.25–10.73)	2.79 (0.21–36.93)
Smoking lifetime pack-years[c]		
Nonsmoker	1.00	1.00
Low no. of pack-years	1.18 (0.75–1.85)	0.89 (0.51–1.57)
Medium/high no. of pack-years	1.52 (0.93–2.47)	1.45 (0.53–2.56)
ICC[b]		
Time since smoking cessation		
Nonsmoker	1.00	1.00
Ever smoker	1.57 (1.15–2.15)	1.55 (1.07–2.23)
Ex-smoker >11 years	1.46 (0.84–2.52)	1.11 (0.60–2.07)
Ex-smoker ≤10 years	1.50 (0.95–2.37)	1.59 (0.95–2.67)
Current smoker	1.61 (1.16–2.24)	1.63 (1.11–2.40)
P trend	0.006	0.01
Use of tobacco type by smokers		
Blond	1.00	1.00
Black	0.91 (0.27–3.04)	0.63 (0.17–2.33)
Both	1.42 (0.40–5.10)	0.83 (0.21–3.31)
Others	0.85 (0.32–2.27)	0.66 (0.21–2.08)

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Table 4. Multivariate associations between selected male smoking characteristics and risk of CIN-3/CIS or ICC (Cont'd)

Male smoking characteristics	OR (95% CI)	
	All couples	Couples with monogamous women
Use of smoking filter type by smokers		
Filter	1.00	1.00
No filter	1.34 (0.55–3.27)	0.95 (0.33–2.69)
Both	1.41 (0.72–2.72)	1.31 (0.63–2.71)
Others	0.98 (0.38–2.55)	0.83 (0.27–2.54)
Smoking lifetime pack-years[d]		
Nonsmoker	1.00	1.00
Low no. of pack-years	1.62 (1.14–2.29)	1.64 (1.09–2.47)
Medium/high no. of pack-years	1.48 (1.03–2.12)	1.39 (0.91–2.10)

[a]CIS multivariate model was adjusted for age of the husband and wife, study country, interaction terms (lifetime number of sexual partners of husband × study country and circumcision status × study country), age at first sexual intercourse of the wife (≥21 years, 17–20 years, ≤16 years), lifetime number of sexual partners of wife (1, ≥2); and husbands with monogamous women model was adjusted for all variables in the table except for circumcision, interaction term (lifetime number of sexual partners of husband × study country), age of the wife and age at first sexual intercourse of the wife.

[b]ICC model for all husbands and husbands with monogamous women were adjusted for age of the husband and wife, study country, interaction term (lifetime number of sexual partners of husband × study country), level of education of the husband and wife (≥secondary level, primary level, no schooling), history of STIs, age at first sexual intercourse of the wife (≥21 years, 17–20 years, ≤16 years), lifetime smoking pack-years of the wife (nonsmoker, low, medium, and high smoking lifetime-pack-years), oral contraceptive use (never, 1–4 years, ≥5 years), parity (nulliparous, 1–6, ≥7), pap smear history 12 months prior to study enrollment (never, ever), and lifetime number of sexual partners of the wife (1, ≥2).

[c]CIN-3/CIS model: Smoking lifetime pack-years for all husbands model is defined as low (36.5–6,022.5 pack-years) and medium/high (6,132–56,611.5 pack-years); and for the husbands with monogamous women model, low (36.5–6,716 pack-years) and medium/high (6,825.5–38,963.8 pack-years).

[d]ICC model: Smoking lifetime pack-years for the all husbands model is defined as: low (36.5–7,300 pack-years) and medium/high (7,354.8–43,435 pack-years); and for the husbands with monogamous women model, low (36.5–7,665 pack-years) and medium/high (7,829.3–43,435 pack-years).

Second, previous studies lacked adequate information on HPV and sexual behavior indicators to control for potential confounding, and we were able to control for both male and female risk factors. Third, as we currently understand the natural history of cervical cancer, not all precancerous lesions will progress to ICC (30), so we were able to evaluate the effect of PS by stage of disease (preinvasive vs. invasive).

Previous studies did not evaluate the combined effects of different exposure of active and passive smoke (both nonsmokers, female ever smoker/male nonsmoker, and female nonsmoker/male ever smoker). Although the other combinations showed an increased risk, only the combination of ever-smoking couples showed a statistically significant increased risk. The lack of an independent association with PS does not necessarily discount its contribution to ICC risk. This may suggest that the direct effect of active smoking outweighs the indirect carcinogenic effects PS may have. One of the limitations of epidemiologic studies by using questionnaire data is its decrease in sensitivity or power of a study to show a positive association when the effect may only be moderately related to PS (17). Lifetime number of sexual partners of the men largely attenuated the observed effect of PS on ICC risk. Studies have suggested that we need to consider the contribution of occupational exposure to tobacco smoke in addition to spousal/household smoking as 76% of nonsmokers who report no exposure to tobacco smoke at home have reported exposure at work (17) and about 75% of women in our study worked outside the home, which could have lead to additional misclassification of exposure and underestimated the impact of PS. In addition, although the possibility of couples not cohabiting together could lead to an overestimated PS impact, we believe the contribution is minimal as only 1.6% of couples with monogamous women reported periods of separation. To fully evaluate the impact of PS, measurement of exposure needs to take into account all environmental exposures within the household and workplace.

A biological mechanism by which active and PS could influence cervical carcinogenesis is not clearly

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Table 5. Association between passive and active smoking history and risk of ICC

	Passive smoking[a]		Active smoking[b]	
	Couples with nonsmoking monogamous women		Couples with monogamous women	
Male smoking characteristics	Cases/controls	OR (95% CI)[c]	Cases/controls	OR (95% CI)[c,d]
Smoking status				
Nonsmoker	112/167	1.00	357/407	1.00
Ever	246/240	1.28 (0.88–1.85)	134/84	1.77 (1.23–2.56)
Ex-smoker	39/54	1.01 (0.56–1.83)	38/31	1.48 (0.83–2.65)
Current smoker	207/186	1.34 (0.91–1.96)	96/53	1.94 (1.26–2.98)
Duration of exposure to smoking				
0 years	112/167	1.00	357/407	1.00
1–20 years	101/108	1.51 (0.93–2.45)	52/35	1.58 (0.91–2.73)
≥21 years	137/124	1.13 (0.73–1.75)	43/30	1.56 (0.88–2.79)
No. of cigarettes per day				
Nonsmoker	112/167	1.00	357/407	1.00
1–10 cigarettes/day	96/84	1.51 (0.95–2.39)	73/46	1.63 (1.07–2.46)
≥11 cigarettes/day	144/152	1.10 (0.73–1.66)	24/17	1.30 (0.91–1.84)
Smoking lifetime pack-years[e]				
Nonsmoker	112/167	1.00	357/407	1.00
Low	77/81	1.44 (0.88–2.36)	29/24	0.56 (0.12–2.56)
Medium	72/78	1.12 (0.68–1.83)	35/18	4.14 (0.96–17.8)
High	84/70	1.25 (0.76–2.05)	31/21	0.55 (0.14–2.25)

[a]For the passive smoking models, characteristics of the husband's smoking history was classified according to the wife's risk period of exposure to HPV and passive smoking as outlined in Figure 1.

[b]For the active smoking models, the risk of cervical cancer is based upon the woman's history of smoking.

[c]Models were adjusted for age of the husband and wife, study country, level of education of the husband and wife, lifetime number of sexual partners of the husband, history of STIs, age at first sexual intercourse of the wife, oral contraceptive use, parity, and pap smear history 12 months prior to study enrollment.

[d]Male smoking characteristics (smoking status, duration of smoking, no. of cigarettes per day, and smoking lifetime pack-years) were adjusted in the final model accordingly to the woman's smoking habits.

[e]Husband's lifetime smoking pack-years for the passive smoking model is defined as: low (36.5–3,832.5 pack-years), medium (3,942–7,884 pack-years), and high (7,938.75–67,890 pack-years); and the smoking lifetime pack-years of women for the active smoking model is defined as: low (18.25–930.75 pack-years), medium (1,022–3558.75 pack-years), and high (3,577–19,710 pack-years).

understood. However, tobacco smoke contains known carcinogens such as polycyclic aromatic hydrocarbons that could potentially have a direct transformation effect on the cervix or could cause immunosuppression, allowing HPV infections to persist and progress to cancer (15). Detectable levels of nicotine and cotinine, a measurement of smoke exposure, have been found in cervical mucus and DNA adduct levels in the cervical epithelium of nonsmokers, supporting the evidence that these chemicals can reach distant sites such as the cervix (16). Another hypothesis includes mutagenic semen due to smoking is plausible and direct cervical contact with semen of smoking partners may represent another source of exposure (17). This study lacked data measurement levels of cotinine/nicotine in the cervix, therefore, additional studies are needed to obtain these data to complement our epidemiologic findings.

Penile HPV detection was more prevalent among current smokers compared with ex-smokers and nonsmokers which is consistent to previous findings (36). This suggests that smokers may be more likely to have persistent infections compared with nonsmokers, making them more likely to expose their wives to HPV infection. However, the interpretation of penile HPV detection at study enrolment is not straightforward as it does not necessarily represent the timepoint of exposure as the current understanding of the natural history of HPV in men shows that HPV is more readily transmitted from men to women than from women to men, and these infections are less likely to persist among men with approximately 75% likely to clear infection at one year (37). Other studies have not found smoking to be associated with penile HPV acquisition nor persistence (38, 39). In addition, we cannot exclude the possibility of reverse causality since

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Table 6. Risk of cervical cancer according to the smoking status of husbands and wives among couples with monogamous women

	Cases/ controls	OR[a] (95% CI)
Both nonsmokers	112/167	1.00
Female nonsmoker/male ever smoker	245/240	1.23 (0.85–1.77)
Female ever smoker/male nonsmoker	30/27	1.63 (0.83–3.22)
Both ever smokers	104/57	2.26 (1.40–3.64)
P trend		0.001

[a]Model was adjusted for age of the husband and wife, study country, level of education of the husband and wife, lifetime number of sexual partners of the husband, history of STIs, age at first sexual intercourse of the wife, oral contraceptive use, parity, and pap smear history 12 months.

HPV-infected husbands could clear HPV, and be reinfected by their wives who have cervical cancer and have been replicating HPV prior to the onset of cancer. Among 116 ICC case husbands who reported no history of sex with a sex worker or a casual partner while living with their wife, 6 were HPV positive (of whom 5 women reported lifetime monogamy), making it impossible to know who was the source of HPV exposure if there was no underreporting. Second, detection of penile HPV DNA (17%) in our study was lower than recently reported prevalence estimates in men and this may result from incomplete sampling of the male genitalia as it has been suggested that for optimal HPV detection, sampling should include multiple anatomic subsites (40).

In conclusion, there are 1 billion active smokers worldwide and one-third of adults are regularly exposed to passive smoke with the burden of tobacco-related disease, disability, and death being the highest in developing regions. Moreover, the rate of increase in cigarette consumption in developing countries is 10 times that of industrialized countries (41). This burden is likely to increase in the coming decades if current trends persist with more than 90% of the world's population not protected by comprehensive smoke-free policies and there is low compliance (2%) in countries where there are comprehensive smoke-free laws (34). Globally, there is an increasing trend of females aged 13 to 15 smoking in recent years (41), which needs to be considered along with reported median age at first sexual intercourse to occur for most women is 15 to 19 years (35) when assessing risk of ICC. The data presented here support that in addition to female tobacco smoking as an established cofactor for cervical carcinogenesis, there is a potential role of passive smoke on ICC, which suggest that the estimated burden of tobacco-related diseases may increase and magnify the need for effective tobacco control, notably in developing countries.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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