RESEARCH COMMUNICATION

Passive Smoking and Cervical Cancer Risk: A Meta-analysis Based on 3,230 Cases and 2,982 Controls

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Abstract

Objective: Passive smoking has been considered as a risk factor of many cancers. To examine whether it might also pose a risk for cervical cancer, we performed a meta-analysis based on published case-control studies. Methods: We searched the PubMed database and references of included studies up to February 10th, 2012 for relevant studies. After two authors independently assessed the methodological quality and extracted data, a meta-analysis was conducted using CMA v2 software. Publication bias was evaluated by funnel plot, using Egger's and Begg's tests. Results: Finally 11 eligible studies yielded, involving 3,230 cases and 2,982 controls. The results showed that women who never smoke but exposed to smoking experience a 73% increase in risk of cervical cancer compared with non-exposed women (OR = 1.73, 95% CI = 1.35 – 2.21, p<0.001). Subgroup and sensitivity analyses indicated this result to be robust. Moderate publication bias was detected by visualing funnel plot, Egger's and Begg's tests. Conclusion: Based on currently available evidence, the findings of this meta-analysis suggests that passive smoking significantly and independently increases the risk of cervical cancer.

Keywords: Passive smoking - cervical cancer - risk factor - meta-analysis

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Introduction

Cervical cancer is the second most common cancer among women worldwide, with approximately 12,710 new cases diagnosed and 4290 deaths occurring in the United States for the year 2011 (Denslow et al., 2012), and cervical cancer killed 200,000 (139,000-276,000) women in 2010, of whom 46,000 (33,000-64,000) were aged 15-49 years in developing countries (Forouzanfar et al., 2011). It is well known that human papilloma virus (HPV) is a necessary but insufficient risk factor for the development of cervical cancer (Faridi et al., 2011). Therefore, many research efforts were taken to identify cofactors for cervical cancer development. Active smoking (Sood, 1991), multiple sexual partners (Smith et al., 2011), first intercourse younger than 20 years (Plummer et al., 2011), and long duration of oral contraceptive use (Urban et al., 2012) are confirmed as the the role of secondary risk factors of cervical cancer apart from HPV. However, it is also well accepted that the cause of development of cervical cancer is of complex interaction (Jee et al., 2003), and as years go by, attention tends to shift towards other possible.

Passive smoking is the inhalation of smoke from tobacco products used by others, and considered from sidestream and exhaled mainstream smoke. Evidences show that at least 17 carcinogenic chemicals contained in tobacco smoke are emitted at higher levels in sidestream smoke than mainstream smoke (Mohtashamipur et al., 1990). And benzo (a) pyrene diol epoxide, one of the metabolites of tobacco smoke is found in both mainstream and sidestream smoke, that shows a direct aetiological association with lung cancer (Denissenko et al., 1996). For active smoking is a well-established risk factor for cervical cancer, it can hypothesis that passive smoking also a risk factor.

In 1989, Slattery et al were the first to study and conclude that a relationship might exist between passive smoke exposure and development of cervical cancer (Slattery et al., 1989). Since then, several epidemiological studies have performed to address that possibility in regards to passive smoke exposure and risk of cervical cancer among non-smokers (Tajima et al., 1990; Nishino et al., 2001; Coker et al., 2002; Wu et al., 2003; Settheetham-Ishida et al., 2004; Sull et al., 2004; Tay et al., 2004; Wu et al., 2004; Trimble et al., 2005; Sobti et al., 2006; Tsai et al., 2007; Sobti et al., 2008). However, the evidence has been suggestive rather than sufficient to indicate the role of passive smoking in the etiology of cervical cancer among non-smoking women, and some revealed different or even contradictory, for limitations include small sample sizes of non-smoker controls and cases of cervical cancer, lack of specific information on HPV and sexual behavior, contained history of smoking, etc.

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So we performed this meta-analysis based on published case-control studies of exposure to passive smoke and the subsequent development of cervical cancer. We followed the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) (Stroup et al., 2000) guidelines to report the present meta-analysis.

Materials and Methods

Literatures search

We initially identified published and unpublished studies which tested the association between passive smoking and risk of cervical cancer by searching the PUBMED databases from January 1st, 1988 to February 10th, 2012. The following search terms were used: (1) "cervical cancer" or "cervical carcinoma" or "uterine cervix cancer" or "CC" or "cervical neoplasia"; (2) "secondhand smoking" or "environmental tobacco smoke" or "ETS" or "passive smoking" or "tobacco smoke pollution"; (3) "case control" or "incidence" or "prognosis" or "early diagnosis" or "survival analysis" or "case-control". These search themes were combined using the Boolean operator "and" in several combinations without restrictions. In addition, we also reviewed the reference lists of retrieved papers and recent reviews.

Study selection

We included any study that met all of the following criteria: 1) the study design was a case-control study; 2) investigated the association between passive smoking and risk of cervical cancer; (3) inclusion of at least 20 cases; (4) the diagnoses of cervical cancer was confirmed either histological, pathologically or cytological; 4) the odds ratios (OR) and the corresponding 95% confidence intervals (CIs), or the number of events that can calculate them were reported. Two investigators independently evaluated the eligibility of all studies retrieved from the database on the basis of the predetermined selection criteria. Studies not designed as case-control, systematic reviews and studies with mutually overlapping populations were excluded from this meta-analysis. Disagreements were resolved by discussion or in consultation with the third one.

For the purposes of this study, cervical cancer included various stages and types: unspecified histology (CC), squamous cell carcinoma (SCC), adeno/adenosquamous carcinoma (ADC), invasive cervical cancer (ICC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), cervical intraepithelial neoplasia (CIN), or carcinoma in situ (CIS).

Data extraction

Two reviewers independently extracted the following data for each eligible study: first author's last name, year of publication, site of origin, histological type and stage of the tumor, source of controls, number of cases and controls, adjusted estimates of risk. Any disagreements were resolved by consensus.

Methodological quality assessment

Two reviewers independently assessed the methodological quality of the included studies with the Newcastle–Ottawa Scale (NOS) (Wells et al., 2009) for case-control studies, which consists of three parameters of quality: selection, comparability, and exposure assessment. The NOS assigns a maximum score of 4 for selection, 2 for comparability, and 3 for exposure. Hence, a score of 9 is the highest and reflects the highest quality. Discrepancies were addressed in consultation with the third one.

The NOS evalution tool included:
(1) selection
  Is the case definition adequate?
  Representativeness of the cases
  Selection of Controls
  Definition of Controls
(2) Comparability
  Comparability of cases and controls on the basis of the design or analysis
(3) Exposure
  Ascertainment of exposure
  Same method of ascertainment for cases and controls
  Non-Response rate

Statistical analysis

We computed a pooled OR and 95% CI by using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey) (Borenstein et al., 2005) to generate forest plots, to determine whether there was a statistical association between cases and controls and to assess heterogeneity of the included studies. Heterogeneity was quantified evaluated using the chi-square based Cochran's Q statistic (Higgins et al., 2002) and the I^2 statistic, this statistic yields results ranged from 0 to 100% (I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; and I^2 = 75-100%, extreme heterogeneity) (Higgins et al., 2003). If heterogeneity existed, the random effects model was used, otherwise, the fixed effects model was used. In addition, we investigated the influence of a single study on the overall risk estimate by removing each study in each turn, to test the robustness of the main results. If significant heterogeneity is identified, subgroup analysis was also conducted according to histological type and stage of the tumor, source of control (population-based and hospital-based case-control studies), and continent in which the study was conducted (North America and Asia). If possible, potential publication bias was assessed by visual inspection of the funnel plots of the primary outcome (Egger et al., 1997). The Begg rank correlation test was used to examine the asymmetry of the funnel plot (Begg et al., 1994) and the Egger weighted linear regression test was used to examine the association between mean effect estimate and its variance (Egger et al., 1997).

Results

Identification of eligible studies

Of the 36 records found initially, eleven studies including a total of 3,230 cases and 2,982 controls were

Table 1. Characteristics of Included Studies

Study	Country	Group	Source of control	Age(yrs)	No. of subjects	OR(95%CI)	Adjustment for covariates
Slattery 1989	USA	control	PB	20-59	408		age, education, church attendance,
		CC			266	1.78(1.08-2.93)	number of sexual partners of the woman, and cigarette smoking
Tajima 1990	Japan	control	HB	50-69	231	2.60(1.15-5.87)	NA
		CC			56		
Coker 2002	USA	control	PB	28.1±6.6	427		age, age at first sexual
	LSIL		25.4±6.2		313	1.40(1.00-2.00)	intercourse, race, HPV status,
		HSIL		24.4±5.7	59	2.20(1.00-4.80)	and active cigarette smoking
Wu 2003	Taiwan	control	PB	>19	175	2.73(1.31-5.67)	educational levels, number of
	of China	≥CIN 2			89		pregnancy, age at first intercourse, and cooking in the kitchen in the ages of 20-40
Settheetham-Ishida 2004	Thailand	control	HB	20-70	1004.73(2.15-10.39)		age, age at first intercourse, number of sexual partners, number of pregnancies and smoking
		CC			90		
Sull 2004	Korea	control	HB	46.2±10.5	454		NA
		CIN 1		39.8±9.6	40	0.82(0.41-1.65)	
		≥CIN 2		43.2±9.9	176	2.78(1.70-4.54)	
		IC		50.3±10.9	246	1.08(0.76-1.53)	
Tay 2004	Singapore	control	HB	48.61	224		age, parity, age at first intercourse, use of oral contraceptive pills, and patient's own smoking status
		LSIL		44.72	139	1.05(1.01-2.11)	
		HSIL		45.32	236	1.03(0.99-1.07)	
Wu 2004	Taiwan	control	PB	>42	197	2.13(1.07-4.26)	NA
	of China	≥CIN 1			100		
Sobti 2006	India	control	HB	48.0±11.3	103	4.96(2.46-10.00)	NA
		CC		48.6±9.9	103		
Tsai 2007	Taiwan	control	PB	>20	513		NA
	of China	CIN 1			58	1.15(0.65-2.03)	
		≥CIN 2			59	0.94(0.54-1.64)	
Sobti 2008	India	control	HB	48.81±9.64	150	2.12(1.34-3.33)	NA
		CC		48.55±9.43	200		

OR, odd ratio; CI, confidence interval; PB, population-based; HB, hospital-based; CC, cervical cancer; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; ICC, invasive cervical cancer; NA, not available

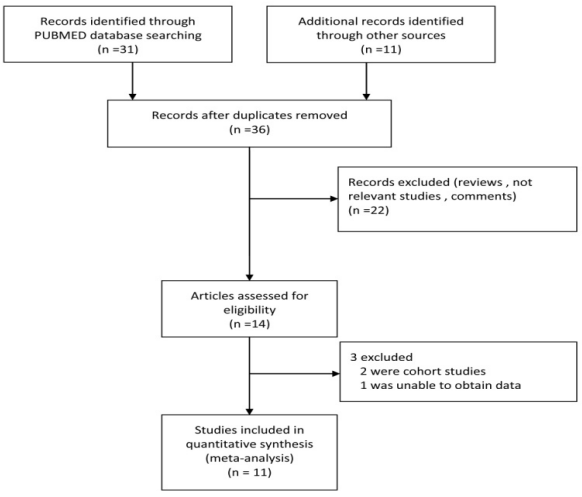

Figure 1. Summary of the Studies Selection Process

Table 2. Quality Assessment According to the Newcastle-Ottawa Scale

Study	Section	Comparability	Exposure	Total
Slattery 1989	4	2	3	9
Tajima 1990	3	2	2	7
Coker 2002	4	2	3	9
Wu 2003	4	2	2	8
Settheetham-Ishida 2004	3	2	3	8
Sull 2004	3	2	2	7
Tay 2004	3	2	3	8
Wu 2004	4	2	2	8
Sobti 2006	3	2	2	7
Tsai 2007	4	2	2	8
Sobti 2008	4	2	3	9
Average	3.5	2	2.5	8

identified. A flow chart for the study selection is shownin Figure 1.

Characteristics of included studies

The detailed characteristics of included studies are summarized in table 1. Of included eleven studies, ten were published in English (Slattery et al., 1989; Coker et al., 2002; Wu et al., 2003; Settheetham-Ishida et al., 2004; Sull et al., 2004; Tay et al., 2004; Wu et al., 2004; Sobti et al., 2006; Tsai et al., 2007; Sobti et al., 2008) and one was in Janpanese (Tajima et al., 1990), the sample sizes ranged from 56 to 462 in cervlcal cancer group while 100 to 513 in control group. All of the cases were histological, pathologically or cytological confirmed as cervical cancer, of them, five studies did not distinguish the type (CC) (Slattery et al., 1989; Tajima et al., 1990; Settheetham-Ishida et al., 2004; Sobti et al., 2006; Sobti et al., 2008), four studies clearly divided indicated the type (CIN) and

Table 3. Stratified Analyses According to Potential Sources of Heterogeneity

Subgroups	Number of studies	ORs	Meta-analyses 95% CIs	Meta-analyses p value	Model	Heterogeneity I^2	Heterogeneity p value
Tumor stage and type							
CC	5	2.77	1.85 - 4.17	<0.001	random	52.66	0.08
LSIL	2	1.43	1.11 - 1.84	0.01	fixed	0	0.87
HSIL	2	1.35	0.66 - 2.77	0.40	random	72.13	0.06
ICC	1	1.08	0.76 - 1.53	0.67	fixed	0	1.00
CIN 1	2	1.00	0.65 - 1.56	0.99	fixed	0	0.46
≥CIN 1	1	2.13	1.07 - 4.25	0.03	fixed	0	1.00
≥CIN 2	3	1.91	0.92 - 3.97	0.08	random	78.75	0.01
Source of control							
PB	5	1.52	1.24 - 1.86	<0.001	fixed	30.42	0.20
HB	6	1.86	1.29 - 2.70	<0.001	random	89.74	<0.001
Continent for study							
USA	2	1.58	1.21 - 2.07	<0.001	fixed	0	0.50
Asia	9	1.75	1.30 - 2.35	<0.001	random	84.4	<0.001
Adjustment for covariates							
Yes	5	1.74	1.23 - 2.48	<0.001	random	82.83	<0.001
No	6	1.71	1.18 - 2.48	<0.001	random	74.65	<0.001

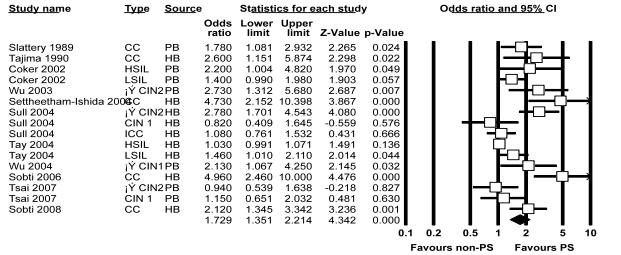

Figure 2. Forest Plot of Odds Ratios and and 95% CI of Cervical Cancer from Studies of Never Smoking Women Exposed to Passive Smoking

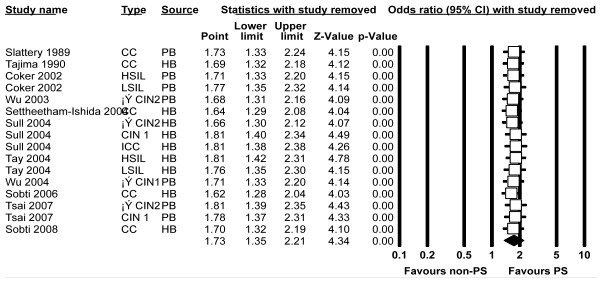

Figure 3. Forest Plot of Sensitivity Analysis by Removing Each Study in Each Turn

divided according to their pathologic stage (CIN 1, 2, or 3) (Wu et al., 2003; Sull et al., 2004; Wu et al., 2004; Tsai et al., 2007), two studies clearly divided the type to HSIL and LSIL (Coker et al., 2002; Tay et al., 2004), one study reported ICC (Sull et al., 2004). Controls were mainly healthy populations, and matched with age, gender, or cancer-free, six were hospital-based (HB) (Slattery et al., 1989; Tajima et al., 1990; Settheetham-Ishida et al., 2004; Sull et al., 2004; Tay et al., 2004; Sobti et al., 2006; Sobti et al., 2008), five were population-based (PB) (Coker et al., 2002; Wu et al., 2003; Wu et al., 2004; Tsai et al., 2007). There were three studies performed in Taiwan of China (Wu et al., 2003; Wu et al., 2004; Tsai et al., 2007), two in the USA (Slattery et al., 1989; Coker et al., 2002), two in India (Sobti et al., 2006; Sobti et al., 2008), one in Japan (Tajima et al., 1990), one in Thailand (Settheetham-Ishida et al., 2004), one in Korea (Sull et al., 2004), and one in Singapore (Tay et al., 2004). Five studies adjusted the conventional covariates (Slattery et al., 1989; Coker et al., 2002; Wu et al., 2003; Settheetham-Ishida et al., 2004; Tay et al., 2004).

Quality of included studies

There was good agreement between the reviewers in regards to the validity assessments, the quality assessment of all the published studies were shown in Table 2. 100% of the studies were of high quality (NOS score higher than 6). The most common selection bias was the selection of controls form hospital controls. In terms of comparability bias, all the studies included adequate matching or adjustments (eg, age and sex). The most common exposure bias was the lack of reporting of nonresponse rates.

Passive smoking and risk of cervical cancer

Figure 2 show the estimated pooled OR associated with exposure to passive smoking. There is significant heterogeneity detected (I^2 = 82.70%, p<0.001), so the random effects model was used. The pooled OR from all eleven studies was 1.73 (95% CI: 1.35–2.21, p<0.001), that meant exposure to passive smoking could increase 73% risk of cervical cancer compared with non-exposure women.

Subgroup analyses

Table 3 showed the subgroup analyses results according to previous criteria. Stratification of the studies by histological type and stage of tumor showed that the OR was 2.77 (95%CI: 1.85 - 4.17, p<0.001) for unspecified histology (CC), was 1.43 (95%CI: 1.11 - 1.84, p = 0.01) for LSIL, was 1.35 (95%CI: 0.66 - 2.77, p = 0.40) for HSIL, was 1.08 (95%CI: 0.76 - 1.53, p = 0.67) for ICC, was 1.00 (95%CI: 0.65 - 1.56, p = 0.99) for CIN 1, was 2.13 (95%CI: 1.07 - 4.25) for ≥ CIN 1, and was 1.91 (95%CI: 0.92 - 3.97, p = 0.08) for ≥ CIN 2. Stratification by source of controls showed that OR was 1.52 (95%CI: 1.24 - 1.86, p<0.001) for population-based controls, and 1.86 (95%CI: 1.29 - 2.70, p<0.001) for hospital-based controls. Stratification by origin shows that the OR for exposure of passive smoking is 1.58 for studies conducted in the USA (95% CI: 1.21 - 2.07, p<0.001) compared with

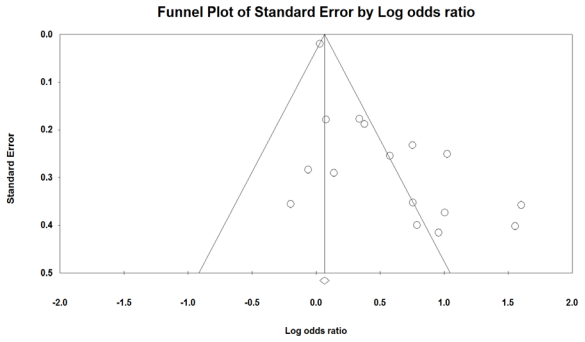

Figure 4. Funnel Plot Based on Odds Ratio for Association Between Passiveing Smoking and Cervical Cancer

1.75 (95% CI: 1.30 - 2.35, p<0.001) for studies conducted in Asia. Stratification by adjustment for conventional risk factors showed that the OR was 1.74 (95%CI: 1.23 - 2.48, p<0.001) while 1.71 for lack of adjustment for covariates (95%CI: 1.18 - 2.48, p<0.001).

Sensitivity analysis

Figure 3 showed the pooled ORs and 95%CIs of sensitivity analysis by removing one study in each turn, the result indicated that the the main result was robustness. When switched random-effects model to fixed-effect moedl, the OR and corresponding 95%CI from 1.73 (95% CI: 1.35–2.21, p<0.001) to 1.01 (95% CI: 1.03–1.11, p<0.001), that also supported the result was robustness.

Publication bias

Figure 4 showed that the funnel plot was unsymmetrical, that indicated there was publication bias existed. The Begg rank correction test and Egger linear regression also detected evidence for publication bias among studies of passive smoking and cervical cancer risk (Begg, p = 0.06; Egger, p<0.001). As exploring the evidence of bias could be due to inadequate statistical power we used a non-parametric method of "trim and fill" and estimated 5 possible missing studies, the estimated OR including the "missing" studies was not substantially different from our estimate with adjustment for missing studies: OR = 1.35 (95%CI: 1.08–1.69).

Discussion

While rates of cervical cancer incidence and mortality extremely high that could be necessary to find the targets for prevention programs aimed at reducing the incidence and mortality. A consistent critical role of HPV infection in the causation of cervical cancer has been identified and well accepted (Guan et al., 2012), and cigarette smoking was deemed as a cofactor that raised the possibility and promoted progression of cervical carcinogenesis (Winkelstein, 1990; Yetimalar et al., 2012). For both active and passive smoking have similar function inducing pro-inflammatory responses by influencing C-respone protein (Azar et al., 2011), and combined effects of exposure to active and passive smoking suggest its potential a increase risk factor of cervical cancer, however, passive smoking could not be detected as an independent risk factor of cervical cancer when lack of active smoking (Louie et al., 2011). In order to determine whether passive smoking was a independent risk factor of cervical cancer, many studies have been conducted, and some results indicated that women married to smokers experience a higher risk of cervical neoplasia than whom married to nonsmokers while some indicated there were no difference. This meta-analysis based on these case-control studies demonstrating an significantly association implicating passive smoking was a independent risk factorof cervical cancer. And the association was robust, could not influence by either source of controls or adjustment of conventional risk factors, and the association was existed in both Northern America and Asia.

To our knowledge, this study is the first meta-analysis based on case-control studies to observe a significantly increased risk of cervical cancer associated with passive smoking. Firstly, our study is a meta-analysis study, which could decrease recall and selection bias of each primary case-control study. In addition, the results remained similar when we changed the effect models, stratified by countries, graded by stage and type of tumors, and separated subgroups of adjust or non-adjust covariates. The sensitivity analysis by removed each study in each turn also showed no substantial change. Secondly, our study collected data on the subject of passive smoking and risk of cervical cancer and the subject did not on this topic but the content refered to this, which enabled us to included more eligible articles as much as possible to examine the relationship. Thirdly, we assessed methodological quality of included studies by using the NOS, that was a recognized criterion currently. And we also explored the publication bias by using a non-parametric method of "trim and fill", except for funnel plot, Begg test, and Egger test, that indicated there was some evidence to show that only a small number of studies were unpublished.

Our study also has limitations. Firstly, although the results were similar of adjust or non-adjust covariates, and population-based or hospital-based studies, the 95%CI was wider of non-adjustment than adjustment, as well as hospital-based wider than population-based ones. Secondly, the most noteworthy finding was that there was substantial heterogeneity. The most important factor that contributed to between-study heterogeneity were source of control and countries. Thirdly, there was a obviously publication bias existed, that may cause by restricting to published papers in PubMed databases. Studies with a statistically significant effect are more likely to be published (Dickersin et al., 1992), to be published in English (Egger et al., 1997), to be cited by other authors (Gotzsche, 1987), and to have multiple publications (Tramer et al., 1997). Moreover, the unpublished studies may show no association between passive smoking and cervical cancer (authors'publication bias). Finally, our meta-analysis based on limited number of studies, that the potential associations were large enough to reach statistical significance despite the context of relatively low statistical power. In addition, the majority of included srudies were lack of stratification by stage and histological type of tumor.

Our meta-analysis supported a causal link between

passive smoking exposure and risk of cervical cancer (OR = 1.73; 95% CI: 1.35–2.21), that is quantitatively similar to the association between active smoking and cervical cancer in the other meta-analysis (RR = 1.60; 95% CI: 1.48-1.73) (International Collaboration of Epidemiological Studies of Cervical et al., 2006).That suggesting doctors should ask the medical history and pay more attention to woman paitient whose husband is a smoker once or currently. And suggesting the women who works in a place that approach to passive smoking condition should take effective measures to protect themselves and receive periodical health examination.

For further research, the researchers are suggested to choose population-based controls, to divide stages and types of tumor as much as possible. And a dose-respone effects s are necessary to be studied. In addition, it is essential to adjust conventional risk factors.

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