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## Tobacco Use and Cervical Intraepithelial Neoplasia

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# TOBACCO CONSUMPTION AND CERVICAL INTRAEPITHELIAL NEOPLASIA

CONSUMO DE TABACO Y NEOPLASIA INTRAEPITELIAL

Noemí Rojas-Cisneros<sup>1,2</sup>, Rony Ruíz-Saucedo<sup>1</sup>

## ABSTRACT

**Objective:** To determine the effect of tobacco consumption with the development in women of cervical intraepithelial neoplasia. **Methods:** A systematic review was conducted. The electronic search was carried out, using the research question: What is the association between smoking and the development of cervical intraepithelial neoplasia? whose PEO question was: Population: Women. Exposure: Tobacco use. Outcome: Cervical intraepithelial neoplasia. Articles published from January 1, 2014 to December 2019 were selected. **Results:** 71 articles were found, 55 being excluded because they did not meet the selection criteria, leaving 16 articles for this paper analysis. Those women who smoked tobacco had a significant association for the development of high-grade intraepithelial neoplasia (OR = 1.43, 95% CI = 1.14-1.80). Likewise, synergy was observed between severe smoking and the use of oral contraceptives, with a greater risk of grade II and III intraepithelial neoplasia (OR = 11.5; 95% CI, 1.88-70.40). **Conclusion:** The available evidence suggests the association between tobacco use and the development of cervical intraepithelial neoplasia, particularly high-grade cervical intraepithelial lesions.

**Key words:** Cervical intraepithelial neoplasia; Tobacco use, Smoking, Smoking women, Lifestyle Medicine (source: MeSH NLM).

## RESUMEN

**Objetivo:** Determinar el efecto del consumo de tabaco en el desarrollo de neoplasia intraepitelial cervical en mujeres. **Métodos:** Se realizó una revisión sistemática. Se realizó la búsqueda electrónica, utilizando la pregunta de investigación: ¿Cuál es la asociación entre el tabaquismo y el desarrollo de neoplasia intraepitelial cervical? cuya pregunta PEO fue: Población: mujeres, Exposición: uso de tabaco. **Resultado:** Neoplasia intraepitelial cervical. Se seleccionaron los artículos publicados desde el 1 de enero de 2014 hasta diciembre de 2019. Resultados: Se encontraron 71 artículos, de los cuales 55 fueron excluidos por no cumplir con los criterios de selección, quedando 16 artículos para el análisis de este artículo. Aquellas mujeres que consumían tabaco tenían una asociación significativa para el desarrollo de neoplasia intraepitelial de alto grado (OR = 1,43, IC del 95% = 1,14-1,80). Asimismo, se observó asociación entre el tabaquismo severo y el uso de anticonceptivos orales, con mayor riesgo de neoplasia intraepitelial grado II y III (OR = 11,5; IC 95%, 1,88-70,40). **Conclusión:** La evidencia disponible sugiere la asociación entre el consumo de tabaco y el desarrollo de neoplasia intraepitelial cervical, particularmente lesiones intraepiteliales cervicales de alto grado.

**Palabras clave:** Neoplasia intraepitelial cervical; Consumo de tabaco, Tabaquismo, Mujeres fumadoras, Medicina del estilo de vida (fuente: DeCS BIREME).

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## INTRODUCTION

Cervical intraepithelial neoplasia (CIN) constitutes a premalignant lesion that precedes the development of cervical cancer. Cervical cancer represents the second most frequent type of cancer that affects women worldwide, annually about 9 million women develop it from which 80% are in developing countries<sup>(1)</sup>.

Cervical intraepithelial neoplasia is characterized microscopically by the presence of a series of manifestations that progress from cellular atypia to varying degrees of dysplasia. Among its conformation there are abnormal squamous cells that will be largely eliminated by the immune system, however, this will depend on the degree of cervical intraepithelial neoplasia (CIN).

It is very important to identify the degree of cervical intraepithelial neoplasia; Grade I is a mild dysplasia, which is why it is considered low grade, while Grade II and III constitute high-grade lesions, Grade II as a moderate dysplasia, and Grade III a severe dysplasia that can compromise all thickness of the lining of the cervix, being considered carcinoma in situ.

Among the risk factors involved in the development of cervical intraepithelial neoplasia are: genital HPV infection, where the most common infection mechanism is sexual transmission; It is estimated that approximately 80% of sexually active women at some time in their life will have contact with the human papillomavirus. In general, HPV infection represents the main factor of development, however, there are other factors that have been linked to being described in the literature, which contribute together to the development of squamous intraepithelial lesions at the cervix level and as a consequence they make women more likely to develop cervical cancer, among these factors are age, sociocultural condition, level of health knowledge, number of pregnancies, number of vaginal births, number of sexual partners, characteristics by the sexual partner, alcohol consumption, tobacco consumption, age of onset of sexual activity, hormonal planning, among others<sup>(2)</sup>.

Currently, it has been shown that women who present smoking within their background are more predisposed to present atypical cells, as well as develop cervical cancer. According to the International Agency for Research on Cancer (IARC) 62 of the 5 000 components of tobacco have been considered, proving to be carcinogenic, placing

cervical cancer among the most associated. It was obtained that there is a greater probability of mortality in 21% of women with cervical cancer and who have a history of smoking, which is why it is important to recognize the intervention of exogenous factors in the onset of cervical cancer<sup>(1,3)</sup>.

Lifestyle factors are currently at the center of the prevention and treatment of chronic diseases, including cancer. The objective of this article was to determine the effect of tobacco consumption with the development in women of cervical intraepithelial neoplasia.

## METHODS

In this work, a systematic review was made using articles in English and Spanish published from January 1, 2014 to December 2019, in PubMed, Scielo and Google Scholar. The PEO question was used: What is the association between smoking and the development of cervical intraepithelial neoplasia? Population: Women. Exposure: Tobacco use. Outcome: Cervical intraepithelial neoplasia. The key words were: "tobacco use" (MeSH Term) in combination with "cervical intraepithelial neoplasia" (used in PubMed); "Tobacco use", "tobacco", "smokers" in combination with "cervical intraepithelial neoplasia" (used in Scielo and Google Scholar). Mentioning the terms "tobacco use" refers to the use of tobacco through cigarettes. The syntax resulting from the advanced search was: (((("Women" [mh] OR Girls \* [tiab] OR Girl \* [tiab] OR Woman \* [tiab] OR Women's Groups \* [tiab] OR Women Groups \* [tiab] OR Women's Group \* [tiab])) AND ("Tobacco Use" [mh] OR Tobacco Use \* [tiab] OR Tobacco Chewing \* [tiab] OR Tobacco Consumption \* [tiab] OR smoking \* [tiab] OR cigarrete \* [tiab])) AND ("Cervical Intraepithelial Neoplasia" [mh] OR Cervical Intraepithelial Neoplasm \* [tiab] OR Cervical Intraepithelial Neoplasia \* [tiab])).

The search strategy can be seen in Tables 1, 2, 3 and 4.

### Inclusion criteria:

- Articles published during the last 5 years.
- Articles that contain any of the following combinations of keywords both in the title or abstract: Cervical intraepithelial neoplasia along with smoking, tobacco or smoking; "Cervical intraepithelial neoplasia" next to "tobacco use" or "tobacco" or "smoking".



**Exclusion criteria:**

- Studies that are not directly related to this topic.
- Articles that do not have an author or Digital Object Identifier (DOI).

The study protocol was registered in Biomedical Sciences Research Institute of Ricardo Palma University.

**RESULTS**

71 articles were found, excluding 20 for not being within the last 5 years, 32 because they did not comply with the combination of keywords in their structure, also 3 were excluded because they were not directly related to the subject to be reviewed. In the end, 55 articles were excluded, so there were 16 articles left for this paper analysis, including one article for theoretical and conceptual purposes.

The study selection diagram can be seen in Figure 1.

**Evidence from prospective studies:**

In the work carried out by Sánchez J. et al, a population of 807 patients were studied, of which 629 (77.9%) denied to be smokers and 178 (21.1%) they to be smoke, taking occasional smoking criteria as exclusion criteria. The smoking rate of the smoking patients was calculated, resulting in: 148 (83.1%) had a mild degree of smoking, 20 (11.3%) a moderate degree of smoking and 10 (5.6%) an intense degree of smoking. Regarding the results of Pap smears, 9 (5%) cases presented low-grade intraepithelial lesions, 3 (1.68%) high-grade intraepithelial lesions. At the time of calculating the odds ratio (RM) 1.90 was obtained with a 65% probability for the presence of cellular atypia in smoking women; also, in relative risk the result was 1.58 higher to have cervical-vaginal atypia in patients who smoked while those who did not had a protective relative risk of 0.63<sup>(1)</sup>.

Fang JH. et al. conducted a study to measure the risk related to the presence of high-grade intraepithelial neoplasia and regarding the changes produced by the human papillomavirus (HPV), as well as smoking, where it was obtained that those women smokers in the long term (more 8 years) and those who were severe smokers (18 or more cigarettes per day) had an increased risk for grade III intraepithelial neoplasia than those women who never smoked, having a HR of 2.31 with a 95% CI, 1.12 to 4.16<sup>(4)</sup>.

**Evidence from retrospective studies:**

In the work done by Min KJ. et al., it was obtained that

passive smoking in those non-smoking patients was associated with an increased risk for the development of cervical intraepithelial neoplasia grade I (OR = 1.53, 95% CI, 1.07-2.18), the risk increased regarding to the longest time exposed to this factor (P for trend <0.0003); the multivariate probabilities of <2 hours = day of passive smoking and ≥2 hours = day of passive smoking was 2.48 (95% CI, 1.49-4.14) and 2.28 (95% CI, 1.21-4.26) for cervical intraepithelial neoplasia (2,5). Oh HY et al., report that those patients who had a history of severe smoking and long-term use of oral contraceptives (OR = 11.5; 95% CI, 1.88-70.4) had a higher risk of grade II and III intraepithelial neoplasia<sup>(6)</sup>.

Xu H. et al., Obtained that in those women who used tobacco during the study had a significant association for the development of grade II and III intraepithelial neoplasia (OR = 1.43, 95% CI = 1.14-1.80)<sup>(7)</sup>. Wudtisan J. et al., observed that among all the associated factors was the presence of smoking history (OR = 2.95; 95% CI, 1.10-7.93; P = 0.032) with significance for development of cervical intraepithelial neoplasia in women under 30 years of age<sup>(8)</sup>. Daily LR. et al., refers that women with an average age of 22.5 years, where the proportion of smokers was 36.1%, it was determined that the history of smoking (OR = 1.64, 95% CI = 1.2-2-25) was associated with a history of high-grade cytology (OR = 2.06, 95% CI = 1.02-4.01) such as cervical intraepithelial neoplasia grade II and III<sup>(9)</sup>. Lee CH. et al., when assessing the risks for the development of cervical intraepithelial neoplasia, obtained that despite the high DNA load of the human papillomavirus, the main predictor of grade I and II intraepithelial neoplasia, factors such as age, age of Sexual onset and active or passive smoking are involved in the development of these lesions<sup>(10)</sup>.

Feng RM. et al., studied the role of smoking, as well as passive exposure to tobacco smoke at home, associated with the risk of infection with human papillomavirus (HPV) and grade II cervical intraepithelial neoplasia. The adjusted OR in those who once smoked versus those who never smoked was 1.45 (95% CI = 1.10-1.91) for HPV infection and 1.89 (95% CI = 1.03-3.44), with respect to cervical intraepithelial neoplasia grade II. Regarding active smokers such as passive smokers, they had an increased risk of 1.57 times (95% CI = 1.14–2.15) of HPV infection and a 1.99 times risk (95% CI = 1.02–3.88) of developing grade II intraepithelial neoplasia<sup>(11)</sup>. Pérez R. et al., obtained that low-grade cervical intraepithelial neoplasms (CIN 1) (n = 115; 48.94%) and grade II cervical intraepithelial neoplasia (n = 76; 32.34%) predominated, it was observed that there

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was a greater correlation between the lesions and the smoking rate (Rho Spearman 0.84;  $P < 0.0001$ )<sup>(12)</sup>. Cifuentes LY. et al., had a population where the age range was from 16 to 71 years, whose mean is 42.2 (SD = 14.57); finding that 11.3% were smokers, with an OR = 12.1 (5% CI, 4.0-36.3)( $p < 0.001$ )<sup>(13)</sup>.

Iwata T. et al., Studied the profile of cytokines present in the cervical mucosa of Japanese patients with cervical intraepithelial neoplasia, obtaining significantly lower levels of cytokine macrophage inflammatory protein-1 $\beta$  (MIP-1 $\beta$ ) ( $P = 0.018$ ) in smoking patients, however, they concluded that this habit further facilitates persistent infection with human papillomavirus (HPV)<sup>(14)</sup>. Roura E. et

al., conducted a study to evaluate the association between smoking and the risk of cervical intraepithelial neoplasia grade III; smoking status, duration and intensity showed a twice-greater risk of cervical intraepithelial neoplasia grade III, while in those who quit smoking, the time elapsed since they stopped smoking was associated with a twice-lower risk<sup>(15)</sup>. Andrade CE. et al., studied the risk factors of recurrence for cervical intraepithelial neoplasia in patients who had undergone surgical treatment, following up with a median time of 22.6 months; in the multivariate analysis, the only independent risk factor for recurrence was tobacco use (HR = 3.5, CI = 95%, 1.6-7.6,  $P = 0.002$ )<sup>(16)</sup>. The designs and results of the studies are found in Table 5.

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**Table 1.** Systematic search: Key terms.

		DeCS	MeSH	
<b>P</b>	Participants	Mujeres	Women	"Women"[Mesh]
<b>E</b>	Exposition	Consumo de Tabaco	Tobacco Use	"Tobacco Use"[Mesh]
<b>O</b>	Outcome	Neoplasia Intraepitelial Cervical	Cervical Intraepithelial Neoplasia	"Cervical Intraepithelial Neoplasia"[Mesh]

**Table 2.** Systematic search: Other terms

		MeSH	Others	
<b>P</b>	Participants	Mujeres	Women	<b>Women</b> Girls Girl Woman Women's Groups Women Groups Women's Group
<b>E</b>	Exposition	Consumo de Tabaco	Tobacco Use	<b>Tobacco Use</b> Tobacco Uses Tobacco Chewing Tobacco Consumption Smoking Cigarette
<b>O</b>	Outcome	Neoplasia intraepitelial cervical	Cervical Intraepithelial Neoplasia	<b>Cervical Intraepithelial Neoplasia</b> Neoplasia, Cervical Intraepithelial Cervical Intraepithelial Neoplasm Intraepithelial Neoplasm, Cervical Intraepithelial Neoplasms, Cervical Neoplasm, Cervical Intraepithelial Neoplasms, Cervical Intraepithelial Intraepithelial Neoplasia, Cervical Cervical Intraepithelial Neoplasia, Grade III



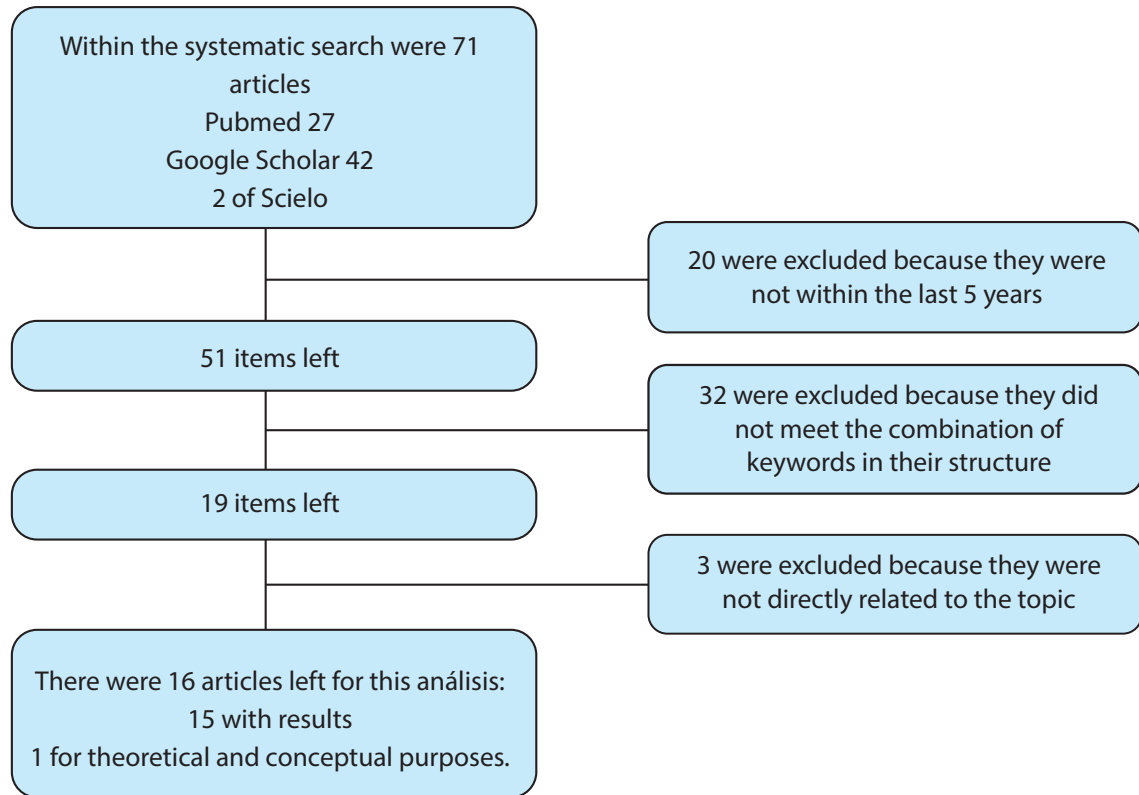
**Table 3.** Systematic search: Assignment of labels to terms.

		MeSH		Otros
<b>P</b>	Participants	Mujeres	"Women"[Mesh]	<b>Women*</b> [tiab] Girls*[tiab] Girl*[tiab] Woman*[tiab] Women's Groups*[tiab] Women Groups*[tiab] Women's Group*[tiab]
<b>E</b>	Exposition	Consumo de Tabaco	"Tobacco Use"[Mesh]	<b>Tobacco Use*</b> [tiab] Tobacco Uses*[tiab] Tobacco Chewing*[tiab] Chewing, Tobacco*[tiab] Tobacco Consumption*[tiab] Consumption, Tobacco*[tiab] Smoking*[tiab] Cigarette*[tiab]
<b>O</b>	Outcome	Neoplasia intraepitelial cervical	"Cervical Intraepithelial Neoplasia"[Mesh]	<b>Cervical Intraepithelial Neoplasia*</b> [tiab] Neoplasia, Cervical Intraepithelial*[tiab] Cervical Intraepithelial Neoplasms*[tiab] Cervical Intraepithelial Neoplasm*[tiab] Intraepithelial Neoplasm, Cervical*[tiab] Intraepithelial Neoplasms, Cervical*[tiab] Neoplasm, Cervical Intraepithelial*[tiab] Neoplasms, Cervical Intraepithelial*[tiab] Intraepithelial Neoplasia, Cervical*[tiab] Cervical Intraepithelial Neoplasia, Grade III*[tiab]

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**Table 4.** Systematic search: Union with Boolean operators.

		MeSH + Otros términos	
<b>P</b>	Participants	Mujeres	<b>"Women"</b> [mh] OR Girls*[tiab] OR Girl*[tiab] OR Woman*[tiab] OR Women's Groups*[tiab] OR Women Groups*[tiab] OR Women's Group*[tiab]
<b>E</b>	Exposition	Consumo de tabaco 1	<b>"Tobacco Use"</b> [mh] OR Tobacco Use*[tiab] OR Tobacco Chewing*[tiab] OR OR Tobacco Consumption*[tiab] OR smoking*[tiab] OR cigarette*[tiab]
<b>O</b>	Outcome	Neoplasia intraepitelial cervical	<b>"Cervical Intraepithelial Neoplasia"</b> [mh] OR Cervical Intraepithelial Neoplasm*[tiab] OR Cervical Intraepithelial Neoplasia*[tiab]



**Figure 1.** Study selection diagram.



**Table 5.** Research papers related to tobacco consumption and intraepithelial neoplasia

	Autóric / año de publicación	Procedencia	Población	Resultados
<b>COhort studies</b>				
Smoking and cervical-vaginal cell atypia <sup>(1)</sup>	Sánchez JM et al. / 2017	Mexico	807	Odds ratio (OR) was 1.90 with a 65% probability for the presence of cellular atypia in smoking patients, and the relative risk was 1.58 higher for having cervical-vaginal cellular atypia in patients who smoked.
Effect of smoking on high-grade cervical cancer in women on the basis of human papillomavirus infection studies <sup>(4)</sup>	Fang JH et al. / 2018	China	7129	For those who were severe smokers (18 or more cigarettes per day) they had an increased risk for grade III intraepithelial neoplasia than those women who never smoked, having a HR of 2.31 with a 95% CI, 1.12 to 4.16.
<b>Case- controls studies</b>				
Association of Combined Tobacco Smoking and Oral Contraceptive Use with Cervical Intraepithelial Neoplasia 2 or 3 in Korean Women <sup>(6)</sup>	Oh HY et al. / 2015	Korea	678	Patients who had a history of severe smoking and long-term use of oral contraceptives (OR = 11.5; 95% CI, 1.88-70.4) had a higher risk of grade II and III intraepithelial neoplasia.
Hormonal contraceptive use and smoking as risk factors for high-grade cervical intraepithelial neoplasia in unvaccinated women aged 30–44 years: A case-control study in New South Wales, Australia <sup>(7)</sup>	Xu H et al. / 2018	Australia	4522	Women who used tobacco during the study had a significant association for the development of grade II and III intraepithelial neoplasia (OR = 1.43, 95% CI = 1.14–1.80), increasing the risk when they increased cigarette consumption / day (trend p = 0.02), while in those ex-smoking patients the risk decreased (p-trend = 0.04) in relation to the time they stopped using tobacco.
Factors Associated with Development of High-Grade Squamous Intraepithelial Lesions of the Uterine Cervix in Women Younger than 30 Years <sup>(8)</sup>	Wudtisan J et al. / 2018	Thailand	345	The history of smoking (OR = 2.95; 95% CI, 1.10–7.93; P = 0.032) with significance for the development of cervical intraepithelial neoplasia in women under 30 years, compared to women over 30 years.
Factors associated with the finding of preneoplastic lesions in vaginal cytology: Case-control study <sup>(13)</sup>	Cifuentes LY et al. / 2014	Colombia	168	It was found that 11.3% were smokers, with an OR = 12.1; 5% CI, 4.0–36.3 (p < 0.001).
Cytokine profile in cervical mucosa of Japanese patients with cervical intraepithelial neoplasia <sup>(14)</sup>	Iwata T et al. / 2014	Japan	130	The significantly lower levels of cytokine MIP-1beta (P = 0.018) in smoking patients, however, it was concluded that this habit further facilitates persistent infection with human papillomavirus.
Smoking as a major risk factor for cervical cancer and pre-cancer: Results from the EPIC cohort <sup>(15)</sup>	Roura E et al. / 2014	Spain	308036	The association between smoking and the risk of cervical intraepithelial neoplasia grade III was evaluated; in the cohort analysis, smoking status, duration and intensity showed a twice as high risk of cervical intraepithelial neoplasia grade III.

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Risk factors for cervical intraepithelial neoplasia (CIN) recurrence in patients with positive cone margins <sup>(16)</sup>	Andrade C et al. / 2014	Brazil	97	When performing the follow-up whose median time was 22.6 months; In the multivariate analysis, the only independent risk factor for recurrence was tobacco use (HR = 3.5, CI = 95%, 1.6-7.6, P = 0.002).
<b>Cross-sectional studies</b>				
Association Between Passive Smoking and the Risk of Cervical Intraepithelial Neoplasia 1 in Korean Women <sup>(5)</sup>	Min KJ et al. / 2017	Korea	1322	Passive smoking in non-smoking patients was associated with an increased risk for the development of grade I cervical intraepithelial neoplasia (OR = 1.53, 95% CI, 1.07-2.18).
High Rates of High-Grade Cervical Dysplasia in High-Risk Young Women With Low-Grade Cervical Cytology <sup>(9)</sup>	Daily LR et al. / 2018	U.S	1058	The history of smoking (OR = 1.64, 95% CI = 1.2-2.25) was associated with a history of high-grade cytology (OR = 2.06, 95% CI = 1.02-4.01) as cervical intraepithelial neoplasia grade II and III.
Role of active and passive smoking in high-risk human papillomavirus infection and cervical intraepithelial neoplasia grade 2 or worse <sup>(11)</sup>	Feng RM et al. / 2017	China	16422	The adjusted OR in those who once smoked versus those who never smoked was 1.45 (95% CI = 1.10-1.91) for HPV infection and 1.89 (95% CI = 1.03-3.44) with respect to cervical intraepithelial neoplasia grade II. Passive smoking had a slightly higher risk of HPV infection with adjusted OR 1.11 (1.00-1.24), but no statistical association was observed between passive smoke exposure and grade II cervical intraepithelial neoplasia.
<b>Descriptive studies</b>				
Risk factors present in patients with squamous intraepithelial lesions of the cervix at the Rafael Calvo Maternity Clinic in the city of Cartagena (Colombia): Descriptive study <sup>(2)</sup>	Barrios L et al. / 2016	Colombia	150	8 women representing 5.33% of the total reported having the habit of smoking, having the histological diagnosis of squamous intraepithelial lesions.
Risk evaluation for the development of cervical intraepithelial neoplasia: Development and validation of riskscoring schemes <sup>(10)</sup>	Lee CH et al. / 2015	Taiwán	51523	It was obtained that, despite the high DNA load of the human papillomavirus, the main predictor of grade I and II intraepithelial neoplasia, active or passive smoking was found within the development of these lesions.
Women smokers and their association with atypia of the uterine cervix in Las Tunas, Cuba <sup>(12)</sup>	Pérez R et al. / 2019	Costa Rica	235	Low-grade cervical intraepithelial neoplasms (CIN I) (n = 115; 48.94%) and grade II cervical intraepithelial neoplasia (n = 76; 32.34%) predominated, with respect to smoking (n = 82; 34.89%). evidenced that there was a greater correlation between the lesions and the smoking rate (Rho Spearman 0.84; P < 0.0001).
Cigarette and cervical cancer <sup>(3)</sup>	Núñez J et al. / 2017	Chile		Theoretical and conceptual purposes.



**Tabla 6.** Importance, strengths and weaknesses of work related to tobacco consumption associated with cervical intraepithelial neoplasia.

Title	Importance of work	Strengths	Weaknesses
Smoking and cervical-vaginal cell atypia	It was possible to identify the existence of a correlation between smoking and cervical-vaginal cellular atypia.	The prospective design, as well as the duration of the study. The sample size was considerable allowing the study to be carried out.	Data directly linked to the development of a specific degree of intraepithelial neoplasia were not included.
Risk factors present in patients with squamous intraepithelial lesions of the cervix at the Rafael Calvo Maternity Clinic in the city of Cartagena (Colombia): Descriptive study	It allowed to determine the risk factors with the highest prevalence in patients diagnosed with cervical squamous intraepithelial lesions.	The sample size was adequate to allow review of the study. The starting age was adequate to delimit the study.	Being a descriptive study, there is information from the database that could not be obtained.
Effect of smoking on high-grade cervical cancer in women on the basis of human papillomavirus infection studies	The risk measure related to the development of high-grade cervical intraepithelial neoplasia was obtained with respect to the changes produced by the human papillomavirus and smoking.	Having a prospective allows you to follow up on cases. The population studied generated significant results.	It did not include assessing additional characteristics linked to smoking as age of onset and frequency.
Association Between Passive Smoking and the Risk of Cervical Intraepithelial Neoplasia 1 in Korean Women	Information was collected that details the presence of smoking in patients with cervical intraepithelial neoplasia, where passive smoking was not related to the risk of cervical intraepithelial neoplasia.	The study allowed to evaluate the specific association with the development of grade I intraepithelial neoplasia. The sample size was really significant to allow an adequate comparison.	The cross design. It did not include data from patients who were tobacco users.
Association of Combined Tobacco Smoking and Oral Contraceptive Use with Cervical Intraepithelial Neoplasia 2 or 3 in Korean Women	It was possible to assess the joint effect of smoking and the use of oral contraceptives against the risk of intraepithelial neoplasia.	He valued the association between tobacco use and oral contraceptives as a greater risk for the development of cervical intraepithelial neoplasia.	He did not value the presence of the characteristics related to tobacco consumption.
Hormonal contraceptive use and smoking as risk factors for high-grade cervical intraepithelial neoplasia in unvaccinated women aged 30-44 years: A case-control study in New South Wales, Australia	It was possible to understand the association between high-grade cervical lesions in older women and the use of hormonal contraceptives together with smoking as recognized cofactors for the development of premalignant lesions.	He assessed the risk caused by the joint use of tobacco and hormonal contraceptives. The age range of the population, since they are premenopausal women.	The magnitude of the association could be affected due to the characteristics of the control group.

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Factors Associated with Development of High-Grade Squamous Intraepithelial Lesions of the Uterine Cervix in Women Younger than 30 Years	The factors associated with the increased risk of developing high-grade cervical intraepithelial lesions in women under 30 years of age could be determined.	The period of time covered by the study allowed the collection of very significant information for the development of the work.	The population size. It did not include the assessment of the quantity of cigarettes.
High Rates of High-Grade Dysplasia in High-Risk Young Women With Low-Grade Cervical Cytology	The rate of grade II intraepithelial neoplasia was determined in high-risk youth.	The age group of the population allowed to provide new data against the risk of developing intraepithelial neoplasia.	The cross design. Data relevant to the study were not included.
Risk evaluation for the development of cervical intraepithelial neoplasia: Development and validation of risk-scoring schemes	Guidelines for the detection of cancer were developed through simple rating schemes in women with high risk factors.	The size of the sample. A different form of contact with tobacco related to the development of cervical intraepithelial neoplasia was evaluated.	Be a descriptive study. Factors were found that generated confusion in the development of work.
Role of active and passive smoking in high-risk human papillomavirus infection and cervical intraepithelial neoplasia grade 2 or worse	Smoking and passive exposure to smoke in the home were examined in relation to the risk of human papillomavirus infection and the development of grade II cervical intraepithelial neoplasia.	It allowed to demonstrate the role of tobacco against the main factor for the development of cervical intraepithelial neoplasia. The size of the sample. The period of time was 8 years.	The study design was transversal. Data on the age of the patients studied were not included.
Women smokers and their association with atypia of the uterine cervix in Las Tunas, Cuba	The correlation between smoking and the presence of uterine cervix cell atypia was identified.	The period of time of the study allowed the collection of relevant information. The sample size was significant.	Being a descriptive study, it cannot be extrapolated.
Factors associated with the finding of preneoplastic lesions in vaginal cytology: Case studies and controls	The sociocultural factors associated with the development of preneoplastic lesions were identified.	It is an analytical study. He selected a population closely linked to the problem under study.	The population size. He did not specify the degree of associated cervical intraepithelial neoplasia.
Cytokine profile in cervical mucosa of Japanese patients with cervical intraepithelial neoplasia	The risk factors associated with recurrence of cervical intraepithelial neoplasia were evaluated after patients received surgical treatment.	He specifically assessed the importance of recurrence in patients who had undergone surgery.	It is a retrospective study. The sample size was small.



## DISCUSSION

Through this systematic review it was observed that there is an association between smoking and the development of cervical intraepithelial neoplasia, which has been evidenced by various authors<sup>(1,3,4,5,14)</sup>. Cohort studies, cases and controls, as well as cross-sectional studies could be reviewed.

Within cohort studies, it was observed that in the work carried out by Sánchez JM et al. in Mexico, those women who smoked had an increased risk of cervical-vaginal cell atypia; also, Fang JH et al. in China, reported a higher risk for grade III cervical intraepithelial neoplasia in severe smokers<sup>(1,4)</sup>.

In case-control studies, the relationship between tobacco consumption and the three degrees of cervical intraepithelial neoplasm could be shown, observing tobacco consumption was present, resulting in one of the factors that increases the risk of intraepithelial cervical lesions in 32% of cases. This effect is greater in relation to the age of onset, whose average age range is between 15 and 19 years, as well as the time of consumption<sup>(7,9,12)</sup>.

Interestingly, in a case-control study it was observed that the risk for cervical intraepithelial neoplasia grade II and III decreased in ex-smokers ( $p$ -trend = 0.004), showing a benefit in relation to the time they stopped using tobacco<sup>(7)</sup>.

Regarding the findings on the use of oral contraceptives, in a study conducted by Oh HY et al, it was observed that those patients who had a history of severe smoking and concomitant use of oral contraceptives as a consequence had a higher risk of grade II and III intraepithelial neoplasia<sup>(6)</sup>.

Currently, the role of inflammation, within the study of the tumor microenvironment, is one of the main fields of cancer research. There is evidence for a strong link between chronic inflammation and cancer. Inflammation has been implicated in initiation and progression of tumors, as well as elimination of cancerous cells.

Many lifestyle habits produce low but constant levels of inflammation that can increase the risk of

cancer. Highlights include food, tobacco, alcohol, infectious agents, obesity, among others. In women, both HPV related to sexual habits and smoking related to socially accepted toxic habits, produce chronic inflammation and meta-inflammation, constituting targets for the prevention and treatment of CIN with Lifestyle Medicine. Numerous anti-inflammatory agents including those identified from natural sources have been shown to exhibit chemopreventive activities.

There is limited publication on clinical trials related to tobacco and CIN. The present work is one of the first systematic reviews on the association between smoking and cervical intraepithelial neoplasia. Our study included an important number of heterogeneous studies. Additionally, inherently it has the recognized limitations of the observational studies.

Overwhelming evidence exists from multiple sources that cigarette smoking significantly increases the risk of multiple chronic diseases including heart disease and stroke, diabetes, and cancer.

Despite the widespread recognition of the important role of lifestyle medicine measures and practices as a key component of the treatment and cancer prevention, scant progress has been made in improving the habits and actions of the women population.

Working on the preventive model of cancer with Lifestyle Medicine is essential for both the medical community and decision makers in public health.

## CONCLUSION

The available evidence supports the association between tobacco use and cervical intraepithelial neoplasia. Likewise, it was evidenced that smoking is not only associated with cervical intraepithelial neoplasia, but particularly high-grade intraepithelial lesions. Finally, more attention should be given to those patients who use oral contraceptives and consume tobacco, since this combination can increase the risk of cervical intraepithelial neoplasia, so it is necessary to deepen further studies.

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