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**Smoking and genital** **human papilloma virus infection in women attending cervical cancer screening in Greece**

**Chatzistamatiou K *et al*.** Smoking and genital HPV infection

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**Abstract**

**AIM**: To investigate whether smoking is associated with human papilloma virus (HPV) infection.

**METHODS**: HPV infection is considered to be a necessary condition for cervical cancer development. The study population included 1291 women, aged 25-55 years, attending cervical cancer screening. All women had a Papanicolaou (Pap) test, with liquid-based cytology (Thinprep®), an HPV-DNA test and an evaluation of smoking habits. The COBAS® 4800 system was used for HPV DNA testing, enabling identification of the following high-risk (h) HPV-types: each of HPVs 16 and 18 separately, and HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 as a cocktail. The evaluation of smoking habits was assessed using the smoking intensity index (SII), a variable formed as the product of cigarettes consumed per day by the days (years × 365) that a woman was a smoker, divided by 1000.

**RESULTS**: There were 136 smokers among 238 women tested positive for hHPV-types (HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and/or 68), and 463 smokers among 1053 hHPV-negative women (OR = 1.7, *P* < 0.001). This association was attributed to the youngest age group of women, aged 25-34 years (OR = 2.3, *P* < 0.001), while there was no association in other age groups. The intensity of smoking (increasing SII) showed no statistically significant association with hHPV infection. Cervical infection with HPV 16 and/or HPV 18 was also not associated with age or smoking habits. Finally, no association was found between Pap test status and smoking habits or smoking intensity.

**CONCLUSION**: Smoking appears to be associated with high-risk HPV infection of the uterine cervix, particularly in younger women. Further studies should investigate whether this association is based on causality and evaluate the role of other possible co-factors.

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**Key words:** Human papilloma virus; High-risk human papilloma virus; Human papilloma virus-DNA test; Smoking; Cervical cancer; Screening

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**INTRODUCTION**

Genital infection by human papilloma virus (HPV) is considered to be a *sine qua non* condition for development of cervical cancer[1]. In general, HPVs are divided into two groups, according to their oncogenic potential: The first group consists of the so-called low-risk and the second of the high-risk (h) HPV-types. Specific types of hHPV can cause cervical cancer, and more than 95% of cervical cancer biopsies contain DNA from hHPV genomes[2].

There are, however, certain other factors that may influence the probability of hHPV infection or accelerate the carcinogenic processes leading to cervical cancer [3]. Transmission of HPV between sexual partners is influenced by the age of a woman and her partner, the number of sexual partners, the age at first sexual intercourse, use of barrier contraceptive methods, co-infections, male sexual behaviour, and male circumcision[4]. In some studies however, age at first sexual intercourse was not identified as an independent risk factor in multivariate analysis[5-7]. Other factors that have similar impact on disease progression include high parity, long-term oral contraceptive use, and smoking[8-10].

Many studies have shown that cigarette and tobacco smoking in general have a moderate and statistically significant association with cervical cancer and cervical intraepithelial neoplasia (CIN)[10-19], although the latter is not supported by other studies[20]. In detail, Syrjänen *et al*[20], by using multivariate analysis, found that cigarette smoking was not an independent risk factor for CIN2 or more advanced lesions; however, there is evidence that suggests a potential role of passive smoking on invasive cervical cancer[21,22]. There is also evidence suggesting an association between smoking and an increased risk of high grade vaginal intraepithelial neoplasia (high grade VAIN)[23].

It is not quite clear though, if tobacco smoking, apart from increasing the risk for invasive cervical cancer and its precursors, may also influence HPV infection, particularly persistent HPV infection. Recent research focusing on the possible association between tobacco smoking and HPV infection has shown a positive association in women[18,24,25], as well as in men[26]. In the present study, this possible association has been investigated in an urban population of women participating in cervical cancer screening in Greece.

**MATERIALS AND METHODS**

***Participants and specimen collection***

Women attending cervical cancer screening in two outpatient clinics of the Hippokrateio Hospital in Thessaloniki, Greece, were recruited for the present study, as well as for an ongoing multi-center study dealing with screening for cervical cancer based on hHPV DNA detection as primary test, using the Cobas® 4800 HPV Test. In total, 1291 women were recruited for the present study between August 2011 and January 2013. Participants were 25-55 years old, living in the urban area of Thessaloniki. The following exclusion criteria were used: pregnancy, treatment for CIN during the previous five years, history of hysterectomy, and use of conventional cytology.

Every woman was informed about all aspects and the rationale of the study, and signed a consent-form in order to participate. After recruitment, women answered certain questions about their smoking habits; if they smoked, and if yes, how many cigarettes per day and for how many years. According to this information, the number of cigarettes per day, multiplied by years of smoking [*n* (cig/d) × 365 × *n* (years) divided by 1000] was calculated, creating a new variable, the smoking intensity index (SII), by which the sample was stratified. Following completion of the questionnaire, all women were examined by a specially trained healthcare professional (either a gynecologist or a midwife), who took cell samples from both the ecto- and the endocervix, using the Cervex brush® (Rovers® Medical Devices, B.V. Oss, The Netherlands). Brushes were inserted in Thinprep® vials containing PreservCyt® Solution (Hologic, Inc, Marlborough, MA, United States), and were discarded after handling according to the instructions of the manufacturer.

***Cytology***

Papanicolaou (Pap) smears were prepared using the Thinprep® liquid-based methodology, as previously described[27] and examined by a specially trained cytologist. The cytological assessment was performed according to the Bethesda 2001 classification[28]. The remaining liquid sample was then sent to the Peripheral Laboratory of Public Health of the Hellenic Center for Disease Control and Prevention andLaboratory of Hygiene and Environmental Protection/Laboratory of Microbiology of the Democritus University of Thrace in Alexandroupoli, Greece, where it was tested for HPV DNA, using the Cobas® 4800 system (Roche® Molecular Diagnostics, CA, United States).

***HPV DNA detection***

The Cobas® 4800 HPV Test is based on two main procedures[29]: (1) automated isolation of viral and human nucleic acids from clinical samples; and (2) enhancement and detection with real-time- polymerase chain reaction of 22 target-DNA sequences. Specifically, the Cobas® 4800 HPV Test employs primers for the determination of a sequence of approximately 200 nucleotides within the L1 polymorphic region of the HPV genome. The HPV primer concentration that exists in the Main Compound has been designed for the DNA enhancement of 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The oligonucleotide fluorescent tracers are bound to the polymorphic regions within the sequence determined by those primers. An additional primer couple and an additional tracer target the beta-globulin human genome -clone (amplicon) 330 bp- in order to supply a control serum. Simultaneous infusion, enhancement and detection of human beta-globulin genome and viral sequences using Cobas® 4800 HPV Test gives the user the added advantage of control during all stages of the examination. The HPV primer concentration in the main compound reagent for the Cobas® 4800 HPV Test has been designed for the DNA enhancement of 14 high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The enhanced signals from HPV 16 and 18 are each detected with a separate special fluorescent stain, while the other twelve hHPV types are detected using the same fluorescent stain[29].

***Statistical analysis***

The association between HPV infection and smoking was evaluated using the chi-square test and Fisher’s exact test. The influence of smoking and smoking intensity on high-risk HPV infection as well as on cytology status was evaluated with the use of cross-tabulation matrices associating age. Frequencies and relative frequencies, as well as their corresponding p-values of the *÷*2 test and the odds ratios are calculated. *P*-values < 0.05 were considered statistically significant. Analyses were performed using the SPSS 20.0 statistical software (IBM Corp., New York, United States).

**RESULTS**

Recruited women (*n* = 1291) were divided into two groups: (1) hHPV-positive women, *i.e.*, women positive for any of the 14 high-risk types (*n* = 238); and (2) hHPV-negative women, *i.e.*, women negative for all 14 high-risk HPV-types (*n* = 1053).

***Smoking and HPV status***

In the younger group of women, aged 25-34 years, 95 out of 158 hHPV-positive women were smokers, as compared with 125 out of 316 hHPV-negative women (60.1% *vs* 39.6%, *P* < 0.001). Hence, in this age group, smokers were 2.3 times more likely to have a high-risk HPV infection than non-smokers. There was no statistically significant difference between hHPV-positive and hHPV-negative women in the 35-44 year-old (46.7% *vs* 45.4%) and the 45-55 year-old age groups (57.1% *vs* 46.3%). Regardless of age, a significantly higher proportion of hHPV-positive women were smokers, as compared with hHPV-negative women (57.1% *vs* 43.8%, *P* < 0.001). The OR for smokers to be hHPV-positive in all age groups, *i.e.,* for ages between 25 and 55, was 1.7 (*P* < 0.001). An overview of these results is presented in Table 1.

No association was found between smoking intensity and hHPV status. These results are presented in detail in Table 2. Figure 1 shows an overview of hHPV-positive women stratified according to age and smoking intensity. The latter is defined according to the calculated smoking intensity index (SII = cigarettes/d × 365 × years of smoking divided by 1000), and a woman is classified as non-smoker if she had never smoked or if she had stopped smoking at least one year earlier. Smokers were classified into one of the following categories according to the previously described variable: SII < 50, if she had smoked less than 50000 cigarettes during her life as a smoker, SII = 50-100, if she had smoked between 50000 and 100000 cigarettes, SII = 100-150 if she had smoked between 100000 and 150000 cigarettes, SII = 150-200 if she had smoked between 150000 and 200000 cigarettes, and SII > 200 if she had smoked more than 200000 cigarettes.

There was no statistically significant association between smoking habits (*i.e.,* smokers *vs* non-smokers) or smoking intensity (increasing SII) and infection from HPV types 16 or 18 in any age group. Table 3 show an overview of the association between smoking and HPV-16 and HPV-18 status, respectively, stratified according to age.

***Smoking and cervical cytology results***

Regarding cervical cytology results, women were divided into two groups: (1) Women with a negative (normal) Pap-smear (*n* = 1246); and (2) women with abnormal Pap smear (ASCUS or worse) (*n* = 45). Comparisons according to smoking habits (smokers *vs* non smokers) or smoking intensity between women with normal and women with abnormal cytology results, using the chi-square test, did not show any statistically significant differences between different age groups (data not shown).

***Smoking, HPV status and cervical cytology results***

Comparisons according to smoking habits between the two groups of women regarding cervical cytology and the two groups regarding hHPV status showed that women with a negative Pap test were more likely to have hHPV infection if they were smokers than if they did not smoke (OR = 1.7, *P* = 0.001). This was not the case if cervical cytology showed ASCUS or worse; however the number of these women was rather low, given that the study was conducted among women attending screening. These findings are presented in Table 4.

On the other hand, similar comparisons for smoking intensity between the two groups of women regarding cervical cytology and the two groups regarding hHPV status showed, based on very low numbers, that smoking intensity (increasing SII) was associated with a higher probability of a positive (*P* = 0.045), but not a negative Pap test (Table 5).

Finally, stratification of all these associations between smoking habits, Pap smear results and hHPV status according to age showed that only younger women (25-34 years old) with a negative Pap test were more likely to have hHPV infection if they were smokers than if they did not smoke (OR = 2.3, *P* = 0.001). These findings are presented in Table 6.

**DISCUSSION**

In the present study, smokers were more likely to be tested positive for high-risk HPV types among women 25-55 years of age in an urban area of Greece. Similar results were found in a population of young women in Brazil: certain HPV types were significantly more frequent in current smokers than non-smokers[30]. Likewise, in a study conducted in Portugal, the CLEOPATRE study group showed that smoking was associated with an increased risk of HPV infection[25]. The association between HPV infection and smoking has also been a consistent finding in other studies, conducted in various countries, including Russia, Belarus and Latvia[20], Germany[31], Costa Rica[7], and Canada[32].

With respect to smoking intensity, the International Agency for Research on Cancer (IARC), in a pooled analysis demonstrated that smoking intensity played a significant role in HPV infection risk[24]. Furthermore, similar results to the IARC study were found in a cohort of Tuscan women[33]. In contrast, Collins *et al*[12] found no evidence linking the risk of acquiring an HPV infection with the intensity of smoking. Likewise, in the present study, there was no association between smoking intensity (expressed by a Smoking Intensity Index) and high risk HPV infection of the uterine cervix. These contradictory findings may be due to geographic variations in the prevalence of HPV-types[34], as well as due to differences in study design and methods used.

Despite the fact that smoking is a well established risk factor for cervical cancer, there are still contradicting reports regarding the association between tobacco use and high-risk HPV infection. In a study conducted in Denmark, current smokers were found to have similar HPV prevalence as compared with women who had never smoked, whereas past smokers had a decreased prevalence of HPV[35]. A significant association between HPV prevalence and smoking was found for HIV positive but not for HIV negative women, in a study comparing these two groups[36].In a nested case control study, smoking was associated with CIN3, but not with HPV infection[37]. In, a study conducted in the United States and Venezuela, risk factors for cervical cancer development appeared to vary between the two countries[38], and this might be possible for HPV infection as well. Therefore, studies evaluating risk factors for HPV infection should be conducted in various places around the world. An interesting finding in the present study was that younger women (25-34 years old) with a negative Pap test were more likely to have hHPV infection if they were smokers as compared with non-smokers. This finding may suggest that smoking might enhance HPV-infection in its early stages, before development of pre-invasive lesions. On the other hand, it might be argued that this is a casual rather than a causal association, since younger women are more likely to smoke, as well as to be HPV-positive.

The exact biological mechanisms by which tobacco use is associated with HPV infection, are not clearly understood yet. Persistence of an HPV infection might have been enhanced, leading to an increased risk of progression to cancer, coupled by the carcinogenic effect of polycyclic aromatic hydrocarbons contained in tobacco smoke[21]. These known carcinogens exert a transformation effect on the epithelium of the cervix uteri[21,39,40]. Smoking may also act by increasing cell-turnover in the transformation zone of the cervix[41]. Finally, another possible mechanism might be aberrant, HPV-induced DNA methylation[42].

HPV infections are usually transient. On the other hand, persistence of HPV infection and progression to high grade lesion are probably facilitated by smoking, due to a local immunosuppression that it causes[21,38,43]. This local immune dysfunction results in prolonged duration of oncogenic HPV infections, as well as a decreased probability of clearing the oncogenic infection[44,45]. Furthermore, smoking appears to decrease the capability of the immune system to develop HPV-16/18 antibodies or maintain HPV-16/18 antibody positivity over time, after a natural HPV infection[46]. In addition, smoking has been also associated with a higher baseline HPV-16 and HPV-18 DNA load[47]. In our study, however, smoking did not seem to be associated with cervical HPV-16 and/or HPV-18 infection. Finally, another possible factor that appears to play a role in the persistence of HPV infection, as well as in its progression to high-grade lesions and invasive cervical cancer, is the interaction between smoking and the genetic background of an individual, which determines her susceptibility to infection and disease progression [43].

A limitation of the present study, as well as of most relevant publications, is that HPV-DNA-testing was done only once for each woman. Sequential HPV genotyping of all participants, at certain intervals, could possibly show if smoking might also influence the course of HPV infection. Another limitation of the present study and most relevant publications is that possible co-factors including age at first intercourse, number of sexual partners and oral contraceptive use have not been considered, and thus the possibility of bias cannot be ruled out.

In conclusion, smoking has a well-documented synergistic role with HPV infection, leading to cervical cancer development[48,49]. Furthermore, smoking seems to be associated with an increased prevalence of HPV, a finding confirmed by the present study. Further studies should investigate whether this association is based on causality and evaluate the role of other possible co-factors. In any case, current smokers with either HPV infection or CIN lesion should be managed cautiously, and they should be advised to quit smoking.

**COMMENTS**

***Background***

Human papilloma virus (HPV) infection is considered to be a necessary condition for cervical cancer development. High-risk HPV types can cause cervical cancer, and more than 95% of tumour samples contain DNA from high risk HPV genomes. Many studies have shown that smoking is associated with cervical cancer and its precursors.

***Research frontiers***

Several studies in various countries, including Brazil, Portugal, Russia, Belarus, Latvia, Germany, Costa Rica, and Canada, have shown that smoking is associated with an increased risk of HPV infection. Regarding smoking intensity, results have been contradictory.

***Innovations and breakthroughs***

In the present study, smokers were more likely to be tested positive for high-risk HPV types, among women 25-55 years of age, in an urban area of Greece. In respect to smoking intensity, no association with high risk HPV infection of the uterine cervix was found in the present study.

***Applications***

The association between smoking and high-risk HPV infection is useful for planning cervical cancer prevention strategies. Furthermore, this association may help to clarify or identify new mechanisms of carcinogenesis.

***Terminology***

HPVs are divided into two groups, according to their oncogenic potential: low-risk HPVs, usually leading to genital warts or low-grade intraepithelial lesions, and high-risk (h) HPV-types, with high oncogenic potential.

***Peer review***

The paper is interesting and well written. I encourage authors to continue to explore this issue, improving their analysis with information on general habits of investigated young women and to discover the further correlations with HPV infection/co-infections and other factors, a part smoking.

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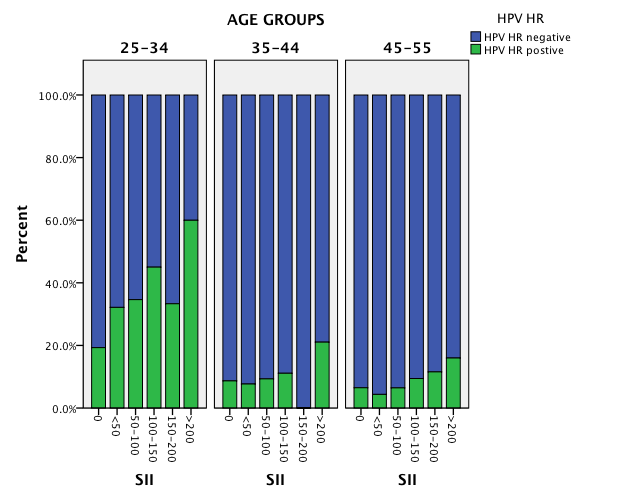
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**Figure 1 Stratification of human papilloma virus-positive and** **human papilloma virus-negative women according to age and smoking intensity.** There was no statistically significant association between smoking intensity and (h) human papilloma virus (HPV) status. SII: Smoking intensity index

**Table 1 Association between smoking and** **(h)** **human papilloma virus status, stratified according to age *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age** **(yr)** | **Smoking** | **HPV (+)** | **HPV (-)** | **Total** | ***P*** | **OR** |
| 25-34 | Yes | 95 (43.2) | 125 (56.8) | 220 | < 0.001 | 2.3 (1.6-3.4) |
| No | 63 (24.8) | 191 (75.2) | 254 |  |  |
| Total | 158 | 316 | 474 |  |  |
| 35-44 | Yes | 21 (12.1) | 152 (87.9) | 173 | NS | 1.1 (0.6-2.0) |
| No | 24 (11.6) | 183 (88.4) | 207 |  |  |
| Total | 45 | 335 | 380 |  |  |
| 45-55 | Yes | 20 (9.7) | 186 (90.3) | 206 | NS | 1.5 (0.8-3.1) |
| No | 15 (6.5) | 216 (93.5) | 231 |  |  |
| Total | 35 | 402 | 437 |  |  |
| Total | Yes | 136 (22.7) | 463 (77.3) | 599 | < 0.001 | 1.7 (1.3-2.3) |
| No | 102 (14.7) | 590 (85.3) | 692 |  |  |
| Total | 238 | 1053 | 1291 |  |  |

*P*-value of *χ*2 test and corresponding odds ratios (95%CI). NS: Not statistically significant; HPV: Human papilloma virus.

**Table 2 Association between smoking intensity and (h)** **human papilloma virus status stratified according to age *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age** **(yr)** | **Smoking** | **HPV (+)** | **HPV (-)** | **Total** | ***P*** |
| 25-34 | < 50 | 58 (41.4) | 82 (58.6) | 140 | NS |
| 50-100 | 23 (44.2) | 29 (55.8) | 52 |  |
| 100-150 | 10 (50.0) | 10 (50.0) | 20 |  |
| 150-200 | 1 (33.3) | 2 (66.7) | 3 |  |
| > 200 | 3 (60.0) | 2 (40.0) | 5 |  |
| Total | 95 | 125 | 220 |  |
| 35-44 | < 50 | 5 (9.6) | 47 (90.4) | 52 | NS |
| 50-100 | 5 (11.6) | 38 (88.4) | 43 |  |
| 100-150 | 6 (11.1) | 48 (88.9) | 54 |  |
| 150-200 | 0 (0.0) | 5 (100.0) | 5 |  |
| > 200 | 5 (26.3) | 14 (73.7) | 19 |  |
| Total | 21 | 152 | 173 |  |
| 45-55 | < 50 | 2 (4.3) | 44 (95.7) | 46 | NS |
| 50-100 | 2 (6.5) | 29 (93.5) | 31 |  |
| 100-150 | 5 (9.4) | 48 (90.6) | 53 |  |
| 150-200 | 3 (11.5) | 23 (88.5) | 26 |  |
| > 200 | 8 (16.0) | 42 (84.0) | 50 |  |
| Total | 20 | 186 | 206 |  |
| Total | < 50 | 65 (27.3) | 173 (72.7) | 238 | NS |
| 50-100 | 30 (23.8) | 96 (76.2) | 126 |  |
| 100-150 | 21 (16.5) | 106 (83.5) | 127 |  |
| 150-200 | 4 (11.8) | 30 (88.2) | 34 |  |
| > 200 | 16 (21.6) | 58 (78.4) | 74 |  |
| Total | 136 | 463 | 599 |  |

*P*-value of *χ*2 test. NS: Not statistically significant; HPV: Human papilloma virus.

**Table 3 Association between smoking and human papilloma virus-16,** **human papilloma virus-18 status stratified according to age *n* (%)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age (yr)** | **Smoking** | **HPV-16 (+)** | **HPV-16 (-)** | **Total** | ***P*** | **OR** | **HPV-18 (+)** | **HPV-18 (-)** | **Total** | ***P*** | **OR** |
| 25-34 | Yes | 24 (10.9) | 196 (89.1) | 220 | NS | 1.5 (0.8–2.8) | 8 (3.6) | 212 (96.4) | 220 | NS | 1.3 (0.5–3.7) |
| No | 19 (7.5) | 235 (92.5) | 254 |  |  | 7 (2.8) | 247 (97.2) | 254 |  |  |
| Total | 43 | 431 | 474 |  |  | 15 | 459 | 474 |  |  |
| 35-44 | Yes | 4 (2.3) | 169 (97.7) | 173 | NS | 0.8 (0.2–2.9) | 1 (0.6) | 172 (99.4) | 173 | NS | 0.4 (0.1–3.8) |
| No | 6 (2.9) | 201 (97.1) | 207 |  |  | 3 (1.4) | 204 (98.6) | 207 |  |  |
| Total | 10 | 370 | 380 |  |  | 4 | 376 | 380 |  |  |
| 45-55 | Yes | - | 206 (100) | 206 |  | - | - | 206 (100.0) | 206 |  |  |
| No | - | 231 (100) | 231 |  |  | - | 231 (100.0) | 231 |  |  |
| Total |  | 437 | 437 |  |  | - | 437 | 437 |  |  |
| Total | Yes | 28 (4.7) | 571 (95.3) | 599 | NS | 1.3 (0.8–2.3) | 9 (1.5) | 590 (98.5) | 599 | NS | 1.0 (0.4–2.6) |
| No | 25 (3.6) | 667 (96.4) | 692 |  |  | 10 (1.4) | 682 (98.6) | 692 |  |  |
| Total | 53 | 1238 | 1291 |  |  | 19 (1.5) | 1272 (98.5) | 1291 |  |  |

*P*-value of *χ*2 test and corresponding odds ratios (95%CI). NS: Not statistically significant; HPV: Human papilloma virus.

**Table 4 Association between smoking habits and** **(h) human papilloma virus status according to** **Papanicolaou test results *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cytology** | **Smoking** | **HPV (+)** | **HPV (-)** | **Total** | ***P*** | **OR** |
| Pap (+) | Yes | 18 (69.2) | 8 (30.8) | 26 | NS | 1.6 (0.5–5.6) |
| No | 11 (57.9) | 9 (42.1) | 19 |  |  |
| Total | 29 | 16 | 45 |  |  |
| Pap (-) | Yes | 118 (20.6) | 455 (79.4) | 573 | **0.001** | **1.7 (1.2–2.2)** |
| No | 91 (13.5) | 582 (86.5) | 673 |  |  |
| Total | 209 | 1037 | 1246 |  |  |
| Total | Yes | 136 (22.7) | 463 (77.3) | 599 | **< 0.001** | **1.7 (1.3–2.3)** |
| No | 102 (14.7) | 590 (85.3) | 692 |  |  |
| Total | 238 | 1053 | 1291 |  |  |

*P*-value of *χ*2 test and corresponding odds ratios (95%CI). Papanicolaou (Pap) test (+) = ASCUS or worse; Pap test (-) = Normal.

NS: Not statistically significant; HPV: Human papilloma virus.

**Table 5 Association between smoking intensity and** **(h) human papilloma virus status according to** **Papanicolaou test results *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cytology** | **Smoking** | **HPV (+)** | **HPV (-)** | **Total** | ***P*** |
| Pap (+) | < 50 | 8 (66.7) | 4 (33.3) | 12 | **0.045** |
| 50-100 | 4 (80.0) | 1 (20.0) | 5 |  |
| 100-150 | 5 (100.0) | 0 (0.0) | 5 |  |
| 150-200 | 0 (0.0) | 3 (100.0) | 3 |  |
| > 200 | 1 (100.0) | 0 (0.0) | 1 |  |
| Total | 18 | 8 | 26 |  |
| Pap (-) | < 50 | 57 (25.2) | 169 (74.8) | 226 | NS |
| 50-100 | 26 (21.5) | 95 (78.5) | 121 |  |
| 100-150 | 16 (13.1) | 106 (86.9) | 122 |  |
| 150-200 | 4 (12.9) | 27 (87.1) | 31 |  |
| > 200 | 15 (20.5) | 58 (79.5) | 73 |  |
| Total | 118 | 455 | 573 |  |
| Total | < 50 | 65 (27.3) | 173 (72.7) | 238 | NS |
| 50-100 | 30 (23.8) | 96 (76.2) | 126 |  |
| 100-150 | 21 (16.5) | 106 (83.5) | 127 |  |
| 150-200 | 4 (11.8) | 30 (88.2) | 34 |  |
| > 200 | 16 (21.6) | 58 (78.4) | 74 |  |
| Total | 136 | 463 | 599 |  |

*P*-value of *χ*2 test and corresponding odds ratios (95%CI). Papanicolaou (Pap) test (+) = ASCUS or worse; Pap test (-) = Normal.

NS: Not statistically significant; HPV: Human papilloma virus.

**Table 6 Association between smoking habits and (h) human papilloma virus status according to Papanicolaou test result and stratified according to age *n* (%)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** **(yr)** | **HPV (cytology)** | **Smoking** | **HPV (+)** | **HPV (-)** | **Total** | ***P*** | **OR** |
| 25–34 | Pap (+) | Yes | 13 (76.5) | 4 (23.5) | 17 | NS |  |
| No | 9 (64.3) | 5 (35.7) | 14 |  |  |
| Total | 22 | 9 | 31 |  |  |
| Pap (-) | Yes | 82 (40.4) | 121 (59.6) | 203 | **<0.001** | **2.3 (1.5–3.5)** |
| No | 54 (22.5) | 186 (77.5) | 240 |  |  |
| Total | 136 | 307 | 443 |  |  |
| Total | Yes | 95 (43.2) | 125 (56.8) | 220 | **<0.001** | **2.3 (1.6–3.4)** |
| No | 63 (24.8) | 191 (75.2) | 254 |  |  |
| Total | 158 (33.3) | 316 (66.7 | 474 |  |  |
| 35-44 | Pap (+) | Yes | 3 (75.0) | 1 (25.0) | 4 | NS |  |
|  | No | 1 (100.0) | 0 (0.0) | 1 |  |  |
|  | Total | 4 | 1 | 5 |  |  |
| Pap (-) | Yes | 18 (10.7) | 151 (89.3) | 169 | NS |  |
|  | No | 23 (11.2) | 183 (88.8) | 206 |  |  |
|  | Total | 41 | 334 | 375 |  |  |
| Total | Yes | 21 (12.1) | 152 (87.9) | 173 | NS |  |
|  | No | 24 (11.6) | 183 (88.4) | 207 |  |  |
|  | Total | 45 (11.8) | 335 (88.2) | 380 |  |  |
| Pap (+) | Yes | 2 (40.0) | 3 (60.0) | 5 | NS |  |
|  | No | 1 (25.0) | 3 (75.0) | 4 |  |  |
|  | Total | 3 | 6 | 9 |  |  |
| Pap (-) | Yes | 18 (9.0) | 183 (91.0) | 201 | NS |  |
|  | No | 14 (6.2) | 213 (93.8) | 227 |  |  |
|  | Total | 32 | 396 | 428 |  |  |
| Total | Yes | 20 (9.7) | 186 (90.3) | 206 | NS |  |
|  | No | 15 (6.5) | 216 (93.5) | 231 |  |  |
|  | Total | 35 | 402 | 437 |  |  |
| Pap (+) | Yes | 18 (69.2) | 8 (30.8) | 26 | NS |  |
|  | No | 11 (57.9) | 8 (42.1) | 19 |  |  |
|  | Total | 29 | 16 | 45 |  |  |
| Pap (-) | Yes | 118 (20.6) | 455 (79.4) | 573 | 0.001 | 1.7 (1.3–2.3) |
|  | No | 91 (13.5) | 582 (86.5) | 673 |  |  |
|  | Total | 209 | 1037 | 1246 |  |  |
| Total | Yes | 136 (22.7) | 463 (77.3) | 599 | NS |  |
|  | No | 102 (14.7) | 590 (85.3) | 692 |  |  |
|  | Total | 238 | 1053 | 1291 |  |  |

*P*-value of *χ*2 test and corresponding odds ratios (95%CI). Papanicolaou (Pap) test (+) = ASCUS or worse; Pap test (-) = Normal.

NS: Not statistically significant; HPV: Human papilloma virus.