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ORIGINAL ARTICLE

# Association of Combined Tobacco Smoking, Hormonal Contraceptive use and Status Matrimonial with Cervical Cancer Evolution in Tunisian Women

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**Abstract**
Status matrimonial, cigarette smoking and hormonal contraceptive (HC) use have been associated with cervical cancer (CC) establishment by influencing the CC carcinogenesis process. In the present study, we aim to confirm this correlation between these factors and the risk of CC occurrence among Tunisian population. To evaluate the role of matrimonial status, smoking and HC as cofactors of CC installation, we performed a random selection of 600 women from Salah Azeiz institute in Tunisia and a questionnaire was conducted by doctors for each patient. Logistic regression after adjustment for potential confounding factors, relative excess risk due to interaction (RERI) and synergy index (S) were used to evaluate the additive interaction. Subgroup analysis was conducted to examine whether the relative risks changed with CC stages. There were an excess risk among smoker patients and patient with HC use ($p < 0.001$) for CC installation. Women who are smokers have a 14 times greater risk of suffering from cervical cancer and approximately 24 times greater to develop an advanced form of CC malignancy. Having a history of using birth control pills increase CC occurrence and aggravation (OR~2). The matrimonial status seems an important factor for CC appearance (OR = 3.58 and 2.46) among CC Tunisian patient. However, no significant biological interaction from this three joint exposure was observed in the early FIGO stages but the risk increase in advanced FIGO stages. In our Tunisian cohort, oral contraception, smoking habit and matrimonial status are associated with an overall increased risk of CC development. Indeed, it may damage the local immunity system and may affect the disease severity in patient carriers of some genetic risk biomarkers. The balance of cancer risks may vary among Tunisian CC patient, depending on some environmental co-factors.

**Keywords** Cervical cancer · FIGO staging · Status matrimonial · Smoking · Hormonal contraceptive

## Introduction

Cervical Cancer (CC) continues to be a significant health problem on a world-wide scale. However, marked differences in the relative frequency of CC are observed due to the variations of screening programs availability and risk co-factors. Although the beliefs that human papillomavirus (HPV) infection is the main risk factor of CC development, a growing body of evidence implicates that several environmental factors influence the appearance of malignancies and affect the clinical course of CC too. Among these factors; cigarette smoking habit, long-term hormonal contraceptive use (HC), matrimonial status and co-infection with human immunodeficiency virus (HIV) [1].. In fact, previous studies have demonstrated the strong correlation between the smoking habit and the risk of carcinogenesis process development [2, 3]. Moreover, the risk of CC among HC users has been long discussed [4–7] and

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it has been established that the risk of CC was modulated with duration of use of combined hormonal contraceptives [6].

Recent systemic reviews proof that the recency of using birth control pills affects the risk for CC, squamous cell carcinoma and adenocarcinoma development. [1, 8, 9]. Therefore, it was hypothesized that the HC duration use could have a combined effect with smoking habit in cervical cancer occurrence by suppression of local cervical immunity [10, 11]. In fact, a Korean study proved that the HC use and smoking habit, individually, did not lead to elevated risk for development of cervical intraepithelial neoplasia (CIN). Contrariwise the combination of the latter was associated with increasing risk of CIN appearance [12].

The influence of those environmental co-factors has been showed in genetic studies among CC Tunisian patient [12, 13]. Herein, Sabrina et al. establish a correlation between, in one hand, Toll like receptors (TLR) genes polymorphisms and menopause status, and, in the other hand, the increasing risk for CC establishment. Suggesting, a possible way to predict the disease installation and aggravation by taking account both of genetic and environmental factors [14, 15].

Interestingly, it is becoming apparent that the interplay between the main factors of CC development and environmental factors influences disease manifestations and its clinical course too. Therefore, we conducted an epidemiological study of CC among Tunisian women to describe the pattern occurrence of CC in interaction with environmental factors.

## Material and methods

### Study design and data collection

This was an observational, monocentric and retrospective study. In the institute of Salah Azeiz Tunisia, patients with CC were included consecutively from 2009 to 2016 and were seen in day clinic. Patients with CC admitted in the day hospital were questioned on their place of birth, menstrual history, oral contraceptive use history (never/ current and duration of alcohol consumption (never/current drinker and duration). All patients included in the present study were with a positive history of HPV infection. Clinical data concerning patients were obtained from a primary medical file and times of assignment of the International Federation of Gynecology and Obstetrics (FIGO) classification score were checked for consistency using institute Salah Azeiz Database. Patients were designed according to FIGO score and they were subdivide in two groups; G1: Early stages (Stage I + II) ($n = 131$) and G2:

**Table 1** Characteristics of study participants

| Characteristics | Controls | Cases | | $P^1$ |
|---|---|---|---|---|
| | | Early FIGO stages | Advanced FIGO stages | |
| n | 300 | 131 | 169 | |
| Age (years) | | | | |
| 30–40 yr | 98(32.6%) | 72(55%) | 35(20.7%) | >0.000 |
| 41–50 yr | 80 (26.6%) | 32(24.4%) | 75(44.3%) | 0.000 |
| 51–60 yr | 112 (37.4%) | 25(19%) | 54(32%) | 0.008 |
| 61–70 yr | 10(3.4%) | 2(1.6%) | 5(3%) | 0.667 |
| Marital status | | | | |
| Married | 256(85.3%) | 125(95.4%) | 158(93.5%) | 0.005 |
| Not married | 44(14.6%) | 6(4.6%) | 11(6.5%) | |
| Menopause status | | | | |
| Pre-menopausal | 208(69.3%) | 110(83.9%) | 128(75.7%) | 0.003 |
| Post-menopausal | 92(30.7%) | 21(16.1%) | 41(24.3%) | |
| Hormonal contraception | | | | |
| Users | 119(39.6%) | 76(58%) | 93(55%) | 0.000 |
| Non-users | 181(60.4%) | 55(42%) | 76(45%) | |
| Tobacco users | | | | |
| Smokers | 18(6%) | 62(47.4%) | 102(60.35%) | 0.000 |
| Non-smokers | 282(94%) | 69(52.6%) | 67(39.65%) | |
| Family history of cancer | | | | |
| With history of cancer | 52(17.3%) | 25(19%) | 32(18.9%) | 0.596 |
| Without history of cancer | 248(82.7%) | 106(81%) | 137(81.1%) | |

FIGO International Federation of Gynecology and Obstetrics; n: Number of women; $P^1$ Student's t-test (continuous variables), Pearson $\chi^2$ test (categorical variables); $P^1$ controls vs patients (early stage+advanced stage)

**Table 2** Implication of environmental characteristics in the development of cervical tumor according FIGO staging

| | Early FIGO stages | | | Advanced FIGO stages | | |
|---|---|---|---|---|---|---|
| | Controls vs Cases | $p_{value}$ | OR(CI 95%) [b] | Controls vs Cases | $p_{value}$ | OR (CI 95%)[b] |
| Marital status[a] | | | | | | |
| Married | 256(85.3%)/125(95.4%) | 0.001 | 3.58(1.48–8.62) | 256(85.3%)/158(93.5%) | 0.005 | 2.46(1.23–4.92) |
| Not married | 44(14.6%)/6(4.6%) | | | 44(14.6%)/11(6.5%) | | |
| Menopause status[a] | | | | | | |
| Pre-menopausal | 208(69.3%)/110(83.9%) | 0.000 | 2.31(1.36–3.92) | 208(69.3%)/128(75.7%) | 0.084 | 1.38(0.89–2.12) |
| Post-menopausal | 92(30.7%)/21(16.1%) | | | 92(30.7%)/41(24.3%) | | |
| Hormonal contraception[a] | | | | | | |
| Users | 119(39.6%)/76(58%) | 0.000 | 2.1(1.38–3.18) | 119(39.6%)/93(55%) | 0.001 | 1.86(1.27–2.72) |
| Non-users | 181(60.4%)/55(42%) | | | 181(60.4%)/76(45%) | | |
| Tobacco users[a] | | | | | | |
| Smokers | 18(6%)/62(47.4%) | 0.000 | 14(7.82–25.32) | 18(6%)/102(60.35%) | 0.000 | 23.85(13.52–42.06) |
| Non-smokers | 282(94%)/69(52.6%) | | | 282(94%)/67(39.65%) | | |
| Family history of cancer[a] | | | | | | |
| With history of C | 52(17.3%)/25(19%) | 0.378 | 1.12(0.66–1.90) | 52(17.3%)/32(18.9%) | 0.376 | 1.11(0.68–1.81) |
| Without history of C | 248(82.7%)/106(81%) | | | 248(82.7%)/137(81.1%) | | |

CI, confidence interval FIGO International Federation of Gynecology and Obstetrics; OR, odds ratio. C, Cancer; vs, versus

[a] Includes both current and past status

[b] Multinomial logistic regression analysis (Control vs early stages vs advanced) were performed after adjustment for age,

Advanced stages (Stage III + IV) ($n = 169$). Control group was selected from an ordinary routine at Charles Nicolle hospital and they are matched on age and ethnicity.

### Standard protocol approvals and patient consents:

All patients and Controls gave conformed consent for their data to be used. Confidentiality and safety of the data were ensured in accordance with the recommendation of the Salah Azeiz ethics committee in Tunisia.

### Statistical analysis

Chi-squared tests and ANOVA containing post-hoc analyses conducted using the Tukey method were used to analyze differences in the distributions of categorical and continuous variables. A multinomial logistic regression model was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of smoking, HC use and status matrimonial for the risks of FIGO stages. Statistical analysis was performed on SPSS v. 21.0 (SPSS Inc., Chicago, IL) and Epi info 7.

## Results

### Demographic and clinical Data:

Demographic and clinical data are shown in Table 1. The median age, was 52 years for patients and 53 years for controls. According to FIGO classification, 131 patients are in early stages (I + II) of cervical cancer and 169 have developed advanced tumor forms (III + IV). Patients who are married are most likely to progress to the advanced stages of CC (44% of married women with early stage of CC vs 56% of married women in advanced tumor stage). Among 283 premenopausal patients, only 45.2% are in advanced CC stage, 55% of women using pills for birth control are exposed to develop aggressive forms of cervical cancer. Moreover, 62.2% of female smokers have developed aggressive forms of CC. The family history of cancer seems an important factor for the clinical course of tumor installation and 57% of patient with clinical history had more risk to a rapid course of malignancy.

### Single effect of co-factors on the risk of CC

After adjustment for all potential confounding factors in this study, Only the marital status[$p = 0.001$; OR = 3.58(1.48–8.62)][$p = 0.005$ OR = 2.46(1.23–4.92)], smoking habit $p = 0.000$;OR = 14(7.82–25.32)][p = 0.000; OR = 23.85(13.52–42.06)] and the use of hormonal contraception pills [p = 0.000; OR = 2.1(1.38–3.18)][p = 0.000; OR = 1.86(1.27–2.72)] still a significant factor for CC clinical course modulation (Table 2).

### Single effect of co-factors on CC evolution

We tested for the influence of the following covariates on CC evolution defined as the stages of cancer according to FIGO

**Table 3** Association between environmental characteristics and cervical cancer evolution

| | Cases | | | |
|---|---|---|---|---|
| | Early FIGO stages | Advanced FIGO stages | $p_{value}$ | OR (CI 95%)[b] |
| Marital status[a] | | | | |
| Married | 125(95.4%) | 158(93.5%) | 0.324 | 1.45(0.52–4.03) |
| Not married | 6(4.6%) | 11(6.5%) | | |
| Menopause status[a] | | | | |
| Pre-menopausal | 110(83.9%) | 128(75.7%) | 0.053 | 1.67(0.93–3.01) |
| Post-menopausal | 21(16.1%) | 41(24.3%) | | |
| Hormonal contraception[a] | | | | |
| Users | 76(58%) | 93(55%) | 0.344 | 1.12(0.71–1.79) |
| Non-users | 55(42%) | 76(45%) | | |
| Tobacco users[a] | | | | |
| Smokers | 62(47.4%) | 102(60.35%) | 0.016 | 1.69(1.06–2.68) |
| Non-smokers | 69(52.6%) | 67(39.65%) | | |
| Family history of cancer[a] | | | | |
| With history of C | 25(19%) | 32(18.9%) | 0.544 | 1.00(0.56–1.08) |
| Without history of C | 106(81%) | 137(81.1%) | | |

CI, confidence interval FIGO International Federation of Gynecology and Obstetrics; OR, odds ratio; C, Cancer

[a] Includes both current and past status

[b] Multinomial logistic regression analysis (early stages vs advanced) were performed after adjustment for age,

**Table 4** Combination between parity, hormonal contraceptive use and smoking status for cervical cancer when stratified as two groups according to the FIGO staging

| | Controls [a] ($n = 300$) | Early FIGO stages [a] ($n = 131$) | | | Advanced FIGO stages [a] ($n = 169$) | | |
|---|---|---|---|---|---|---|---|
| | | Cases | $p_{value}$ | OR(CI 95%) [b] | Cases | $p_{value}$ | OR (CI 95%)[b] |
| Not Married & Not HC users | 27 (9%) | 2 (1.5%) | – | Reference | 3 (1.80%) | – | Reference |
| Married & HC users | 102 (34%) | 72 (54.9%) | 0.000 | 0.10(0.02–0.45) | 85 (50.30%) | 0.000 | 0.13(0.03–0.45) |
| Married & Not HC users | 154 (51.3%) | 53 (40.5%) | 0.045 | 0.21(0.04–0.93) | 73 (34.20%) | 0.000 | 0.08(0.02–0.27) |
| Not Married & HC users | 17 (5.7%) | 4 (3.05%) | 0.387 | 0.31(0.05–1.90) | 8 (4.70%) | 0.000 | 0.05(0.01–0.30) |
| Not Married & Not Smokers | 34 (11.4%) | 4 (3.05%) | – | Reference | 8 (4.70%) | – | Reference |
| Married & Smokers | 8 (2.6%) | 60 (45.8%) | 0.000 | 0.01(0.00–0.05) | 99 (58.57%) | 0.000 | 0.01(0.00–0.05) |
| Married & Not Smokers | 248 (82.6%) | 65 (49.6%) | 0.119 | 0.44(0.15–1.31) | 59 (34.93%) | 0.855 | 0.98(0.43–2.24) |
| Not Married & Smokers | 10 (3.4%) | 2 (1.6%) | 0.951 | 0.58(0.09–3.69) | 3 (1.80%) | 0.936 | 0.78(0.17–3.52) |
| Not Smokers & not HC users | 166 (55.3%) | 38 (29%) | – | Reference | 61 (36.10%) | – | Reference |
| Smokers & HC users | 3 (1%) | 45 (34.35%) | 0.000 | 0.01(0.00–0.05) | 87 (51.50%) | 0.000 | 0.01(0.000–0.04) |
| Smokers & Not HC users | 15 (5%) | 17 (12.98%) | 0.000 | 0.20(0.09–0.44) | 15 (8.85%) | 0.017 | 0.36(0.16–0.79) |
| Not Smokers & HC users | 116 (38.7%) | 31 (23.67%) | 0.330 | 0.85(0.50–1.45) | 6 (3.55%) | 0.000 | 7.10(2.97–16.98) |
| Not Married & Not HC users & Not Smokers | 27 (9%) | 2 (1.52%) | – | Reference | 3 (1.80%) | – | Reference |
| Married & HC users & Smokers | 8 (2.7%) | 3 (2.29%) | 0.228 | 0.19(0.02–1.39) | 85 (50.30%) | 0.000 | 0.01(0.00–0.04) |

CI, confidence interval FIGO International Federation of Gynecology and Obstetrics; OR, odds ratio

[a] Includes both current and past status

[b] Multinomial logistic regression analysis (Control vs early stages and vs advanced) were performed after adjustment for age,

classification (Table 3). The patients with smoking habit have a higher probability (approximately 2 times greater) to rapid evolution of CC into more severe FIGO stages [$p = 0.016$; OR = 1.69(1.06–2.68)].

### Joint effect of co-factors on early and advanced CC stages

A joint effect model was designed based on an additive scale of smoking, hormonal contraception use to evaluate the biological interaction (Table 4). Subjects who are married and use pills of birth control had a higher risk of CC in early and advanced stages [$p = 0.000$; OR = 0.10(0.02–0.45)] [p = 0.000; OR = 0.13(0.03–0.45)] successively. The combination of matrimonial status and smoking covariates leads to a higher probability for CC development compared to non-married women and who are no smokers neither [p = 0.000; OR = 0.01(0.00–0.05)] [p = 0.000; OR = 0.01(0.00–0.05)].

## Discussion

The present study highlights the implication of different social habits that could be attributable to the increased risk of CC in Tunisia. Evidence from this study suggests that the status of menopause, status matrimonial, use of hormonal contraception and smoking are associated with increased risk of tumor development but no significant association was found between CC incidence and family history of cancer. The majority of patients with tumor in early stages are pre-menopausal (83.9%) and no significant association was found among women in advanced stage of CC. Menopausal status can't be considered as a risk factor for CC development. Our results showed a significant association between status matrimonial and CC incidence. Smoking has been considered as the most significant environmental risk factor for cancer occurrence. Previous review has demonstrated that the risk of CC increases with the intensity and duration of smoking [8]. In fact, it was reported that the latter was associated with CC appearance due to the chemical carcinogen substance of benzopyrene which cigarette's contains. These chemical substances have been shown to enhance the HPV synthesis in cervical cells and might lead to virus persistence in most of cases [10, 20, 21]. Moreover, smoking may block the glutathione S-transferases activity and detoxify the activated forms of the carcinogen in epithelial tumor cells [22, 23] and it has been established the correlation between the smoking habit and the decrease of number of Langerhans cells and helper T cells in the squamous epithelial transformational zone of the cervix [23] Meanwhile, other study suggest the absence of correlation between smoking habit and cancer progression to severe forms [16].

Although, the smoking among Tunisian women is a rare habit (6.8% of female were smokers in 2011),the proportion of current smokers in this study (58% among patient in early FIGO stages and 55% among women in advanced FIGO stage) was considerably high.. Similar results among Asian countries admit the possible effect of exposure to secondhand smoke on the risk of cervical neoplasia [17–19]. However, a Korean study did not confirm the previous result [12]. In fact, Oh et al., demonstrated that the absence of smoking did not effect on CIN risk probability and affirmed that such result may be due to the dilution of current smoking's effect by the inclusion of former smokers [12].

Few comparative data regarding disease severity have been available in different ethnic groups throughout the world. The present study is the first to investigate the epidemiological, clinical and pathological profile of CC in Tunisia. In fact, environmental influences might regulate disease presentation by adjusting the epigenome and CC could result from additive changes of environmental factors on the immune system. However, Further studies of environmental and gene-environment interactions are necessary in Tunisian population.

There are some limitations to our study that should be addressed. First, we studied a hospital-based population in one oncogenic institute, which could contribute to recruitment bias and a selection of more severe cases. Since HPV genotyping was not available, it was not considered as a cofactor. Thus, these results should be interpreted with care as HPV genotype may be different from patient to another. Second, we did not study the role of passive smoking and duration of smoking influences on disease progression. For that, we are working on a project to follow up the kinetics of the pathology's evolution and the response to therapy among, smokers and passive smokers, patients.

## Conclusion

Our results suggest the influence of environmental factors that exist in Tunisia on CC clinical course. The additive effect of matrimonial status, hormonal contraceptive use and smoking habits should be regarded as co-factors risk for severe cervical dysplasia. Clinicians are, therefore, encouraged to recommend to patients to avoid the exposition to such factors in order to prevent the CC installation or/and aggravation.

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## Compliance with ethical standards

**Ethics approval and consent to participate** The study protocol was approved by the Ethics Committee at Salah Azeiz Oncology Institute in Tunis, Tunisia.

**Consent to publish** All authors are in agreement to publish this paper.

**Competing interests** The authors declare that they have no conflicts of interest concerning this article.

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