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THE RELATIONSHIP OF PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION AND STRESS AT THE WORKPLACE

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Abstract

Introduction: Human papillomavirus (HPV) is one of the most common sexually transmitted infections. While most genital HPV infections regress spontaneously, some persist and can progress to cervical cancer. The biological susceptibility to acquire HPV and the immunological capacity to eliminate the infection are influenced by various factors, including occupational roles, work-related stress, and burnout syndrome.

Materials and methods: In our study, relevant data were collected from 71 patients, 38 of whom had documented persistent HPV infections, while 33 patients were included in the study as a control group. Among those with persistent HPV infections, HPV 16 was the most common type, followed by HPV 31 and HPV 52.

Results: Job demands were assessed using the Job Demands Questionnaire. The burnout syndrome was evaluated with the Maslach Burnout Inventory. Job resources were investigated using the Hospital Survey on Patient Safety Culture Questionnaire and the English version of the Questionnaire sur les Ressources et Contraintes Professionnelles.

Conclusion: Preliminary data analysis revealed significantly higher levels of stress factors in the group of patients with persistent HPV infections compared to the control group. The insights gained from assessing the impact of workplace stress on HPV infection progression will help formulate recommendations to promote the health of the working population.

Keywords: HPV, persistent infection, job stress, burnout

Introduction

Human papillomavirus (HPV) infection is now a well-established cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) as well as head and neck cancers[1]. The majority of cases are squamous cell carcinomas, followed by adenocarcinomas. According to GLOBOCAN data, in 2020, there were 604,127 new cases and 341,831 deaths from cervical cancer worldwide[2].

HPV is one of the most frequent sexually transmitted infections. Most cases of genital HPV infection are transient and regress spontaneously, but some become persistent and can eventually progress to cervical cancer[3].

The International HPV Reference Center (IHRC) officially established 227 HPV types, approximately 40 infecting the genital area[4]. According to the epidemiological classification based on the risk of developing cancer, the types of HPV are grouped as “high risk (HR)” (HPV

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), "probably high-risk (pHR)" (HPV 26, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85 and 97),"low-risk (LR)" (HPV 6, 11, 13, 40, 42, 43, 44, 54, 61, 72, 81 and 89) and "undetermined-risk" (HPV 2a, 3, 7, 10, 27, 28, 29, 30, 32, 34, 55, 57, 62, 71, 74, 77, 83, 84, 86, 87, 90 and 91)[5,6].

HPV is a small virus with a diameter of 55 nm. The HPV genome consists of a single molecule of double-stranded, circular DNA approximately 7900 bp long associated with histones. HPV transmission primarily occurs through skin-to-skin contact. Papillomaviruses replicate exclusively in keratinocytes, which form the basal layers of the skin and mucosal surfaces. To infect the basal layers, there must be a minor abrasion or microtrauma on the epidermis[7,8].

Cervical cancer is one of the best-known examples of how viral infection can lead to malignant transformation. Products of the E6 and E7 genes deregulate the host cell growth cycle by binding and inactivating two tumor suppressor proteins: the E6 gene product binds to p53 and the HPV E7 gene product binds to pRb, Inactivation of p53 and pRb proteins can lead to enhanced proliferation rate and genomic instability[9].

A high percentage of sexually active young women are exposed to HPV infections, but approximately 90% of lesions regress spontaneously within 12 to 36 months. The natural course of cervical cancer is a continuous process of the disease, progressing from mild cervical intraepithelial neoplasia (CIN1) to more serious stages of neoplasia (CIN2 or CIN3) and finally to invasive cancer[10,11].

Definitions of HPV persistence have varied significantly across studies, and there is no definitive international definition for the duration of infection that defines HPV persistence. HPV viral persistence is often defined as detection of the same HPV type in two or more intervals. According to most studies, the shortest period from HPV detection required to classify it as a persistent infection in women is 6-12 months[12].

The development of cervical cancer from genital HPV infections is influenced by many factors. High-risk HPV infections are necessary, but not sufficient for the development of cervical cancer. The risk for HPV infection is increased if an individual has multiple sexual partners simultaneously, as well as early onset of sexual activity. Primary immune response to HPV infection, long-term use of oral contraceptives, smoking, and parity are significant risk factors for cervical dysplasia.

Few studies have been published on the association between HPV infection and various types of occupations. For example, the sedentary and restricted work environment of taxi drivers may alter their vaginal microbiome and favor HPV infection[13,14].

Psychological factors also play a significant role in the development and course of a range of diseases, including infectious diseases such as HPV infection. Changes in cellular immunity in HPV infection are associated with changes in cytokine levels, induction of cellular adhesion molecules, and changes in molecules of tissue histocompatibility, human leukocyte antigens (HLA). The immune response may vary depending on the duration of stress and how it is managed. Stress can increase the severity and duration of infectious diseases and promote reactivation of latent viruses.

Psychosocial factors may affect the development and persistence of HPV, primarily by acting on the immune response. An association between psychosocial stress and CIN development in women has been established. According to research data, a strong association between stress and a high viral load infection includes the promoting of overexpression and malignant transformation of HPV oncogenes, and a strong association between repeated infections and stress may compromise host immunosurveillance and mediate HPV persistence or reactivation[15,16].

Research in recent decades reveals that burnout syndrome is often the result of high workplace demands, stressful aspects of work associated with continuous physical, emotional,

or cognitive effort imposed on the worker. Burnout syndrome is a psychological syndrome involving a prolonged response to psychological demands and chronic interpersonal stressors at work. This syndrome refers to an individual's prolonged sense of exhaustion and decreased interest in work. Burnout syndrome is often described as an inability to cope with work-related stress or as excessive use of energy and resources leading to feelings of failure and exhaustion. This syndrome is characterized by three dimensions: emotional exhaustion, negative attitude towards work, and a feeling of reduced personal accomplishment[17,18].

Workplace resources (e.g., support from colleagues and supervisors, teamwork, adequate salary, career advancement opportunities, and status) are aspects of work that protect workers from workplace demands and psycho-physical burdens that arise from them. It has been proven that resources additionally stimulate personal development, learning, and development of the worker[19-22].

Results from previous studies and the Job Demands-Resources Model (JD-R Model) show that workplace resources increase workers' willingness to commit to their work tasks. In a work environment where various resources are available, positive outcomes are observed in workers who are engaged in performing work tasks and who are satisfied with their work[19,23,24].

The connection between workplace demands and resources and health effects on workers has been presented in various studies. An association has been established between workplace resources and a higher level of general health status, a lower likelihood of burnout syndrome, and a lower likelihood of work absenteeism due to illness[25-28].

Several factors influence the course and persistence of HPV infection itself. Work-related stress and burnout syndrome have been insufficiently studied as factors that might affect the persistence of HPV infection, despite the knowledge that the psycho-physical state of patients impacts their immune response. The main objective of our study was to evaluate the impact of work-related stress on the course of HPV infection, considering profession and job satisfaction.

Materials and methods

In the preliminary phase of the study, data from 38 patients with persistent HPV infection and 33 control subjects without persistent HPV infection were analyzed. Data were collected from each patient using standardized and specially designed questionnaires. Data were collected only from patients who provided written consent, after detailed explanation of the procedure, objectives, and their rights. Permission to use patients' data for the purposes of the study was obtained from the Ethics Committee for Human Research at the Faculty of Medicine in Skopje.

The analysis of the samples, cervical swabs taken from patients, was performed in the HPV Typing Laboratory at the University Clinic for Gynecology and Obstetrics, Skopje. HPV detection was carried out using commercial kits based on the multiplex testing method, cyclic-CMTA (Cyclic-Catcher Melting Temperature Analysis). This testing method is a multiplex real-time PCR analysis that enables simultaneous amplification, detection, and differentiation of target nucleic acids from 19 high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types (6, 11, 40, 42, 43, 44, 54, 61, 70), as well as an internal control (IC).

Patients were divided into two groups:

Group I included patients with persistent HPV infection, i.e., patients whose HPV infection was present 24 months after the initial diagnosis.

Group II included patients in whom the HPV infection was not persistent, i.e., patients whose HPV infection was not present 24 months after the initial diagnosis.

To achieve the study's objectives, a series of questionnaires were used as measurement tools, including standardized and specially designed questionnaires.

Demographic characteristics and job characteristics of the participants were obtained using the specially designed Demographic and Job Characteristics Questionnaire. Workplace demands were investigated using the Workplace Demands Questionnaire. This questionnaire was specially designed for the research needs, following a systematic literature review and analysis of methods used in other similar studies. The obtained questions were categorized according to the type of workplace demands: physical, emotional, organizational, and cognitive.

The section of the questionnaire related to physical demands of the workplace included 8 questions about the fast work pace, lack of staff, lack of equipment and materials for work, and administrative burden. Organizational demands were defined by 6 questions, describing strict hierarchical positioning of superiors, poor communication between departments, unclear and ambiguous roles and tasks, frequent changes in rules and regulations in the healthcare facility, and the impact of media on the negative image of healthcare workers from the specific institution. The section of the questionnaire related to emotional demands contained of 6 statements representing: lack of cooperation among colleagues, high competition among colleagues, inadequate handling of negative emotions at work, fear of making mistakes, and conflicts between home and work demands.

Five questions from the Workplace Demands Questionnaire define cognitive demands of the workplace, addressing lack of feedback on work results, decision-making under time pressures, insufficient participation in decision-making, obligation to train new employees, and decision-making with insufficient information. Respondents assign scores to each statement using a Likert scale, with five ratings from 1 for "very rarely" to 5 for "always." The scores assigned to statements belonging to any of the four types of workplace demands (physical, emotional, organizational, and cognitive) were summed, and the average value was calculated to obtain scores for each type individually.

The part of the questionnaire used to analyze teamwork was represented by four questions regarding mutual support, assistance, and respect among colleagues. The reward resource was defined by four questions describing satisfaction with salary, whether the salary was fair compared to other employees in the department, and whether the salary was sufficient for a comfortable life. Four questions from this questionnaire define the resource of relationships with superiors, addressing respect and assistance from the superior, as well as the atmosphere in working with the superior.

Statistical significance was considered for values of $p<0.05$, while highly significant values were $p<0.01$. For the purposes of our study, only some of the obtained results are presented.

Results

During this phase of the study, data from a total of 71 patients were analyzed, of which 38 were with persistent HPV infection, and 33 were included in the control group - subjects without persistent HPV infection.

High-risk HPV types 16, 18, 31, 33, 39, 45, 51, 52, 53, 56, 58, and 68 were prevalent in persistent HPV infections (Table 1). Out of 38 analyzed patients with persistent HPV infection, 19 had a mixed infection with the presence of 2 or more HPV types, and 19 had an infection caused by only one HPV type.

Table 1. Percentage representation of specific HPV types in patients with persistent HPV infection

HPV Type	Total Prevalence
16	52.6 %
18	7.9 %
31	15.8 %
33	2.6%
39	2,6%
45	10.5%
51	10.8%
52	15.8%
53	5.3%
56	2.6%
58	0.3%
59	7.9%
68	2.6%

The most prevalent HPV type was HPV 16, both as the sole HPV type present in 29.7% of subjects and in mixed infections with one or more HPV types in 52.6%. It was followed by HPV 31 and HPV 52, each with 15.8% total prevalence.

Table 2. Comparison of the two groups of subjects by age, total work experience, and number of working hours per week

Variable	Group	Mean ± Std. Dev.	t (p)
Age (years)	Persistent HPV	35.34 ± 9.29	1.92 (0.059)
	Control Group	35.11 ± 9.02	
Total work Experience (years)	Persistent HPV	8.76 ± 6.16	0.59 (0.56)
	Control Group	7.76 ± 8.21	
Working hours per week	Persistent HPV	40.03 ± 9.19	0.78 (0.439)
	Control Group	38,33 ± 9,07	

Significant *P<0.05

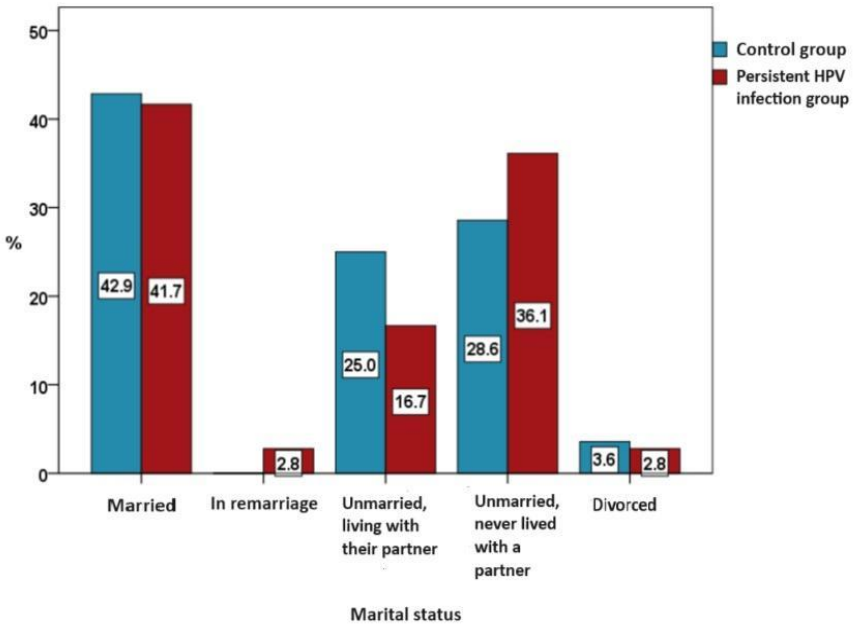

Fig. 1. Comparison of the two groups of subjects by marital status

No significant difference was found between the two groups regarding age of the subjects, their total work experience, and number of working hours per week.

No significant difference was found between the two groups regarding the marital status of the subjects (χ^2=1.63; p=0.804) (Figure 1).

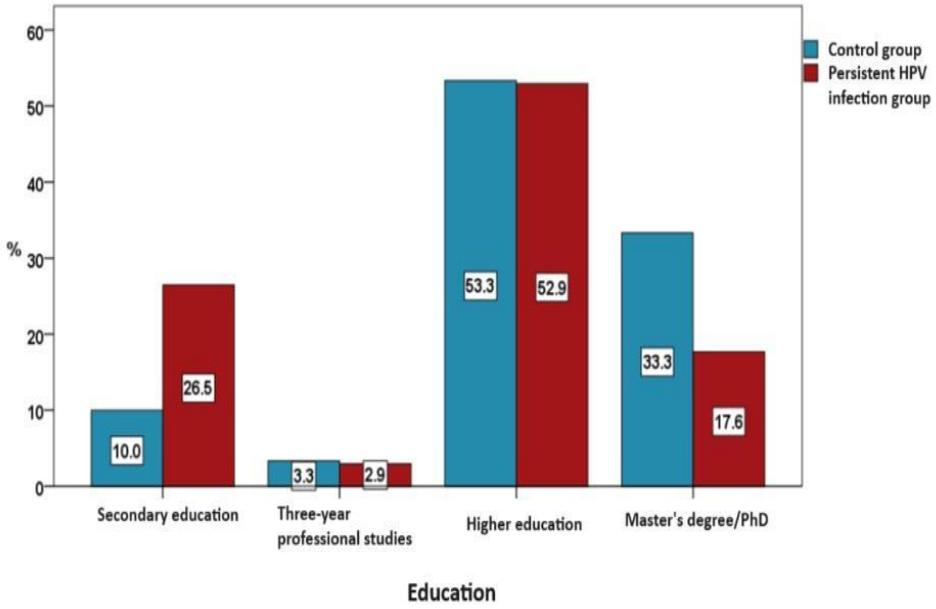

Fig .2. Comparison of the two groups of subjects by educational level

The prevalence of subjects with secondary education was higher in the group with persistent HPV infection (26.5% *vs*. 10%), while the prevalence of subjects with a completed master's degree or doctorate was higher in the control group (33.3% *vs*. 17.6%), although the differences were not significant (χ^2=3.88; p=0.274) (Figure 2).

When comparing the two groups by employment contract type, no significant difference was found between the groups (χ^2=2.25; p=0.522).

The characteristics of the workplace of the subjects vary by sector. Table 3 shows the distribution by sectors where most of the subjects with persistent HPV infection are employed.

Table 3. Sector where subjects from the persistent HPV infection group were employed

Sector	N	%
Manufacturing Industries	6	15.8
Wholesale and Retail Trade	3	7.9
Transportation, Logistics, and Storage	2	5.3
Accounting, IT, and Telecommunications	5	13.2
Economic-Legal Consulting, Scientific, Technical, and Similar Activities	1	2.6
Financial Intermediation and Banking	2	5.3
Education	1	2.6
Healthcare and Social Work	4	10.5
Other Service Activities	2	5.3
Own company (business)	3	7.9
NGOs (non-governmental organizations)	1	2.6
International Organizations	1	2.6
Unknown	7	18.4
Total	**38**	**100.0**

The highest percentage of subjects with persistent HPV infection worked in the Manufacturing sector, followed by Accounting, IT, and Telecommunications, and Healthcare and Social Work.

Table 4. Sector where subjects from the control group were employed

Sector	N	%
Manufacturing Industries	1	3.0
Construction	2	6.1
Wholesale and Retail Trade	2	6.1
Accounting, IT, and Telecommunications	4	12.1
Financial Intermediation and Banking	1	3.0
Education	1	3.0
Healthcare and Social Work	4	12.1
Public Administration	4	12.1
Artistic, Theater, Cultural, Sports, and Recreational Activities	1	3.0
Other Service Activities	6	18.2
Own company (business)	2	6.1
Unknown	5	15.2
Total	**33**	**100.0**

The largest percentage of subjects from the control group worked in the sector of Other Service Activities, followed by Accounting, Informatics, and Telecommunications, Healthcare and Social Work, and Public Administration.

In Table 5, a comparison of the responses of the two groups to some of the questions related to job demands is presented.

Table 5. Comparison of the two groups regarding workplace stress factors

Stress Factor	Group	Avg. ± Std. Dev.	t (p)
I am responsible for a lot of work in the organization	Persistent HPV	4.21 ± 1.11	2.11 (0.045)*
	Control Group	3.59 ± 1.08	
The institution is a very noisy place	Persistent HPV	2.93 ± 1.51	2.25 (0.031)*
	Control Group	2.11 ± 1.08	
There is not enough staff relative to the work we have to finish	Persistent HPV	3.15 ± 1.21	2.15 (0.041)*
	Control Group	2.54 ± 1.32	
The equipment is problematic	Persistent HPV	2.28 ± 1.23	2.13 (0.043)*
	Control Group	1.66 ± 1.09	
I have to make decisions without enough information	Persistent HPV	3.06 ± 1.25	2.2 (0.035)*
	Control Group	2.42 ± 1.2	

Significant *P<0.05

For the stress factors listed in Table 5, a significantly higher level was found in the group of respondents with persistent HPV infection compared to the control group.

Discussion

Our study presents a portion of the descriptive analysis and part of the processed data obtained from questionnaires completed by 71 female patients.

HPV 16 was the most prevalent type among our patients, followed by HPV 31, HPV 52, HPV 51, and HPV 45. Our results are similar with findings from other clinical studies published over the last two decades[10-12]. This is in line with the fact that HPV 16 is the most potent carcinogen among all HPV types, likely due to its potential for persistent infection. According to data from 2015 provided by the HPV Information Centre of the World Health Organization, HPV types 16, 18, 45, 33, 58, 31, and 52 are responsible for approximately 90%

of cervical carcinomas worldwide, regardless of the carcinoma type. Following HPV 16, there is variation in the prevalence of other HPV types in the world[29].

There was no significant difference observed between the groups based on education level, although the prevalence of patients with secondary education was higher in the group with persistent HPV infection. Conversely, the control group had a higher prevalence of patients who had completed a master's degree or doctorate. In contrast, Benard VB *et al*. analyzed data from cancer registries for site-specific invasive cancer diagnoses between 1998 and 2003, inclusive, among adults aged >20 years at the time of diagnosis. Their findings indicated that lower education, lower income, and higher poverty were associated with increased cervical and vaginal cancer incidence rates. Additionally, rural and suburban residence correlated with higher cervical cancer rates[14].

Similarly, a 2017 study by Abulizi *et al.* found that higher HPV infection rates were more prevalent among those with higher education levels, including those with junior college experience or advanced degrees. The study also noted that remarried women had a higher rate of HPV infection compared to those who were married only once or were single (widowed or divorced). However, in our study, no significant difference was found between the two groups concerning their marital status[32].

The highest percentage of participants with persistent HPV infection worked in the Manufacturing sector, followed by Accounting, IT and Telecommunications, and Healthcare and Social Work. In the control group, the largest percentage of participants worked in the sector of Other Service Activities, followed by Accounting, Informatics and Telecommunications, Healthcare and Social Work, and Public Administration.

There are very few studies that explore the relationship between HPV infection and occupation. However, Yang *et al.* (2019) conducted a study involving 8,297 female employees participating in a screening program. Their findings indicated that certain occupations, including taxi drivers, medical workers, factory workers, as well as single women with a history of sexual activity, were significantly associated with a higher prevalence of HPV infection[13].

From the collected data and their analysis, it can be assumed that employment status and job demands may contribute to the increased risk of persistent HPV infection. A significant difference was found between the two groups regarding stress factors, with a significantly higher level of stress factors observed in the group of patients with persistent HPV infection. This aligns with the study by Kuebler *et al.* from 2021, in which the authors found a significant association between chronic stress and excessive job demands with an increased prevalence of high-risk HPV infections. Based on their results, they concluded that chronic stress was an independent risk factor for the persistence of infections with high-risk HPV types[30].

Fang *et al*., in their study from 2008, concluded that psychological stress was associated with an increased risk for the development and progression of CIN. According to them, this occurs due to reduced immune function under psychological stress[31].

This scoping review was conducted in 2023 by searching for related articles across SID, PubMed, MagIran, IranDoc, Science Direct, Scopus, and Google scholar databases. Based on the findings of this review, it can be concluded that some psychological disorders such as stress and its types, depression, their associated disorders can be related to the continuation or aggravation of the HPV infection or its complications[33].

Ghilotti *et al*. in the study from 2020, included 25,029 employed individuals who filled-out a questionnaire in September 1997 and were followed through record linkages until retirement or December 2016. Work stress was assessed at baseline using a Swedish version of the Demand-Control Questionnaire. They found that employees reporting high job demands had a higher risk of infections, specifically upper respiratory tract infections and urinary tract infections, than those reporting a lower level of demands at work. This result is in line with the hypothesis that work stress due to high psychological job demands might be involved in the

pathogenesis of infections. They conclude that stressful jobs are unlikely to substantially increase the risk of infections requiring medical attention. However, occupational stress as assessed as high job demands might increase the risk of such infections, in particular upper respiratory tract infections and urinary tract infections[34].

During chronic stress, reduced lymphocyte count, decreased NK cell activity, lymphocyte proliferation in response to mitogen stimulation and phagocytosis, decreased cellular immunity, and delayed hypersensitivity reactions were observed. Increased psychological stress can result in a higher occurrence of viral infections, especially those mediated by IL-6. The influence of stress on cell apoptosis can also be observed, where apoptosis disruption can lead to immunosuppression.

Increased psychological stress can result in a higher occurrence of viral infections, especially those mediated by IL-6. The influence of stress on cell apoptosis can also be observed, where apoptosis disruption can lead to immunosuppression. These mechanisms may influence the progression of HPV infection. In women, it has been shown that HPV infection and stress result in the disruption of IL-6 secretion and the progression of cervical lesions to cervical dysplasia.

Psychosocial factors may affect the development and persistence of HPV, primarily by acting on the immune response. An association between psychosocial stress and CIN development in women has been established[16].

Conclusion

Present findings suggest that stress is an important risk factor for the development of HPV manifestation and carcinogenesis. Understanding the key factors and processes is crucial for developing effective prevention and therapeutic interventions. Although psychological factors are not considered in most epidemiological studies, it is already known that they significantly influence the frequency and sometimes the severity of certain diseases, such as HPV infection. A better understanding of experienced stress and biological changes that occur under stress, as well as the evaluation of immune response, provide researchers with a better insight into how stress affects HPV infection and how we can improve the management and final outcome of these infections.

Through a comprehensive analysis of the data obtained by using various methods and questionnaires, it is expected to determine the existence of a correlation between persistent HPV infections and job satisfaction.

Conflict of interest statement. None declared.

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