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Human papillomavirus infection is not related with prostatitis-related symptoms: results from a case-control study

Riccardo Bartoletti, Tommaso Cai, Enrico Meliani, Nicola Mondaini, Francesca Meacci, Patrizia Addonisio, Sara Albanese, Gabriella Nesi, Sandra Mazzoli

Department of Urology (RB, EM, NM); Department of Pathology and Oncology (GN), University of Florence, Florence; Department of Urology, Santa Chiara Regional Hospital (TC), Trento and Sexually Transmitted Diseases Center, Santa Maria Annunziata Hospital (FM, PA, SA, SM), Florence, Italy

ABSTRACT

Purpose: To investigate the relationship between human papillomavirus (HPV) infection and prostatitis-related symptoms.
Materials and Methods: All young heterosexual patients with prostatitis-related symptoms attending the same Center from January 2005 to December 2010 were eligible for this case-control study. Sexually active asymptomatic men were considered as the control group. All subjects underwent clinical examination, Meares-Stamey test and DNA-HPV test. Patients with prostatitis-related symptoms and asymptomatic men were compared in terms of HPV prevalence. Moreover, multivariable Cox proportional hazards regression analysis was performed to determine the association between HPV infection and prostatitis-related symptoms.
Results: Overall, 814 out of 2,938 patients (27.7%) and 292 out of 1,081 controls (27.0%) proved positive to HPV. The HPV genotype distribution was as follows: HR-HPV 478 (43.3%), PHR-HPV 77 (6.9%), LR-HPV 187 (16.9%) and PNG-HPV 364 (32.9%). The most common HPV genotypes were: 6, 11, 16, 26, 51, 53 and 81. No difference was found between the two groups in terms of HPV infection (OR 1.03; 95% CI 0.88-1.22; p = 0.66). We noted a statistically significant increase in HPV infection over the period 2005 to 2010 ($p < 0.001$) in both groups. Moreover, we found a statistically significant increase in HPV 16 frequency from 2005 to 2010 (p = 0.002).
Conclusions: This study highlights that prostatitis-like symptoms are unrelated to HPV infection. Secondary, we highlight the high prevalence of asymptomatic HPV infection among young heterosexual men.

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INTRODUCTION

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections in both genders (1). HPV infection is the main cause of cervical cancer in women and is responsible for other cancers such as penile, oral--neck and anal cancer in men (2). Men are key to the transmission of HPV to women, but relatively little is known about the natural history of HPV infection in men (3). The prevalence of HPV in males ranges from 7% to 45% (4), but the majority

of studies have been conducted on homosexuals, HIV patients or infertile men (5,6). Recently, Klinglmair et al. found a high prevalence of HPV infection in a cohort of 250 young males, including children (0-10 years), indicating non-sexual transmission pathways (7). Genital infection is often asymptomatic and undiagnosed. In a recent study on 2,702 uncircumcised, HIV sero-negative males, Rositch et al. found that 51% of them presented occult HPV infection, of whom 57% with HPV multiple types (8). Thus, HPV prevalence data in men vary widely depending on the anatomical sites sampled, populations studied and analytical methods used for HPV detection (9). Several authors suggest that HPV tends to infect the prostatic epithelium (9), however, no correlation between symptoms from prostate pathology and HPV infection has ever been reported. On the basis of HPV DNA PCR findings, it has been suggested that the male genitourinary tract, including sperm cells, might act as a reservoir for HPV persistence and infection (9,10). On the other hand, prostatitis--related symptoms are recognized as an important socio-economical problem and several sexually transmitted infections are linked to the presence of prostatitis-related symptoms (11,12). We investigated HPV infection prevalence in young heterosexual males with prostatitis-related symptoms in order to find a possible relationship between HPV infection and prostatitis-related symptoms. The present case-control study aimed to determine whether HPV infection could be considered a risk factor of prostatitis-related symptoms in young heterosexual males.

MATERIALS AND METHODS

Study design

The study population consisted of two groups of young heterosexual men attending the same Sexually Transmitted Diseases Center from January 2005 to December 2010: Group A (cases), all consecutive patients with prostatitis-related symptoms, and Group B (controls), sexually active asymptomatic men whose female partners were infected with Chlamydia trachomatis. All patients and controls were screened for this study using the 4-glass Meares-Stamey test and and DNA-HPV test. All controls underwent 4-glass Meares-Stamey test and DNA-HPV test due to the fact that they were partners of female affected by Chlamydia trachomatis infection. This is the routinely practice in our STDs Centre. Clinical and laboratory findings for the two groups were compared. This case-control study aimed to determine whether exposure to HPV infection could be associated with clinical outcomes such as the presence of prostatitis-related symptoms. This study was conducted in line with the STROBE statement (http://www.strobe-statement.org). Italian law does not require authorization from the institutional review board (IRB), nor informed consent from the patients (http://www.agenziafarmaco.gov.it/it/content/linee-guida-studi-osservazionali). Nevertheless, our study was conducted in line with the Good Clinical Practice guidelines and with the ethical principles laid down in the latest version of the Declaration of Helsinki.

Inclusion and exclusion criteria

Group A patients were selected consecutively from a series of individuals suffering from chronic prostatitis-related symptoms for over 6 months, as defined in the latest version of the European Association of Urology (EAU) guidelines (13). In particular, the patients were selected and categorized according to Nickel's criteria for perineal or ejaculatory pain. All enrolled patients must have had a pain score equal to or greater than 4, defined as "mild prostatitis" if the pain score ranged from 4 to 7 and "moderate or severe prostatitis" if the score was 8 or greater (14). Subjects under 18 and over 45 years of age, affected by major concomitant diseases, with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases, and diagnosed with genital or anal warts, participating in an HPV vaccine study, were excluded as well as patients with suspected urothelial cell carcinoma at cytological urine analysis or who had previously undergone prostate surgery. Group B patients were included in the study only if asymptomatic and falling within the age range of 18 - 45 years, and with no known major concomitant diseases. All homosexuals were excluded from both study groups due to their increased risk of exposure to

HPV infection. Moreover, all patients have been asked about the sexual experience and the circumcision status. A detailed assessment about the sexual behavior has been carried out.

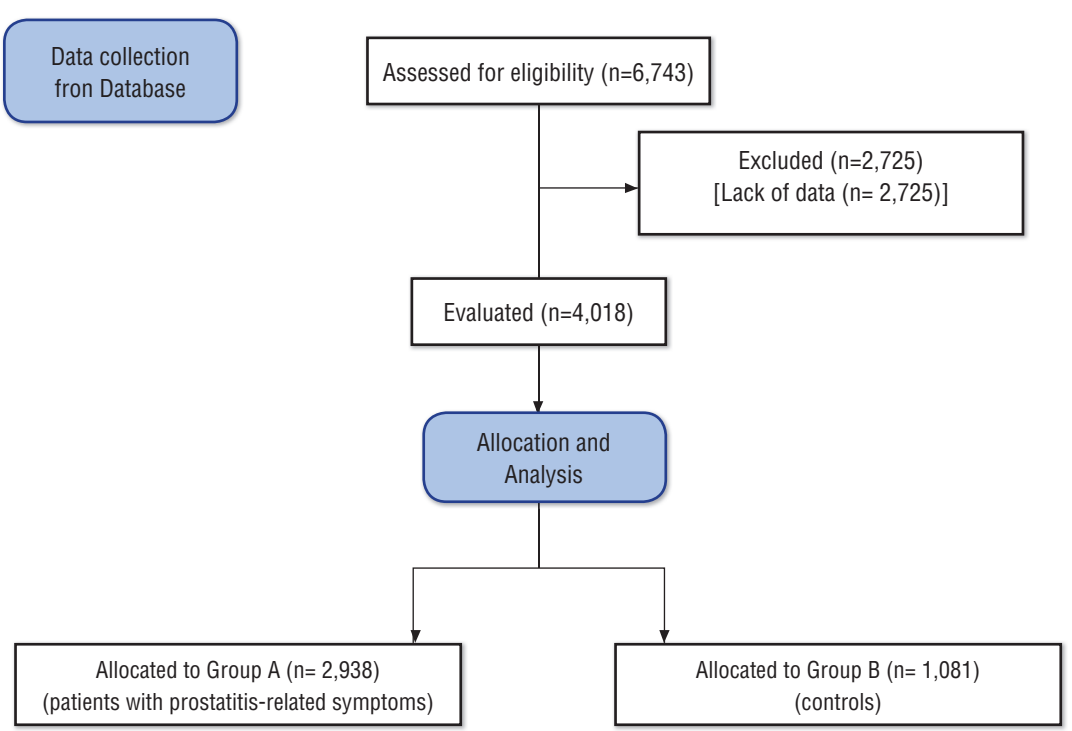
Study schedule and sample collection

We retrospectively collected anamnestic, clinical, laboratory and microbiological data for 6,743 patients from our database (Advanced PROSTATitis DataBase, Microsoft Access format). From these, we excluded 2,725 due to lack of data. Finally we considered 4,018 individuals for this study (2,938 patients and 1,081 controls) (Figure-1). 2,938 patients with prostatitis-related symptoms were assigned to Group A while 1,080 to Group B. We collected the validated Italian versions of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) (15) and the International Prostatic Symptom Score (IPSS) (16) for all patients and controls. All microbiological data were collected in accordance with indications described by Mazzoli et al. first void early morning urine (VB1), mid-stream urine (VB2), expressed prostatic secretion (EPS), post prostate massage urine (VB3) and total ejaculate (TE) (12). In order to evaluate the HPV infection in the urethra, a urethral swab (UR_SW) was taken from all subjects. Moreover, in our Centre we did not routinely performed the HPV specific antibodies.

Laboratory procedures and microbiological considerations

Microbiological cultures were performed in accordance with the methods described by Motrich et al. (17). DNA extraction and purification of all biological materials was performed using the DNeasy® Tissue Kit by QIAGEN Spa, Italy. 200µL of pellet was pre-incubated overnight with proteinase k and the next day extracted and purified following the manufacturer's instructions. All the biological material from the whole study population was tested for the presence of genital HPV using Alpha Watch HPV, Alphagenic-Diaco-Biotechnology, Trieste, Italy. All biological materials from our patients were analyzed by Inno-Lipa HPV Genotyping Extra (Innogenetics, Italy). Amplification of a

Figure 1 - The figure shows the Study flow-chart.



fragment of the b-globin gene served as an internal quality control for each specimen. In accordance to Munoz et al., we classified the following genotypes as high risk-HPV (HR-HPV): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; as probable high-risk (PHR-HPV): 26, 53, and 66; and as low risk (LR-HPV): 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 8118. HPV positive samples which did not hybridize with any of the type-specific probes were referred to as positive non genotype-able (PNG-HPV) (18). According to Giuliano et al., a participant was considered positive for "any HPV" if he tested HPV-positive by PCR or by genotyping (19). The category "any oncogenic type" included those who were positive for only oncogenic genotypes and those who were positive for both oncogenic and non-oncogenic types. Only single or multiple infections with non--oncogenic HPV types were classified as "any non--oncogenic type". This STDs laboratory is registered by the United Kingdom National External Quality Assessment (NEQUAS) for microbiology for molecular detection of Ct (Quality Assurance Laboratory, Health Protection Agency Centre for Infection, 61 Colindale Avenue, London NW 95HT, United Kingdom). All microbiological analyses were performed blindly. Following Nickel et al., white blood cell (WBC) counts in all biological samples were carried out, though not considered in this study (20).

Statistical analysis and considerations

Pearson's coefficient was adopted to evaluate the correlation between the different parameters in all patients, and Fisher's exact test or Chi-square test (χ^2) used to assess statistical significance with $p < 0.05$ accepted as significant. Multivariable Cox proportional hazards regression analysis was then performed to determine the association between HPV infection and prostatitis-related symptoms. The ANOVA test was applied to evaluate the difference between the two groups in terms of NIH--CPSI and IPSS questionnaire scores. The Bonferroni adjustment test was also used at the second stage of the analysis of variance. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to determine the significance of differences. Statistical significance was set at $p < 0.05$. All reported p-values are two-sided. All statistical analyses were performed by using SPSS 11.0 for Apple-Macintosh (SPSS, Inc., Chicago, Illinois).

RESULTS

Data from 4,018 subjects were collected and analysed. A total of 2,938 patients were assigned to Group A (cases, prostatitis-related symptoms) while 1,080 to Group B (controls, asymptomatic subjects).

Clinical and microbiological evaluation

Detailed information about demographic and socioeconomic variables, medical history and clinical data at enrollment are given in Table-1. All cases revealed a mean symptom time of 15.4 months (range 10-26 months) but none presented genital or anal warts on physical examination. Overall, 814 out of the 2,938 patients (27.7%) and 292 out of the 1,081 controls (27.0%) proved positive to HPV (Odds ratio [OR] 1.03; 95% CI 0.88-1.22; $p = 0.66$). The HPV genotype distribution is as follows: HR-HPV 478 (43.3%), PHR-HPV 77 (6.9%), LR-HPV 187 (16.9%) and PNG-HPV 364 (32.9%). Data stratification according to age is given for both groups in Tables 2 and 3. In Group A, 28 out of 814 (3.4%) were also positive to Chlamydia trachomatis vs 31 out of 292 (10.6) in Group B, with a statistically significant difference ($p < 0.001$; Chi square 20.5; df = 1).

HPV prevalence and genotype distribution

Patients with prostatitis-related symptoms (Group A)

HPV genotype distribution was as follows: HR-HPV 417 (51.3%), PHR-HPV 70 (8.7%), LR-HPV 64 (7.7%) and PNG-HPV 263 (32.3%). The most common HPV genotypes were: 16 (18%), 31 (29%) and 33 (24%). HPV genotype distribution stratified per year is detailed in Table-2. HPV 16 and PNG--HPV frequencies were found to significantly increase over the period 2005 to 2010 ($p = 0.002$ and $p = 0.003$, respectively). No statistically significant increase in frequency was found for the other HPV types. In addition, there was a decrease in HR-HPV and PHR-HPV incidence in 2009.

Asymptomatic patients (Group B)

HPV genotype distribution for asymptomatic subjects was as follows: HR-HPV 116

Table 1 - Patient's sociodemographic anamnestic, clinical characteristics at enrolment time.

No. of total enrolled subjects	4,019		
	Patients	Controls	
	2,938	1,081	p
Median age (± SD*)	35.7 ± 5.8	36.0 ± 5.9	0.14
Educational level			
Primary school	-	-	
Secondary school	2,001 (68.1)	716 (66.2)	0.25
Post-secondary education	937 (31.9)	365 (33.8)	
Sexually active (past month)	2,899 (98.6)	1,070 (99.0)	0.45
Sexual behavior			
1 partner	2,376/2,899 (81.9)	881/1,070 (82.3)	0.81
> 1 partners	523/2,899 (18.1)	189/1,070 (17.7)	
Contraceptive use	1,903/2,899 (65.6)	693/1,070 (64.7)	0.59
Condom	1,302/1,903 (68.5)	479/693 (69.2)	0.77
Coitus interruptus	601/1,903 (31.5)	214/693 (29.8)	
Clinical data			
Clinical presentation			
Dysuria	1,292 (43.9)	-	-
Urgency	1,478 (50.3)	-	-
Dysuria + Frequency	1,123 (38.2)	-	-
Burning	981 (33.3)	-	-
Pain			
Perineal	1,341 (45.6)	-	-
Scrotal	742 (25.2)	-	-
Suprapubic	311 (10.5)	-	-
Lower Abdominal	214 (7.2)	-	-
Start of CP# history (months)	15.4 ± 8.2	-	-
Symptoms Score at baseline (mean) (range)			
NIH-CSPI§	18.9 (13-26)	2.8 (0-3)	< 0.001
IPSS†	17.3 (1-24)	2.2 (0-6)	< 0.001

SD* = Standard Deviation; **CP # =** Chronic prostatitis; **NIH-CSPI§** = NIH- Chronic Prostatitis Symptom Index; **IPSS† =** International Prostatic Symptom Score.

Table 2 - Summary results for grouped HPV type distribution by years (Patients).

	Year						Total
	2005	2006	2007	2008	2009	2010	
Number of patients	584	446	523	547	427	411	2,938
HPV positive	86 (14.7)	123 (27.5)	112 (21.4)	183 (33.4)	134 (31.3)	176 (42.8)	814 (27.7)
Sub-analysis on HPV positive patients							
HR-HPV	62 (72.0)	81 (65.8)	79 (70.6)	86 (46.9)	26 (19.4)	83 (47.1)	417 (51.2)
PHR-HPV	5 (5.8)	11 (8.9)	5 (4.4)	20 (10.9)	5 (3.8)	24 (13.6)	70 (8.6)
LR-HPV	4 (4.6)	7 (5.7)	8 (7.2)	12 (6.6)	24 (17.9)	9 (5.2)	64 (7.8)
PNG-HPV	15 (17.4)	24 (19.6)	20 (17.8)	65 (35.6)	79 (58.9)	60 (34.1)	263 (32.4)

HR-HPV = High-Risk HPV; **PHR-HPV =** Probable High-Risk HPV; **LH-HPV =** Low-Risk HPV; **PNG-HPV =** Positive Non Genotype-able HPV.

Table 3 - Summary results for grouped HPV type distribution by years (Controls).

	Year						Total
	2005	2006	2007	2008	2009	2010	
Number of patients	205	171	189	165	134	217	1,081
HPV positive	33 (16.0)	42 (24.5)	37 (19.5)	51 (30.9)	39 (29.1)	90 (41.4)	292 (27.0)
Sub-analysis on HPV positive patients							
HR-HPV	15 (45.3)	18 (42.8)	17 (45.9)	19 (37.2)	8 (20.5)	39 (43.3)	116 (39.7)
PHR-HPV	4 (12.1)	4 (9.5)	5 (13.5)	3 (5.9)	1 (2.6)	9 (10)	26 (8.9)
LR-HPV	2 (6.0)	5 (11.9)	3 (8.1)	9 (17.6)	2 (5.2)	5 (5.5)	26 (8.9)
PNG-HPV	12 (36.6)	15 (35.8)	12 (32.5)	20 (39.3)	28 (71.7)	37 (41.2)	124 (42.5)

HR-HPV = High-Risk HPV; **PHR-HPV =** Probable High-Risk HPV; **LH-HPV =** low-risk HPV; **PNG-HPV =** positive non genotype-able HPV.

(39.7%), PHR-HPV 26 (8.9%), LR-HPV 26 (8.9%) and PNG-HPV 124 (42.5%). The most common HPV genotypes were: 11 (17.2%) and 31 (30.2%). Table-3 shows HPV genotype distribution per year. There was no statistically significant increase in PCN-HPV prevalence from 2005 to 2010 ($p = 0.68$). As in Group A, we found a decrease in HR-HPV and PHR-HPV incidence in 2009. There was a statistically significant increase in HPV prevalence from 2005 to 2010 ($p < 0.001$) in both patients and controls (Figure-2). On the other hand, there was no increase in HR-HPV infection prevalence from 2005 to 2010 (Figure-3).

HPV incidence and distribution per biological sample

We collected 18,351 samples from the all patients. We found 2,276 positive samples from 1,106 subjects (814 Group A and 292 Group B) (Table-4). There was no difference in HPV detection rate among VB1, TE and UR_SW were found ($p = 0.30$), nor be-

Figure 2 - The figure shows the prevalence of HPV-positive patients and the High-Risk-HPV positive patients in both patients and controls.

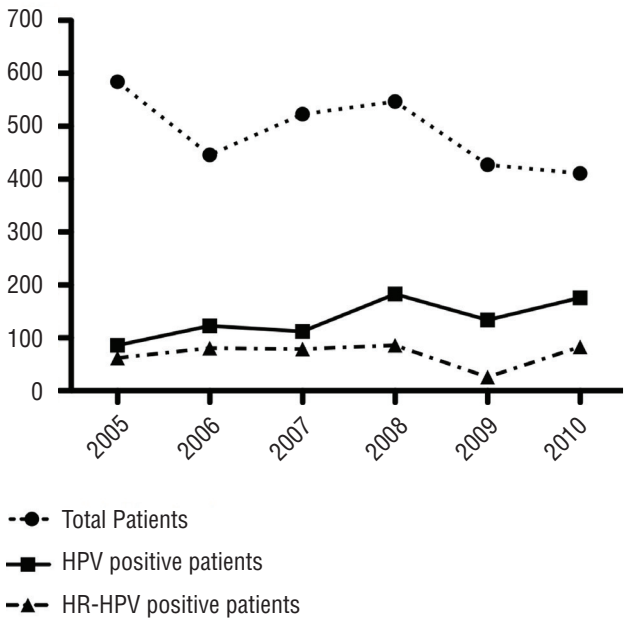
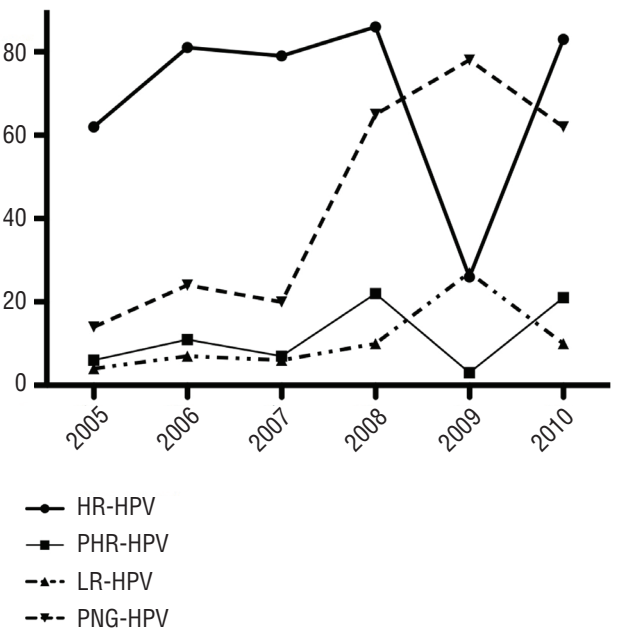


Figure 3 - The figure shows the prevalence of all HPV-positive patients stratified by risk class.



tween VB1 and UR_SW (p = 0.69). We also noted a statistically significant difference among VB1, VB2 and VB3 (p < 0.001) (Figure-4). We did not include the EPS data in the analysis due to the limited number of samples collected (81 out of 814 patients for Group A, 18 out of 292 controls for Group B).

HPV and other related risk factors

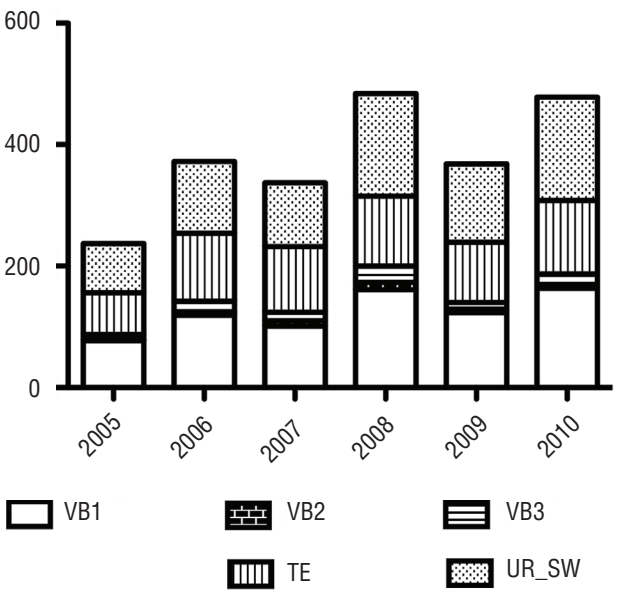
No significant difference in overall HPV prevalence was found in the different age categories in either group (Table-1). Finally, we found a higher HR-HPV prevalence in Group A compared with Group B patients (39.7% vs 51.2%) (p = 0.008).

Table 4 - HPV prevalence according to collected biological samples and years.

Sample		VB1	VB2	VB3	TE	UR_SW	
	Year						Total
	2005	77	2	8	69	81	237
	2006	119	5	18	112	118	372
	2007	101	9	14	108	105	337
	2008	161	12	27	115	169	484
	2009	123	6	11	99	129	368
	2010	163	5	19	121	170	478
Total		744	39	97	624	772	2,276

VB1 = First void early morning urine; **VB2 =** Mid-stream urine; **VB3 =** Expressed prostatic secretion; **TE =** Total ejaculate; **EPS =** Expressed prostatic secretion; U**R_SW =** Urethral swab.

Figure 4 - The figure shows the prevalence of HPV-positive biological samples according to each analyzed sample.



There was no difference in terms of sexual behavior or use of contraceptives (Table-1).

DISCUSSION

HPV transmission normally occurs through sexual intercourse with commonly recognized infection distribution. In the absence of any obvious clinical manifestations, such as genital warts, a male is often considered as a healthy disease-carrier (21). Genital infection is often asymptomatic in both genders, although genital warts can generate local symptoms such as burning, itching and occasional bleeding (22). In the present study, no significant difference in prevalence of HPV infection-related symptoms was found between the two groups, although approximately 33% of Group A patients complained of burning during micturition. This symptom should be considered part of chronic pelvic pain syndrome, since all these patients had VB2 samples negative for bacteria at the 4-glass Meares--Stamey test. The cohort of young heterosexual males with prostatitis-related symptoms was selected on the basis of the recent literature on HPV reporting a high prevalence of infection (over 70% of cases) in men between 17 and 45 years of age. Similarly, the control group was selected from asymptomatic and sexually active males, because their female sexual partners were infected with Chlamydia trachomatis, thus more exposed to the risk of developing sexually transmitted infections. Homosexuals were excluded from the study due to their increased risk of developing HPV infection (23). Several authors have demonstrated the presence of HPV in the semen, although none of them has suggested any relationship with male infertility. Perino et al. showed that the abortion rate in male-infected couples is significantly higher (66.7%) than in normal couples (15%) (24). Indeed, viral bodies adhere to spermatozoa, subsequently reducing their motility (25). HPV could then be transmitted from men to women during sexual intercourse through sexual "contact" as well as through biological fluids. Moreover infection of the seminal tract (prostate, seminal vesicle, vas deferens) could also be hypothesized on the basis of HPV presence in the semen of asymptomatic patients. Our results partially contradict this hypothesis. The HPV prevalence was higher in VB1 and urethral swabs than in VB2 and VB3 samples. Several authors report HPV prevalence in the urethra ranging from 20 to 48%, although these data could be influenced by either the limited number of subjects evaluated, the wide age range of selected subjects or the difference in their sexual habits, activity and attitudes. On the other hand, for the same reasons, the prevalence of HPV infection in the semen has been investigated by various authors with conflicting results. Foresta et al. found 40.9% prevalence in subjects with infected sexual partners and 2.2% in fertile controls, while Nielsen et al. found 5.3% prevalence in 463 heterosexual men (26,27). Our study confirmed the high prevalence of HPV infection (27.7%) in a large cohort of young heterosexual men and an increasing positive trend of HPV infection over a 5 year period. No significant difference in prevalence was found between the group with prostatitis-related symptoms and the asymptomatic control group, although Group A patients exhibited an increased prevalence in HR-HPV genotypes. Despite the lack of differences in sexual behavior or contraceptive use between the two groups, the control group would have been expected to show a higher rate of HR-HPV infection due to their increased risk of developing Chlamydia

trachomatis co-infection, commonly considered a sexually transmitted infection. HPV infection prevalence in the control group was independent from Chlamydia trachomatis co-morbidity (28). These results confirm that an increased risk of developing HPV infection in young heterosexual men is not related to the number of sexual partners but to the social diffusion of the disease in both genders. This is also supported by the increasing trend of HPV infection over the five-year period. The present study shows few limitations that should be taken into account. Firstly, the retrospective nature of this study. Secondly, the highly selected patient population due to the fact that we have enrolled patients attending a specific STDs Centre. Finally, the fact that we have no data about the impact of female vaccination on HPV male prevalence.

CONCLUSIONS

In conclusion, we found no correlation between the presence of prostatitis-related symptoms and HPV infection, highlighting an asymptomatic and increasing prevalence of HPV in young heterosexual males.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Tommaso Cai, MD
Department of Urology
Santa Chiara Regional Hospital
Largo Medaglie d'Oro, 9
Trento, 38123, Italy
E-mail: ktommy@libero.it