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HPV AND URINARY BLADDER CARCINOMA: A REVIEW OF THE LITERATURE

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Abstract – *Human Papillomavirus (HPV) is considered to be the second cause of virus-related cancer, as it is associated to the 30% of infection-related cancer cases. Many studies showed that HPV detection in the urinary tract depends on the sample considered. HPV infection in men is often detected in the glans, corona, prepuce, shaft of the penis, and distal urethra.*

Oncoproteins E6 and E7 play an essential role in the onset of HPV-related cancers, even if their expression is not sufficient to transform the host cell.

Two possible hypotheses are considered in the association HPV-BCs. The first involves an anatomical reason. The second hypothesis considers the natural epithelial tropism of HPV. Current evidence in literature fails to show strong associations between HPVs and these cancers.

The aim of this review was to identify key data and factors about the potential role of HPV in the genesis of BCs.

KEYWORDS: *Papillomavirus, HPV, Bladder cancer, Urinary bladder cancer, Urinary tract cancer*

INTRODUCTION

Viruses are responsible for up to 10-15% of all human cancers[1-5]. The American Association for Cancer Research (AACR) established in 2017 that infectious pathogens are the third cause of cancer worldwide. Human Papillomavirus (HPV) is considered to be the second cause of virus-related cancer, as it is associated to the 30% of infection-related cancer cases. It is preceded by *Helicobacter pylori* (32.5%) and closely followed by HBV/HCV (29.5%)[3]. Infectious agents-related cancers are of particular interest for a number of reasons. First of all, they allow to determine cellular and genetic mechanisms involved in cancer development. Secondly, but maybe more importantly, it could be possible to use selected screening programs, monitoring and vaccination to fight them[6-10].

HPVs are a group of DNA-viruses that cause one of the most common sexually transmitted infections worldwide[11]. The infection is generally asymptomatic, self-limiting, and the virus is normally cleared by the host's immune system[12]. HPV serotypes are divided in low-risk HPVs (lr-HPVs), and high-risk HPVs (hr-HPVs). This second group is involved in carcinogenesis[13].

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Many epidemiological studies showed that healthy men, who are usually considered only a reservoir, have a higher prevalence of the HPV infection than healthy women[14-16].

A persistent HPV infection has been historically identified as the first cause of cervical cancer. Furthermore, recent studies showed that hr-HPVs have a role in the development of cancers of other districts[17,18]. A significant association has been demonstrated for anal-genital and oropharyngeal cancers, while there is a debate whether the virus might play a role in the development of urinary bladder cancers (BC)[19-26]. The aim of this review was to identify key data and factors about the potential role of HPV in the genesis of BCs.

DETECTION OF HPV IN URINARY TRACT SAMPLES

Many studies showed that HPV detection in the urinary tract depends on the sample considered. HPV infection in men is often detected in the glans, corona, prepuce, shaft of the penis, and distal urethra[15,27]. However, some previous studies using urine samples were not able to detect HPV infection in the urinary tract.

Many authors reported that urine samples are not a good sample for HPV detection (0.8-7%), while rubbing the urethral-coronal sulcus, the inner prepuce, the distal urethra, the glans, the external prepuce and the scrotum led to a 10-44% detection, depending on the source[22,27-29].

However, more recent studies showed how using polymerase chain reaction (PCR)-based methods the HPV detection improved even in urine samples[16,30-35]. These studies show that HPV can infect many sites of the urinary tract, especially urethra, prostate and urinary bladder.

A study by Kawaguchi et al[30] highlighted that liquid-based cytology can lead to a 21% detection of HPV-DNA in urine samples in patients affected by urethritis, a prevalence seven times higher than that found in healthy patients. Moreover, findings by Piyathilake et al[36] showed a substantial to almost perfect agreement in the detection of any HPV genotype in urine compared to cervical specimens regardless of population characteristics. Therefore, testing urine for HPV-DNA could become, in the future, even a replacement for the classical and annoying procedure which is the Pap-test. In addition, there is evidence suggesting that HPV infection would start on the distal urethra following a sexual contact and, from this site, it would ascend through into the bladder urothelial epithelium[37-40]. Further studies about sampling and testing techniques are needed to understand the utility of detecting HPV-DNA in urines.

ROLE OF DNA DAMAGE AND CHRONIC INFLAMMATION IN HPV-CARCINOGENESIS

HPV-induced carcinogenesis is a complex process following the infection. However, not every infection ends as cancer. Integration of viral DNA into the host genome, inflammation and high levels of inflammatory mediators have been reported in cervical neoplastic lesions as well in other cancers[41-45]. The inflammatory process promotes the integration of HPV-DNA and, consequently, the cancer progression, causing genomic instability and increased susceptibility to DNA damage[46]. Oncoproteins E6 and E7 play an essential role in the onset of HPV-related cancers, even if their expression is not sufficient to transform the host cell. As a matter of fact, genomic instability is necessary to acquire the malignant phenotype. E6 and E7 inactivate and/or degrade respectively p53 and pRb suppressor gene-associated proteins. Molecular studies suggest that the HPV related oncoproteins E6 and E7 would play a role also in bladder carcinogenesis via the same mechanisms[47,48].

Several studies showed that the increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) happening during inflammation, leading to oxidative and nitrative stress, is responsible for the rupture of cell double-stranded DNA[49-52]. This kind of damage is necessary for hr-HPV integration[53]. Moreover, ROS are able to induce the formation of oxidative DNA mutagenic products, promoting carcinogenesis especially during viral infections[49,50,54-58].

Therefore, chronic inflammation (Figure 1) can increase DNA mutations through ROS/RNS production and can promote proliferation. Other works about the association of cancer stem cells with infection and inflammation also support this idea[50,59].

However, more studies are needed to determine if this model can be applied to bladder neoplasms as well.

HPV PREVALENCE IN BLADDER CARCINOMA

BC accounts for about 3.2-4% of all cancers worldwide, and it is considerably more frequent in males than in females. Three histological types of cancers represent almost the whole amount of the urinary bladder cancers: urothelial carcinoma (UC), squamous cell carcinoma (SCC) and adenocarcinoma (AD) (Figure 2). UC is the histological type most frequently diagnosed, representing more than 90% of all cancers identified on this site[60]. Much lower frequency are SCC and AD[61]. In the past three decades, there was an increasing incidence of bladder carcinoma and this aspect has increased interest for identification of possible etiological agents. Several

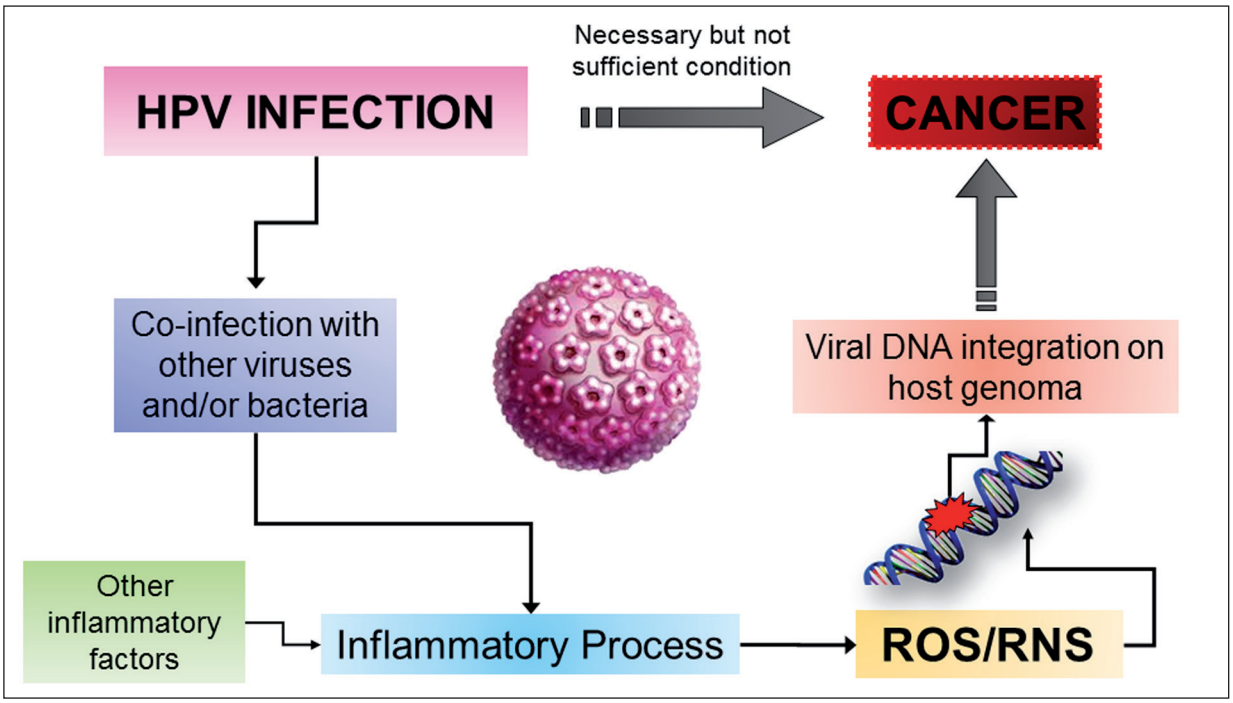

Fig. 1. Role of chronic inflammation in HPV-carcinogenesis.

risk factors have been considered in the development of this cancer type, including smoking, certain industrial exposure, arsenic in drinking water, chronic irritation as well as bacterial and viral infection[62,63].

Although UC of the bladder often showed focal squamous differentiation, is different from SCC, which contains solely keratin-forming carcinoma cells. BCs composed of mixed urothelial and squamous phenotypes are known as UC with squamous

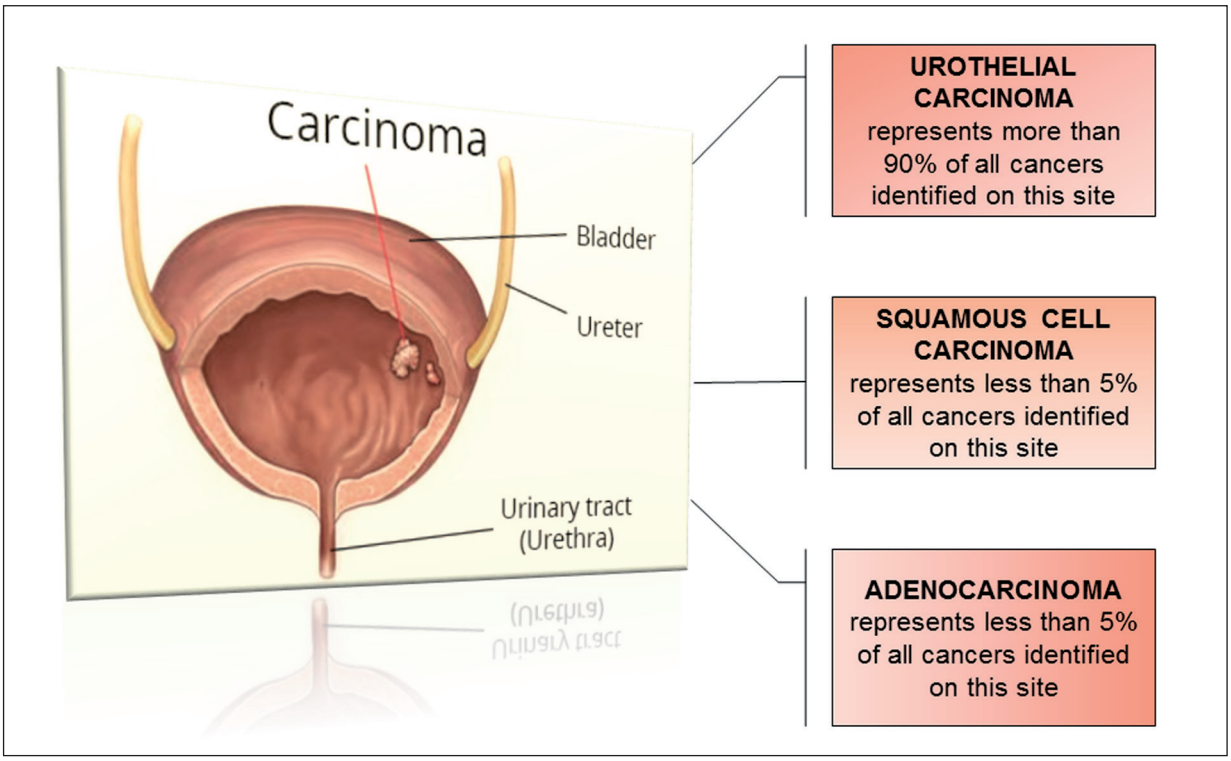

Fig. 2. Histological types of bladder cancer.

differentiation (UC/SCC)[64]. UC and SCC represent the histologic subtypes most commonly associated with HPV-induced cancer.

Several studies evaluated the potential causative role of HPV infection in BC[65-68], but the real impact in this field is still highly controversial[20,22]. Even in the most up to date studies, there is no agreement about the role of HPV in BC, with an extremely wide percentage of positive cases ranging from 0 to 80%[20]. Some studies suggested that HPV is the most important risk factor for development of carcinoma in urogenital system[16,47,69]. Moreover, other studies found an association between HPV and SCC of the urinary bladder ranging from 0% to 17%[70,71].

Two possible hypotheses are considered in the association HPV-BCs. The first involves an anatomical reason. The urethra represents a reservoir for the virus and because it directly connects urinary bladder with genital area, it can represent a natural way for viral migration. The second hypothesis considers the natural epithelial tropism of HPV. In fact, these viruses infect epithelial cells with a high tissue tropism and affinity for squamous epithelium[72]. This affinity could well explain the probable association between HPV and BCs. However, because most BCs are not SCC but UCs, this association may be weak in the majority of BCs patients.

Current evidence in literature fails to show strong associations between HPVs and these cancers. The reduced size of the studies is probably the main reason why this association cannot be demonstrated, but the rarity of this entity makes virtually impossible to conduct larger studies.

In the following sections, we reviewed the studies offering evidence in favour or against the association between HPV infection and the three principal histological forms of BCs.

Urothelial carcinoma

The first study that showed a HPV prevalence rate of 10% in UC/AD was published in 1988[73]. Since then, several studies have detected HPV in at least a subset of the analysed cases with results of HPV prevalence that varied dramatically.

Of 70 studies considered in this review, 50 showed a HPV detection in BCs, and a cause-effect association was found in 20 studies.

Studies that showed an association HPV-UC

Several investigations assigned to HPV a role in the genesis of UCs (Table 1)[19-21,23,26,47,71,73-114]. Khaled et al[95] in 2001 studied the presence of HPV serotypes 16/18 in 50 BCs using the technic of "*in situ* hybridization" with a HPV-detection on 46% of cases (23/50). Positivity was 47.8% for SCCs and 36.4% for UCs. Moreover, the authors state that HPV could be implicated also in the etiology of bilharzial bladder cancer (BBC). To this latter aim, the same author in 2003, considering 99 cases of BBCs, detected HPV-DNA in 49% of them, the majority of which (64.6%) belonging to serotype 16. These results suggest an etiological role of HPV in this type of neoplasm. Moreover, this study showed a positive trend in the correlation between tumour grade/stage and hr-HPV infection[99].

In a 2007 study, 166 bladder wash samples were obtained from 107 patients. The prevalence of all-types and hr-HPVs infection in bladder cancers was 15.2% and 8.1%, respectively. Concerning the grading, in grade 1, 2 and 3 cancers, the infection rate of hr-HPV types was 0%, 3.3%, and 10.6%, respectively (trend test: p=0.221). Finally, in Ta, T1, and T2-T4 tumours, the hr-HPVs infection rate was 0%, 12.5% and 18.2%, respectively[101].

Shigehara et al[102] in 2011, evaluated HPV-DNA in 117 cases of BCs founding the virus in 18 of them (15%). In this study, 15 (83%) of the HPV-positive cancers showed a non-invasive growth pattern and most of them had been classified as low-grade.

In 2012 Barghi et al[106] carried out a cross-sectional study in 82 male patients with BCs and their wives. Bladder tissue specimens of patients with UCs were analysed for HPV infection using a PCR method for subtypes 16 and 18. The results showed that 24 (29.3%) BC samples were positive for HPV infection. Of these, it was found HPV-18 in 9 (37.5%) and HPV-16 in 3 (12.5%). In the wives of those men, 4 (4.9%) cases showed cellular dysplasia on their Pap-tests. In those women whose husbands had BCs but no HPV infection, the authors found no case of dysplasia.

In a study carried out by Kim et al[71] the detection rate of HPV-DNA was 2-fold higher in a group of 35 patients with mixed UC/SCC of the bladder (17.5%) than the control group of 12 patients with squamous metaplasia of the bladder (8.3%). However, due to the small sample size, it is not possible establish a real statistically significant increase in risk of HPV infection in the study group. These findings agree with other investigations in which HPV-DNA was detected in both UCs and SCCs of the bladder[20].

Shigehara et al[107] in a 2013 study provided an important evidence that HPVs play an etiological role in UC of the bladder. This work involved 84 female patients with primary BCs. After DNA extraction from paraffin-embedded tissue samples, HPV-DNA and relative genotype were checked. The results showed that HPV-DNA was detected in 5 (6.0%) of 84 patients. Concerning the genotypes, HPV16 was detected in 3 patients, HPV6 and HPV52 were detected in one case, respectively. HPV-DNA detection was more frequent in younger patients and in patients with a past cervical cancer. In four hr-HPV-positive cases, hr-HPV-DNA was present in cancer tissues. Two cases had a history of

TABLE 1. Study that showed an association HPV-Bladder Cancer (UC, SCC, AD).

Year	Author	Pathology	N	HPV detection (%)	Detected HPV types (number)
1988	Kitamura	UC/AD	10	1 (10%)	16 (1)
1991	Bryant	UC/AD	100	12 (12%)	16/18 (12)
1991	Kerley	UC/SCC/AD	27	1 (3.7%)	11 (1)
1992	Chetsanga	UC	44	1 (2.3%)	16 (1)
1992	Shibutani	UC	20	4 (20%)	6/11 (2), 16/18 (1), 31/33 (1)
1992	Anwar	UC/SCC	48	39 (81%)	18 (18), 33 (14), 16 (13)
1993	Yu ST	UC	53	30 (57%)	16 (28), 18 (2)
1993	Wilczynsky	SCC	22	1 (4.5%)	6 (1)
1993	Furihata	UC	90	28 (31%)	—
1994	Mincione	UC	18	1 (5.6%)	31/33/51 (1)
1994	Agliano	UC	46	23 (50%)	16 (11), 18 (7), 16/18 (7)
1994	Maloney	UC/SCC	42	1 (4.4%)	18 (1)
1994	Noel	UC	75	2 (2.7%)	16 (2)
1995	Kamel	UC/SCC	47	27 (57%)	31 (19), 18 (16), 33 (13) 16 (10), 11 (10), 6 (13)
1995	Kim	UC	23	8 (35%)	16 (4), 18 (8)
1995	Smetana	UC	110	59 (54%)	—
1995	LaRue	UC	71	28 (39%)	16 (27), 6/11 (1)
1995	Lopez-Beltran	UC	76	7 (9.2%)	16 (7)
1995	Gopalkrishna	UC	10	1 (10%)	16 (1)
1996	Tenti	UC	79	26 (33%)	16 (21), 18 (8)
1996	Lopez-Beltran	UC	76	7 (9.2%)	16 (7), 6 (1)
1996	Mvula	UC/SCC	36	1 (2.8%)	16 (1)
1997	Chan	UC	20	6 (30%)	18 (6)
1998	Gazzaniga	UC	35	11 (31%)	16 (6), 18 (5)
1999	De Gaetani	UC	43	17 (40%)	6/11 (3), 16/18 (6), 31/33/35 (10)
1999	Simoneau	UC	187	16 (8.5%)	16 (6), 6 (3), 11 (3)
1999	Tekin	UC	42	2 (4.8%)	16 (2)
2001	Khaled	UC/SCC/AD	50	23 (46%)	16/18 (23)
2001	Sur	UC	91	1 (1.5%)	—
2003	Fioriti	UC	32	1 (3%)	6 (1)
2003	Khaled	UC/SCC	99	48 (49%)	16 (36), 18 (14), 6 (3), 11 (3)
2005	Barghi	UC	59	21 (36%)	18 (17), 6 (4), 33 (3)
2006	Helal	UC/SCC	114	1 (0.9%)	16 (1)
2007	Moonen	UC	107	15 (15%)	18 (3), 16 (2), 6 (1), 11 (1) 31 (1), 40 (1), 52 (1), UK (1)
2008	Badawi	UC/SCC	20	9 (45%)	16 (9), 18 (2)
2011	Shigehara	UC/SCC/AD	117	18 (15%)	16 (6), 18 (4), 33 (3), 31 (1) 52 (1), 56 (1), 58(1), UK (1)
2011	Cai	UC	78	27 (35%)	16 (4), 18 (6), 31 (3), 45 (5)
2011	Shigehara	AD	6	1 (16.6%)	
2012	Polesel	UC	114	7 (6.1%)	56 (2), 31 (1), 35 (1), 45 (1) 58 (1), 70 (1)
2012	Barghi	UC	82	24 (29%)	18 (9), 16 (3), UK (12)
2013	Berrada	UC/SCC	43	22 (52%)	18 (21), 31 (1)
2013	Shigehara	UC	84	5 (6%)	16 (3), 6 (1), 52 (1)
2013	Shaker	15 SQCC 45 UC		SQCC 33.3% UC 76.6% SQCC 44.4%, UC 91.6%	16/18 6/11
2013	Chapman	SCC	14	3 (21.4%)	16 (2), 35 (1)
2014	Kim	UC	35	6 (17%)	18 (6)
2016	Golovina	UC	101	38 (37.6)	16
2016	Guma	SCC	1	1 (100%)	6/11
2017	Jørgensen	SCC	1	1 (100%)	52, 66, 44, 67
2017	Abdollahzadeh	UC	67	15 (22.4%)	-

HPV, human papillomavirus; UC, urothelial carcinoma; AD, adenocarcinoma; SCC, squamous cell carcinoma; SQCC, schistosomal squamous cell carcinoma; UK, unknown.

TABLE 2. Study that refuse the association HPV-Bladder Cancer (UC, SCC, AD).

Year	Author	Pathology	N	HPV detection (%)	Detected HPV types (number)
1992	Knowles	UC/SCC/AD	108	0 (0%)	None
1993	Sinclair	UC	14	0 (0%)	None
1993	Saltzstein	UC	33	0 (0%)	None
1994	Chang	UC	108	0 (0%)	None
1995	Sano	BT	93	0 (0%)	None
1996	Boucher	UC/SCC	55	0 (0%)	None
1997	Lu	UC/SCC/AD	31	0 (0%)	None
1997	Cooper	SCC	25	0 (0%)	None
1998	Aynaud	UC	57	0 (0%)	None
2001	Westenend	SCC	16	0 (0%)	None
2005	Youshya	UC	78	0 (0%)	None
2009	Guo	SCC	16	0 (0%)	None
2010	Ben Selma	UC/SCC/AD	125	0 (0%)	None
2011	Yavuzer	UC	70	0 (0%)	None
2012	Polesel	UC	114	0 (0%)	None
2012	Blochin	SCC	2	0 (0%)	None
2012	Alexander	SCC	42	0 (0%)	None
2013	Steinestel	CIS	45	0 (0%)	None
2014	Alexander	AD	36	0 (0%)	None
2015	Schmid	BC	109	0 (0%)	None

HPV, human papillomavirus; UC, urothelial carcinoma; AD, adenocarcinoma; SCC, squamous cell carcinoma; UK, unknown.

cervical cancer with the same HPV type (HPV16) detected both from BC and cervical cancer[108].

Golovina et al[111] in 2016 collected UC tissue samples from 101 patients. Morphological analysis and HPV biomolecular detection were conducted in the cancer specimens. HPV16-DNA was detected in 38 specimens, while mRNA of E6 and E7 oncogenes and E7 oncoprotein of HPV16 were found in 13 specimens. In HPV-positive samples, it was found an association between HPV detection and a higher degree of cell anaplasia than HPV-negative cancers. Moreover, HPV was detected in primary BCs more often than in recurrent those. These data showed a sure involvement of HPV16 in the genesis of BC. No correlations were found between HPV status of BCs and patient's sex, age, and invasion into the muscle layer, which were revealed.

In a 2017 study carried out by Abdollahzadeh et al[114] in 97 biopsy specimens, including 67 patients with UCs and 30 controls, the authors identified HPV-DNA in 22.4% of patients with cancers and 3.3% of controls were positive for HPV. The HPV prevalence was 4.3-fold higher in men than women. Most UC patients belonged to grades II and III.

Study that refuses the association HPV-UC

In contrast with the above-described studies, a number of investigations did detect no presence of HPV in the evaluated cases (Table 2[67,70,105,115-131]). Many of these investigations have included a large patient subset as well. For example, Youshya et al[67] considered 78 cases of UCs but any HPV detection was observed. Likewise, Ben Selma et al[125] investigated a group of 125 BC cases, of which 119 were UCs, but the authors found no evidence of HPV detection in any case. Yavuzer et al[126] in 2011 carried out a study involving 70 UC tissues that were screened by nested-PCR for HPV-DNA with a control group of 18 cervical tissues with invasive cervical carcinoma and Cervical Intraepithelial Neoplasia III (CIN III). In the study group, the authors did not find HPV-DNA positivity in any of the considered UCs.

In 2012, a study of Polesel et al[105] considering 114 UC cases, screened urine samples to detect DNA of 22 mucosal HPVs using highly sensitive PCR assays. HPVs were detected only in seven cases and five controls (OR=1.52; 95% CI: 0.42-5.45). The study does not suggest an involvement of HPVs infection in UC aetiology in immunocompetent individuals.

Steinestel et al[129] in 2013 collected 60 specimens of urothelial carcinoma *in situ* (UCIS) from 45 patients, and a control group with CIN. In the specimens, the authors performed p16(INK4a) immunohistochemistry followed by detection and subclassification of HPV-DNA. The results showed the presence of hr-HPV-DNA in 80% of CIN, but none in UCIS.

Finally, Schmid et al[131] in 2015 conducted a study involving 109 cases of BC with 41 superficial (pTa low grade) cancers, 56 invasive (pT1-T4) high grade cancers and 12 other types (pTa high grade + pTis). The authors did not detect HPV-DNA in any sample (95% Confidence Interval (CI) 0-3.3%). The results suggest that it is improbable that HPV infections can play an important role in the development of UC.

Squamous Cell Carcinoma (SCC)

The literature concerning the hypothetical role of HPV in SCC pathogenesis is poor and provides conflicting results. Some investigations have identified a link between HPV and this kind of cancer, while other studies have reported no association between HPVs and SCC pathogenesis (Table 1 and 2).

Study that showed an association HPV-SCC

Chapman-Fredricks et al[110] enrolled 14 cases of primary bladder SCC, positive for p16 by immunohistochemistry, to detect hr-HPV by *in situ* hybridization and the signal amplification Invader assay. The results showed that the hr-HPV detection by the *in-situ* hybridization method was negative in all cases. However, in 3 of 14 cases (21.4%), the presence of hr-HPV-DNA was detected with the Cervista hr-HPV Invader assay, with the subsequent identification of genotype. hr-HPV type specific amplification followed by DNA sequencing confirmed all positive cases. Identified genotypes were HPV 16 in 2 cases and HPV 35 in 1 case. This study concluded that hr-HPV-DNA is detectable in a subset of primary bladder SCCs.

At the same time in 2013 Shaker et al[109] investigated the HPV role on 60 bladder specimens, of which 15 were schistosomal squamous cell carcinoma (SQCC) and 45 were schistosomal and non-schistosomal UCs. The results showed that HPV 16/18 were found in 33.3%, 50% and 26.6%, respectively, while the positivity to HPV 6/11 were 44.4%, 58.3% and 33.3% for SQCCs, UCs and UC/SCC, respectively. Seven cases of UCs had both HPV6/11 and 16/18.

A study carried out in 2016 by Guma et al[112] demonstrates that the infection with HPV 6/11 was associated with an UC with squamous differentiation and condylomatous features. This is a case report on a high-grade UC with focal areas of squamous differentiation. These areas showed koilocytic differentiation, which was positive for strong p16 expression. In this cancer, it was found positivity for lr-HPV 6/11 by *in situ* hybridization technic.

Jorgensen et al[113] reported in a case of bladder SCC the presence of four different HPV types: hr-HPV-52, hr-HPV-66p, lr-HPV-44 and HPV-67. However, the association between the risk to develop SCC in the urinary bladder and the multiple infection with different HPV genotypes as seen in this patient is still unknown.

Study that refuses the association HPV-SCC

Westenend et al[70] in 2001 and Guo et al[124] in 2009 carried out two small investigations involving both 16 cases of SCC of the urinary bladder. In both studies no cases of HPV were detected.

A larger and more recent study conducted by Alexander et al[128] did not find evidence of HPV presence in 42 SCC cases. Moreover, the same authors performed the analysis on 27 cases of UCs with squamous differentiation, a morphologically similar entity to SCC of the urinary bladder. Even in this case, the results showed no evidence of HPV. These studies agree with the findings reported on UC with squamous differentiation from Blochin et al[127] in 2012. Other previous studies also failed to find HPV infection in bladder SCC cases. In conclusion, the role of detecting HPVs in the urinary bladder SCC is uncertain. HPV infection could have a little or no influence in the development of SCC of the bladder, but there is necessity of further researches to clarify this association.

Adenocarcinoma of urinary bladder (AD)

Even in case of AD of urinary bladder, the literature is quite poor and conflicting (Table 1 and 2). A study carried out by Alexander et al[130] on 36 cases of clinically confirmed cases of primary AD of the urinary bladder has not detected HPV in any of the examined cases. Conversely, a large study on BCs conducted by Shigehara et al[104] evaluated six AD of urinary bladder cases founding HPV-DNA in one case using PCR method; however, the extremely small number of considered specimens, do not allow any significant conclusions.

CONCLUSIONS

In the past three decades, the incidence of bladder carcinoma increased worldwide inducing the authors to identify possible etiological agents. Among the well-known cancer causes (smoking, industrial exposure, heavy metals in drinking water, chronic irritation) an increasing interest there was about a possible role played by HPVs in the pathogenesis of this kind of cancers. A thirty years' literature was not able to clearly demonstrate the real contribute of HPV in this oncologic disease. The difference among the studies is probably due to sampling problems, contamination, sensitivity of the detection systems, geographic variation and size of the studies, especially regarding the rarer forms[129]. Further studies are required to understand and clarify the role of HPV in the pathogenesis of this kind of urinary cancers.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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