African Journal of Urology

REVIEW

Open Access

# Human papillomavirus and bladder cancer: literature review and meta-analysis

Daria S. Dolgasheva[1,2*†], Marina K. Ibragimova[1,2,3†], Matvey M. Tsyganov[1] and Nikolai V. Litviakov[1,2,3]

## Abstract

**Background** The aim of this study was to evaluate data over the past 25 years to assess the prevalence of the virus in patients with bladder cancer and to evaluate the association between human papillomavirus (HPV) and bladder cancer risk.

**Main text** Major databases were searched for published studies from October 1995 to May 2022. The present study evaluated the prevalence of HPV in patients with bladder cancer and the prevalence according to patients' ethnicity. The incidence of HPV in bladder cancer patients varies widely, ranging from complete absence of the virus in tissues to 64.6%. The meta-analysis was performed using Meta-Essentials_1.5 software. Begg's and Egger's methods were used to assess publication bias. Cochran's *Q* test was used to assess heterogeneity and the *I*2 index was employed for calculating the variation in the pooled estimations.

**Conclusions** A weak association of HPV infection with the risk of bladder cancer was found. The risk of bladder cancer with HPV infection has clear ethnic characteristics and is statistically significant in Arabs and Asians.

**Keywords** Human papillomavirus, Bladder cancer, Meta-analysis, Urologic cancer

## 1 Introduction

Bladder cancer is a malignant neoplasm from the epithelial tissue of the bladder mucosa. According to literature it is included in the top 10 most common cancer disease in the world. There were 573,278 new cases of bladder cancer and 212,536 deaths in 2020, the incidence is growing every year. It should be noted that bladder cancer occurs in men much more often than in women [1]. The following histological types exist: transitional cell carcinoma (or urothelial carcinoma), squamous cell carcinoma, and adenocarcinoma. Transitional cell carcinoma accounts for more than 90% of all bladder cancer cases; while, the latter two types are much less common [2]. There are many factors for the development of bladder cancer, including effects of industrial carcinogens, lifestyle, or existing chronic medical conditions. However, researchers have focused on HPV infection as a key factor in the development of bladder cancer. To date, it has been demonstrated that the human papillomavirus is an etiological factor in cervical cancer, and it is also often found in tumors of the anogenital region [3]. However, the role of HPV infection in urological tumors is still unclear. There is a need to systematize the available data from recent studies to establish the association of HPV infection with the risk of bladder cancer.

### 1.1 Epidemiology and etiology of bladder cancer

According to the Global Cancer Observatory, bladder cancer is the 10th most common cancer among all types and the 13th leading cause of cancer death worldwide [4]. This pathology is typical for residents of developed

†Daria S. Dolgasheva and Marina K. Ibragimova have contributed equally to this work.

*Correspondence:
Daria S. Dolgasheva
normikus.18.97@gmail.com
[1] Cancer Research Institute Tomsk National Research Medical Center of the Russian Academy of Sciences, Kooperativniy Lane, 5, Tomsk, Russia 634028
[2] National Research Tomsk State University, Tomsk, Russia 634050
[3] Siberian State Medical University, Tomsk, Russia 634050

Springer Open

© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

countries. Despite the rapid development of science and new medical technologies, the incidence of bladder cancer continues to grow every year around the world. In 2020, according to the GCO, there were about 580,000 cases of bladder cancer, which is about 3% of all new diagnoses in the field of oncology. It is known that 18 thousand new cases of bladder cancer have been registered in Russia [4] (Fig. 1).

The highest incidence of bladder cancer is typical for the countries of Southern and Western Europe and North America. Greece has the highest incidence of this cancer type among men, but among women, the highest incidence is shown in Lebanon. However, the region with the highest incidence of bladder cancer in both sexes is Southern Europe. The regions with the lowest incidence are Central Africa, Central America and West Africa [5].

In 2018, 624,709 cases of malignant neoplasms were detected for the first time in Russia. Bladder cancer takes 13th place in the oncology disease (2.8%). It most often affects the male population. Tumors of the genitourinary system in men account for 25.1% of all malignant neoplasms, of which 4.7% are bladder tumors. The absolute number of diagnoses made for the first time in Russia for bladder cancer was 13,479 cases in 2018. The average age of patients suffering from this pathology is 67.6 years (for men 66.9 years, for women 69.7 years) [6].

Bladder cancer is a malignant neoplasm that forms from the elements of bladder mucous membrane epithelium. According to the 10th revision international classification of diseases, bladder cancer has the C67 code [7]. The main histological types of bladder cancer include urothelial or transitional cell carcinoma, adenocarcinoma, and squamous cell carcinoma. Urothelial bladder cancer has a calm course and rare metastasis. According to the literature, transitional cell carcinoma of the bladder is diagnosed in 95% of cases [8]. Chen and colleagues showed in 2017 that the incidence of the urothelial type was 86% (86 out of 100 samples) [9].

Many studies have shown that the etiology of bladder cancer is mainly associated with tobacco smoking, secondhand smoke, and various background diseases of the urinary system, such as urolithiasis. A 2018 meta-analysis found a statistically significant increase (22%) in bladder cancer risk with lifelong exposure to secondhand smoke in non-smokers compared to non-smokers not exposed to secondhand smoke [10]. Smoking cigarettes significantly increases the risk of bladder cancer, especially when combined with infectious diseases such as

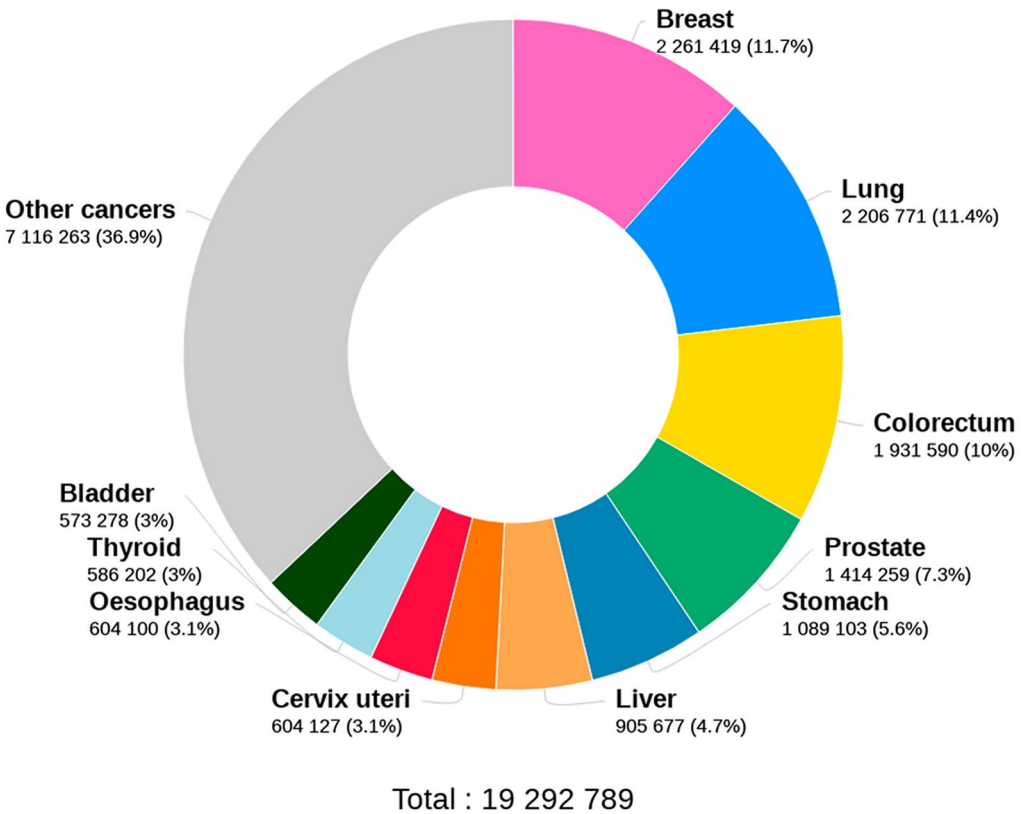


**Fig. 1** The number of new cases of cancer in the world in 2020

schistosomiasis [11]. It has also been shown that smokers with a family history of bladder cancer have a four times higher risk than non-smokers [12]. There is evidence that bladder adenocarcinoma often results from chronic inflammation or infectious of the bladder wall. Schistosoma haematobium infection provokes urogenital schistosomiasis and correlates with bladder cancer occurrence [13].

However, there is more and more studies focusing on the viral etiology of bladder cancer. In particular, scientists focus on the presence of HPV infection in patients with bladder cancer.

Human papillomaviruses are a large family of shoeless epitheliotropic viruses containing double-stranded circular DNA within the capsid. There are more than 150 different HPV genotypes. HPV is a widespread sexually transmitted infection. To date, a large number of studies have been published looking at the role of HPV in the development of other cancer types. For example, HPV is frequently found in anogenital tumors, head and neck tumors, and even in lung tumors [14–17]. However, a clear association has only been shown for cervical cancer: HPV DNA has been shown to be detected in 99.7% of cervical cancer samples [18].

At this time, the exact mechanism of HPV-associated bladder tumor development has not been described. However, there are studies that suggest that HPV DNA can be transported by the bloodstream from the original site of infection to other organs and possibly contribute to tumor development, including bladder cancer [19]. Also, a recent study showed a putative mechanism for the development of HPV-induced bladder cancer. Given that the urinary tract is anatomically close to the genital tract, it is hypothesized that HPV may spread upward through the urethra to the bladder epithelium, thereby causing the development and progression of bladder cancer. It is hypothesized that after exposure of bladder uroepithelial cells to the virus, DNA repair returns damaged cells to normal. In this case, cells that failed to repair become precancerous after persistent chronic infection. In the absence of tumor suppressors and under genomic changes, precancerous cells gradually turn into malignant cells [20, 21].

The data available to date are insufficient to state that HPV is an etiologic factor in the development of bladder malignancies, but it is important to realize that HPV infection may be an important co-factor in the development of this malignancy. In this regard, it is particularly relevant to investigate the association of HPV with the risk of bladder cancer.

To date, few studies have been conducted to determine the association of HPV with bladder cancer. A 2011 meta-analysis reviewed 21 case–control studies that analyzed the prevalence of HPV in this type of cancer, using different methods of virus identification. The pooled odds ratio was 2.13 [22]. Li and colleagues (2011) presented a paper that included 19 case–control studies, where samples of fresh and fixed tissue were used. The presence of HPV in the material was detected using PCR analysis, as well as in situ hybridization and Southern blotting. It has been shown that the HPV prevalence among patients with bladder cancer was 16.88% [23].

However, the presented results of HPV infection studies in bladder cancer are ambiguous; the data show both a high association of HPV infection with bladder cancer and a complete lack of association, which makes the study of the HPV role in bladder carcinogenesis relevant question.

## 2 Methods

### 2.1 Literature search strategy

A systematic literature search was performed using PRISMA guidelines. We searched PubMed, Web of Science, and Google Scholar for articles published between October 1995 and May 2020. The terms used to search for potentially relevant studies were: "cancer," "human papillomavirus," "bladder cancer," "association," "urologic cancer," and "bladder."

## 3 Research selection criteria

Mandatory criteria for inclusion in the meta-analysis were:

1. Study design: we included case–control studies published between October 1995 and May 2020.
2. Participants: studies including patients with bladder cancer.
3. Primary outcome: presence of human papillomavirus in bladder cancer patients.
4. Secondary outcome: prevalence of human papillomavirus in bladder cancer patients.

We excluded a series of cases where urothelial smears and urine were used as material, as well as studies involving positive controls. No language restrictions were applied.

### 3.1 Statistical analysis

The meta-analysis was performed using Meta-Essentials_1.5 software. We used Begg's and Egger's methods to assess publication bias. The funnel plots shape is used to show symmetry and Egger's methods are applied to indicate significant publication bias for the analysis exploring association between risk of prostate cancer and HPV. The Egger test uses linear regression to assess the relationship between standardized effect estimates

and standard error. For this test, a significant result is an indication that publication bias may influence the results. Egger's test reduces the standardized effect size by their precision; in the absence of publication bias, the regression crossover point is expected to be zero. Cochran's *Q* test was used to assess heterogeneity and the $I^2$ index was employed for calculating the variation in the pooled estimations. All *p* values are two-tailed, $\alpha \leq 0.05$ was considered statistically significant ($p \leq 0.05$).

## 4 Results

This meta-analysis provides literature data for the last 25 years (1995–2020). The chronology of data is observed over the years. There were 56 studies selected, the total number included for the analysis of HPV infection was 4613 cases of bladder cancer and 636 control samples (Table 1).

The prevalence of HPV in bladder cancer was approximately 16.3%. The virus was detected in 5.95% of cases in the control group. The incidence of HPV in patients with bladder cancer varies widely from the complete absence of tissue virus to 64.6%. The most common HPV types are 16 and 18, with HPV types 31 and 33 in second place.

Next, we performed meta-analysis with 23 studies with the selection criteria for inclusion in the meta-analysis of the data to determine the risk of bladder cancer with HPV infection.

The studies of the "case–control" type were taken into account, samples of tumor (case) and normal tissue (control) were used as the material, and the main methods were real-time PCR and quantitative PCR. In particular, case–control studies using frozen tumor tissue or paraffin-embedded (FFPE) tissue (case) were included. Frozen normal tissue or FFPE samples obtained from the same patients or from healthy donors were used as controls. The main methods were real-time PCR and quantitative PCR. The PRISMA tool (Preferred Reporting Items for Systematic reviews and Meta-analysis) was used to improve the quality of data and the review result [24]. A flowchart of study search and analysis for inclusion in meta-analysis is shown in Fig. 2.

It should be noted that studies that urothelial smears and urine were used as the test material, as well as studies involving a positive control, were excluded. A total of 1324 patients' bladder tumors and 599 normal bladder tissues were included in the meta-analysis. Meta-analysis was performed using the Meta-Essentials_1.5 program. The result of a meta-analysis of 23 studies is presented in Table 2 and Fig. 3.

Analysis of HPV prevalence according to the meta-analysis studies showed that HPV occurs in bladder cancer in 20.2% of cases, while in samples of the control group the virus was detected in 6.7% of cases.

In accordance with the literature data, the most common HPV genotypes were 16 and 18, in addition, 6, 31, 33 and 45 types are often found. A high incidence of human papillomavirus among patients with bladder cancer was shown in five studies [22, 25, 29, 32, 37].

At the same time, the total RR (RR 95CI) of developing bladder cancer with HPV infection was 1.21 (1.09–1.34), with $p = 0.00253$. The heterogeneity index of the sample $I2 = 84.68\%$ and the Cochrane *Q*-test was $p = 4.5*10–20$, with the required level $p < 0.1$, therefore the Random model was used. The funnel plot does not show significant asymmetry (Fig. 1) and according to Begg's test there was no significant publication bias in this meta-analysis ($p = 0.054$). Egger's test result was not significant ($p = 0.265$).

At the next stage, a subgroup analysis of the data was carried out depending on the ethnic origin of the patients. Table 3 shows the results of the subgroup analysis.

The highest risk of bladder cancer with HPV infection is observed in patients of Arab ethnicity OR (95CI OR) 1.49 (1.30–1.70). In Asians, the risk of developing bladder cancer with HPV infection was RR (RR 95CI) 1.15 (1.05–1.26) with $p = 0.007$. In patients of European ethnicity, the risk of developing bladder cancer in the presence of HPV infection RR (RR 95CI) 1.04 (0.99–1.09) at $p = 0.129$ does not reach statistically significant values, as well as in patients of Turkish ethnicity: OR (RR 95CI) 1.03 (0.81–1.33), at $p = 0.438$. Thus, the risk of developing bladder cancer with HPV infection has different ethnic characteristics and is statistically significant in Arabs and Asians.

## 5 Discussion

There is a large number of studies on the relationship of putative etiologic factors with bladder cancer, each of which plays a significant role in carcinogenesis. For example, a recent meta-analysis showed that smoking is associated with a high risk of recurrence and mortality in patients with bladder cancer [78].

However, the presence of papillomavirus infection is also of greater interest as a risk factor for bladder cancer. Human papillomavirus is an etiologic factor for cervical cancer, which in recent decades makes it relevant to study the association of this virus with the etiology and risk of other malignant pathologies, especially tumors of the genitourinary system.

To date, the global literature has presented studies examining the correlation between HPV infection and the risk of bladder malignancy. Nevertheless, unequivocal results remain elusive due to the relatively small number of homogeneous studies and small sample sizes. In addition, it remains unclear whether there are clear geographic differences in the risk of bladder malignancy

**Table 1** Prevalence of HPV in bladder cancer

| Author. year. country | Material | Method | HPV genotypes | Case | | Control | | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | | | | Total | HPV+ | Total | HPV+ | |
| K.H. Kim. 1995. Korea [25] | Tissue | PCR. dot blot | 16, 18 | 23 | 8 (34.8%) | – | – | – |
| Smetana Z. 1995. Israel [26] | Tissue | ISH. IHC. PCR | 16, 6, 11, 8, 18 | 110 | 59 (53.6%) | 41 | 2 (4.9%) | – |
| H. LaRue. 1995. Canada [27] | Tissue | PCR. SBH | 16, 6, 11 | 71 | 28 (39.4%) | – | – | – |
| A. Lopez-Beltran. 1995. Spain [28] | Tissue | PCR P. ISH | 16 | 76 | 7 (9.2%) | – | – | – |
| V. Gopalkrishna. 1995. India [29] | Tissue | PCR. ISH | 16 | 10 | 1 (10.0%) | – | – | – |
| P. Tenti. 1996. Italy [30] | Tissue | PCR. SBH | 16, 18 | 79 | 26 (32.9%) | – | – | – |
| A. Lopez-Beltran. 1996. Spain [31] | Tissue | PCR | 16, 6 | 76 | 7 (9.2%) | – | – | – |
| M. Mvula. 1996. Japan [32] | Tissue | PCR | 16 | 36 | 1 (2.8%) | – | – | – |
| M. Ludwig. 1996. Germany [33] | Tissue | PCR | 6, 16, 18 | 32 | 6 (18.8%) | – | – | – |
| D.L. Wang. 1996. China [34] | Tissue | PCR | 16, 18 | 72 | 40 (55.6%) | 20 | 1(5%) | – |
| W. Hui. 1996.China [35] | Tissue | PCR | – | 52 | 28 (53.9%) | – | – | – |
| W. Zengjun. 1996. China [36] | Tissue | PCR | 16, 18 | 34 | 14 (41.2%) | 30 | 0 | – |
| K. Cooper. 1997. South Africa [37] | Tissue | ISH. PCR | – | 25 | 0 | – | – | – |
| K.W. Chan. 1997. China [38] | Tissue | SBH. PCR | 18 | 20 | 6 (30.0%) | – | – | – |
| O. Aynaud. 1998. France [39] | Tissue | PCR. dot blot | – | 57 | 0 | – | – | – |
| P. Gazzaniga. 1998. Italy [40] | Tissue | PCR. dot blot | 16, 18 | 35 | 11 (31.0%) | – | – | – |
| Ya L.S.. 1998. China [41] | Tissue | PCR | 16, 18 | 50 | 5 (10.0%) | – | – | – |
| Chaomei T.W.X.Y.L.. 1998. China [42] | Tissue | PCR | – | 20 | 8 (40.0%) | 5 | 0 | – |
| C. Giudici. 1998. Italy [43] | Tissue | PCR | 6, 11, 16, 18, 31, 33 | 37 | 3 (8.1%) | – | – | – |
| M. Simoneau. 1999. Canada [44] | Tissue | PCR. dot blot | 6, 11, 16 | 187 | 16 (8.5%) | – | – | – |
| M.I. Tekin. 1999. Turkey [45] | Tissue | PCR | 16 | 42 | 2 (4.8%) | 10 | 0 | – |
| W. Dinghai. 1999. China [46] | Tissue | PCR | – | 42 | 22 (52.4%) | 20 | 2 (10.1%) | – |
| T. Chen. 2000. China [47] | Tissue | PCR | 6, 11, 16, 18 | 75 | 33 (44.0%) | – | – | – |
| M. Sur. 2001. USA [48] | Tissue | ISH. PCR | – | 91 | 1 (1.5%) | – | – | – |
| D. Fioriti. 2003. Italy [49] | Tissue | PCR | 6 | 32 | 1 (3.1%) | 20 | 0 | – |
| H.M. Khaled. 2003. Egypt [50] | Tissue | PCR | 16, 18, 6, 11 | 99 | 48 (48.5%) | – | – | – |
| M.R. Barghi. 2005. Iran [51] | Tissue | PCR | 18, 6, 33 | 59 | 21 (35.6%) | 20 | 1 (5.0%) | $P=0.008$ |
| S. Youshya. 2005. UK [52] | Tissue | ISH. PCR | – | 78 | 0 | 20 | 0 | – |
| P.M.J. Moonen. 2007 [53] | Tissue | PCR | 16, 18, 6, 11, 31, 40, 52 | 99 | 15 (15.2%) | – | – | – |
| H. Badawi. 2008. Egypt [54] | Tissue | PCR | 16, 18 | 20 | 9 (45.0%) | 20 | 2 (10.0%) | – |
| G. Eslami. 2008. Iran [55] | Tissue | PCR | 16, 18, 33, 31, 52 | 147 | 51 (34.7%) | 39 | 3 (7.6%) | $P<0.008$ |
| K. Shigehara. 2009. Japan [56] | Tissue | PCR ISH | 16, 18, 56, 33 | 72 | 14 (19.4%) | 10 | 0 | – |
| T. Cai. 2010. Italy [57] | Tissue | PCR | 6, 11, 16. 18, 45, 51, 58, 59, 66 | 78 | 41 (52.6%) | 59 | 16 (27.1%) | $P=0.032$ |
| K. Shigehara. 2010. Japan [58] | Tissue | PCR. ISH | 16, 18, 31, 33, 52, 56, 58 | 117 | 18 (15.4%) | 10 | 0 | – |
| W.B. Selma. 2010. Tunisia [59] | Tissue | PCR | – | 125 | 0 | – | – | – |
| A. Sorlozano. 2010. Spain [22] | Tissue | PCR | 18, 33, 35, 39, 51, 52, 82 | 34 | 2 (5.9%) | 51 | 3 (1.5%) | – |
| D. Yavuzer. 2011. Turkey [60] | Tissue | PCR | 6, 11, 16, 18, 31 | 70 | 0 | – | – | – |
| J. Xiao. 2011. China [61] | Tissue | PCR | 16, 18 | 90 | 7 (7.8%) | 30 | 2 (5%) | $P<0.05$ |
| T. Cai. 2011. Italy [57] | Tissue | PCR | 16, 18, 31, 45 | 78 | 27 (34.6%) | 59 | 6 (10.1%) | $p=0.0009$ |
| M.R. Barghi. 2012. Iran [62] | Tissue | PCR | 16, 18 | 82 | 24 (29.3%) | – | – | – |
| G. I. Panagiotakis. 2013. Greece [63] | Tissue | PCR | – | 30 | 0 | 30 | 0 | – |

**Table 1** (continued)

| Author. year. country | Material | Method | HPV genotypes | Case | | Control | | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | | | | Total | HPV+ | Total | HPV+ | |
| J. Steinestel. 2013. Germany [64] | Tissue | PCR | 16 | 60 | 4 (6.7%) | – | – | – |
| N. Berrada. 2013. Morocco [65] | Tissue | PCR | 18, 31 | 43 | 22 (51.2%) | 5 | 0 | – |
| S.H. Kim. 2014. Korea [66] | Tissue | DNA chips | 18, 35 | 35 | 6 (17.1%) | 12 | 1 (8.3%) | $P=0.659$ |
| S.C. Schmid. 2015. Germany [67] | Tissue | PCR | – | 109 | 0 | 6 | 0 | – |
| R. Pichler. 2015. Austria [68] | Tissue | PCR. RLB | 6, 16, 18, 45, 33 | 186 | 4 (2.2%) | – | – | – |
| U.K. Mete. 2018. India [69] | Tissue | PCR | – | 50 | 0 | 10 | 0 | – |
| H. Badawi. 2018. Egypt [70] | Tissue | PCR. ISH | 6, 11, 35, 39, 52, 56 | 70 | 24 (34.3%) | 30 | 0 | – |
| M.A. Llewellyn. 2018.UK [71] | Tissue | PCR | 16, 18 | 689 | 1 (0.2%) | – | – | – |
| I.V. Kosova. 2018. Russia [72] | Tissue | PCR | 16, 39, 45, 52, 59 | 100 | 5 (5.0%) | – | – | – |
| M. Yıldızhan. 2020. Turkey [73] | Tissue | PCR | 6, 84, 53, 66 | 113 | 4 (3.5%) | 99 | 0 | $P=0.125$ |
| S.O. Moghadam. 2020. Iran [74] | Tissue | PCR ISH | 6, 11, 16, 18 | 106 | 24 (22.6%) | – | – | – |
| Y. Yan. 2020. China [75] | Tissue | PCR | 16, 18, 33, 39 | 146 | 42 (28.8%) | – | – | – |
| J. Gordetsky. 2020. USA[76] | Tissue | ISH, P16 IHC | – | 204 | 1(0.5%) | – | – | – |
| T.A. Zykova. 2020. Russia [77] | Tissue | PCR | 18, 31, 39, 56, 33, 52, 59 | 46 | 6 (13.0%) | – | – | – |
| Total | | | | 4619 | 753 (16.3%) | 656 | 39 (5.95%) | |

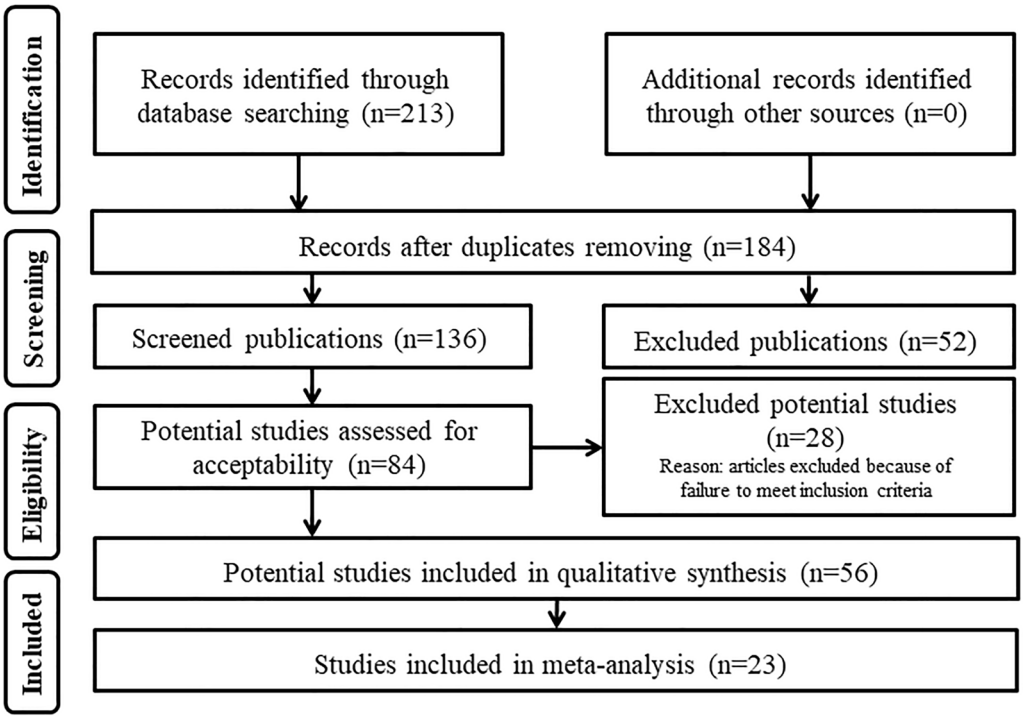


**Fig. 2** Flowchart for search and analysis of meta-analysis, drawn up taking into account the requirements of PRISMA

with HPV infection. Thus, in the present study, we evaluated the overall impact of papillomavirus infection on the development of bladder cancer as well as the dependence of the bladder tumor risk of HPV infection on the ethnic aspect.

According to the presented meta-analysis, HPV was found in bladder cancer in 20.2% of cases, whereas in control group samples the virus was detected in 6.7% of cases. The findings are consistent with earlier meta-analyses [23, 79] as well as recent studies [80, 81]. In an

**Table 2** Meta-analysis results for 23 studies

| # | Study name | Risk ratio | CI lower limit | CI upper limit | Weight (%) |
|---|---|---|---|---|---|
| 1 | Smetana Z., 1995, Israel | 2.05 | 1.66 | 2.54 | 4.08 |
| 2 | W. Zengjun, 1996, China | 1.68 | 1.26 | 2.24 | 3.21 |
| 3 | Chaomei T.W.X.Y.L., 1998, China | 1.54 | 0.98 | 2.42 | 1.96 |
| 4 | M.I. Tekin, 1999, Turkey | 1.01 | 0.87 | 1.18 | 4.98 |
| 5 | W. Dinghai, 1999, China | 1.89 | 1.32 | 2.70 | 2.55 |
| 6 | D. Fioriti, 2003, Italy | 1.02 | 0.92 | 1.13 | 5.63 |
| 7 | M.R. Barghi, 2005, Iran | 1.48 | 1.19 | 1.83 | 4.05 |
| 8 | S. Youshya, 2005, UK | 0.98 | 0.92 | 1.05 | 5.97 |
| 9 | H. Badawi, 2008, Egypt | 1.64 | 1.06 | 2.53 | 2.00 |
| 10 | G. Eslami, 2008, Iran | 1.41 | 1.22 | 1.64 | 4.98 |
| 11 | K. Shigehara, 2009, Japan | 1.19 | 1.00 | 1.42 | 4.64 |
| 12 | T. Cai, 2010, Italy | 1.54 | 1.16 | 2.04 | 3.23 |
| 13 | K. Shigehara, 2010, Japan | 1.13 | 0.97 | 1.32 | 4.95 |
| 14 | A. Sorlozano, 2010, Spain | 1.00 | 0.90 | 1.12 | 5.52 |
| 15 | J. Xiao, 2011, China | 1.01 | 0.90 | 1.13 | 5.47 |
| 16 | T. Cai, 2011, Italy | 1.37 | 1.14 | 1.65 | 4.49 |
| 17 | G. I. Panagiotakis, 2013, Greece | 1.00 | 0.94 | 1.07 | 6.01 |
| 18 | N. Berrada, 2013, Morocco | 1.88 | 1.26 | 2.79 | 2.24 |
| 19 | S.H. Kim, 2014, Korea | 1.11 | 0.88 | 1.40 | 3.88 |
| 20 | S.C. Schmid, 2015, Germany | 0.93 | 0.76 | 1.15 | 4.17 |
| 21 | U.K. Mete, 2018, India | 0.96 | 0.84 | 1.10 | 5.21 |
| 22 | H. Badawi, 2018, Egypt | 1.50 | 1.26 | 1.79 | 4.61 |
| 23 | M. Yıldızhan, 2020, Turkey | 1.04 | 1.00 | 1.08 | 6.19 |
| 24 | Total | 1.21 | 1.09 | 1.34 | |

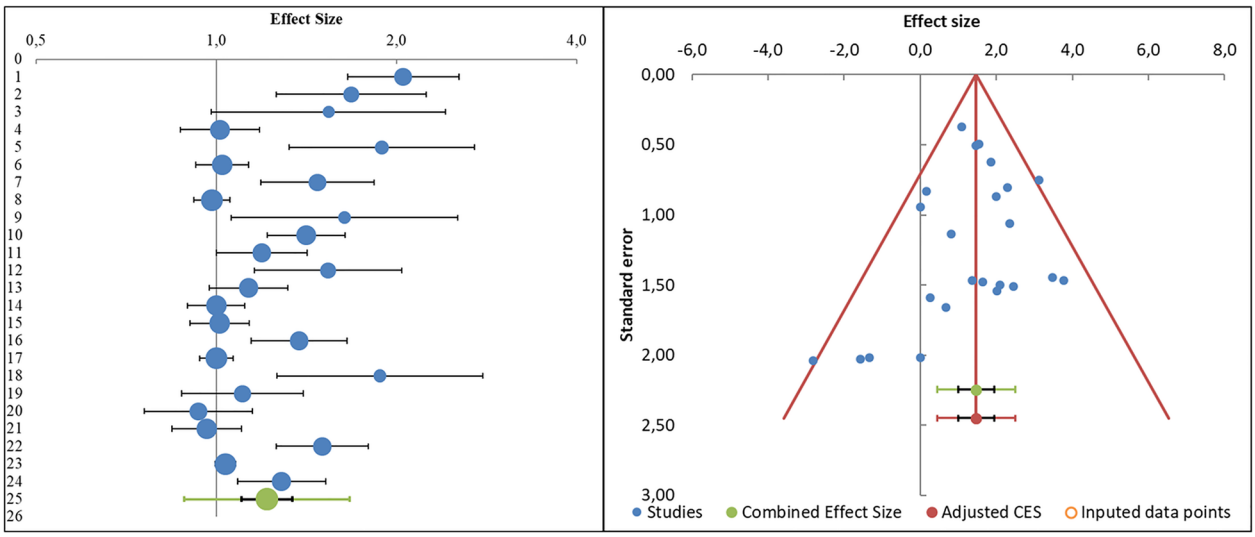


**Fig. 3** Results of a meta-analysis of the relationship between the presence of HPV infection and the risk of developing bladder cancer

earlier 2011 study, Li N and colleagues also showed that HPV prevalence was highest in Asia (24.25% [95% CI 21.12–27.60%]); while, North America (13.49% [95% CI 10.21–17.36%]) and Europe (13.11% [95% CI 11.26–15, 15%]) had significantly lower HPV prevalence in bladder cancer cases (adjusted odds ratio [OR], 0.30 [95% CI 0.20–0.44] for North American cases and 0.41 [95% CI 0.32–0.52] for European cases). In a study by Reinstatler

**Table 3** Results of a subgroup meta-analysis by ethnicity of patients

| # | Study name/subgroup name | Risk ratio | CI lower limit | CI upper limit | Weight (%) |
|---|---|---|---|---|---|
| 1 | M.R. Barghi, 2005, Iran | 1.48 | 1.19 | 1.83 | 19.37 |
| 2 | H. Badawi, 2008, Egypt | 1.64 | 1.06 | 2.53 | 5.00 |
| 3 | G. Eslami, 2008, Iran | 1.41 | 1.22 | 1.64 | 40.42 |
| 4 | N. Berrada, 2013, Morocco | 1.88 | 1.26 | 2.79 | 5.97 |
| 5 | H. Badawi, 2018, Egypt | 1.50 | 1.26 | 1.79 | 29.24 |
| 6 | **Arabic** | **1.49** | **1.30** | **1.70** | **22.82** |
| 7 | W. Zengjun, 1996, China | 1.68 | 1.26 | 2.24 | 6.22 |
| 8 | Chaomei T.W.X.Y.L., 1998, China | 1.54 | 0.98 | 2.42 | 2.71 |
| 9 | W. Dinghai, 1999, China | 1.89 | 1.32 | 2.70 | 4.06 |
| 10 | K. Shigehara, 2009, Japan | 1.19 | 1.00 | 1.42 | 16.70 |
| 11 | K. Shigehara, 2010, Japan | 1.13 | 0.97 | 1.32 | 21.85 |
| 12 | J. Xiao, 2011, China | 1.01 | 0.90 | 1.13 | 38.88 |
| 13 | S.H. Kim, 2014, Korea | 1.11 | 0.88 | 1.40 | 9.57 |
| 14 | **Asian** | **1.15** | **1.05** | **1.26** | **24.55** |
| 15 | Smetana Z., 1995, Israel | 2.05 | 1.66 | 2.54 | 3.03 |
| 16 | D. Fioriti, 2003, Italy | 1.02 | 0.92 | 1.13 | 13.71 |
| 17 | S. Youshya, 2005, UK | 0.98 | 0.92 | 1.05 | 28.75 |
| 18 | T. Cai, 2010, Italy | 1.54 | 1.16 | 2.04 | 1.74 |
| 19 | A. Sorlozano, 2010, Spain | 1.00 | 0.90 | 1.12 | 11.66 |
| 20 | T. Cai, 2011, Italy | 1.37 | 1.14 | 1.65 | 4.10 |
| 21 | G. I. Panagiotakis, 2013, Greece | 1.00 | 0.94 | 1.07 | 33.77 |
| 22 | S.C. Schmid, 2015, Germany | 0.93 | 0.76 | 1.15 | 3.24 |
| 23 | **European** | **1.04** | **0.99** | **1.09** | **26.35** |
| 24 | M.I. Tekin, 1999, Turkey | 1.01 | 0.87 | 1.18 | 6.65 |
| 25 | M. Yıldızhan, 2020, Turkey | 1.04 | 1.00 | 1.08 | 93.35 |
| 26 | **Turkic** | **1.03** | **0.81** | **1.33** | **26.29** |

Meta-analysis results obtained for patients of different ethnic groups are shown in bold

L., the prevalence of HPV in US patients with bladder cancer was shown to be: HPV type 18 was 5.5%, HPV 16 was 13.2%, HPV 11 was 6.4%, and HPV 6 was 17. 4%. A high prevalence of the virus was noted in male patients (80% vs. 53%, $p=0.0056$). In logistic regression adjusting for sex, smoking status, weight gain (OR 1.01, $p<0.0001$) and HPV type 6 infection (OR 1.9, $p<0.0001$) were associated with increased odds of developing bladder cancer [82].

Review article by K.R Jorgensen published in 2020 reviewed 7 publications with 100 or more cases. A total of 877 patients were analyzed for the presence of HPV. The study material in all studies was frozen tumor tissue or tissue fixed with formalin and encapsulated in paraffin. The presence of HPV was determined by PCR, but in some studies PCR was combined with other tests to determine other HPV genotypes. As a result, the incidence of HPV in bladder tumors was found to vary widely, approximately 0–37.6%, and the most common HPV types, as in other localizations, were types 16, 18, 33, 6, and 31 [79].

In the present study, we also showed that the risk of bladder cancer in HPV infection has different ethnic characteristics. We found that the highest risk of bladder cancer with HPV infection was observed in Arab patients RR (RR 95CI) 1.49 (1.30–1.70) and Asian patients RR (RR 95CI) 1.15 (1.05–1.26) at $p=0.007$. In Europeans and Turkish patients, the risk of developing bladder cancer with HPV infection was RR (RR 95CI) 1.04 (0.99–1.09) at $p=0.129$ and RR (RR 95CI) 1.03 (0.81–1.33), at $p=0.438$, respectively. The results for these patient groups do not reach statistically significant values.

Thus, in the presented work we analyzed both the general impact of papillomavirus infection on bladder cancer development and the risk of bladder tumor development in HPV infection for different ethnic groups of patients.

The analysis of literature data showed that HPV, though it cannot be recognized as an etiological factor in the development of bladder cancer, is definitely an important concomitant factor in the occurrence of this oncopathology. It is important to note that the obtained results confirm that the presence of HPV infection is important

in order to create risk groups for the development of the studied oncopathology, as well as the need to monitor papillomavirus infection in patients with bladder pathology.

## 6 Conclusion

The data obtained are consistent with previously published studies. Despite the fact that this meta-analysis found a weak association of HPV infection with the risk of developing bladder cancer, it should be noted that the risk of developing bladder cancer with HPV infection has clear ethnic characteristics. Thus, the highest risk of bladder cancer with HPV infection is observed in Arab and Asian patients, which is not the same for European and Turkish patients.

**Abbreviations**

| | |
|---|---|
| BC | Bladder cancer |
| HPV | Human papillomavirus |
| GCO | Global Cancer Observatory |
| OR | Odds ratio |
| RR | Risk ratio |
| PCR | Polymerase chain reaction |

**Acknowledgements**
Not applicable.

**Author contributions**
DSD—data collection, drafting the article; MKI—conception or design of the work, data analysis and interpretation; MMT—data collection; NVL—critical revision of the article, final approval of the version to be published.

**Funding**
Not applicable.

**Availability of data and materials**
Not applicable.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

Received: 13 November 2023 Accepted: 13 February 2024
Published online: 11 March 2024

**References**

1. Rudman SM, Crawley D (2017) Epidemiology of bladder cancer. In: Loda M, Mucci LA, Mittelstadt ML, Van Hemelrijck M, Cotter MB (eds) Pathology and Epidemiology of Cancer. Springer, Cham, pp 511–522
2. Chissov VI, Daryalova SL (2008) Clinical guidelines. Oncology. https://www.studmed.ru/view/chissov-vi-daryalova-sl-onkologiya_6156f95d325.html
3. Heidegger I, Borena W, Pichler R (2015) The role of human papilloma virus in urological malignancies. Anticancer Res 35(5):2513–2519
4. GLOBOCAN 2020. http://globocan.iarc.fr
5. Saginala K, Barsouk A, Aluru JS et al (2020) Epidemiology of bladder cancer. Med Sci 8(1):15
6. Kaprin AD, Starinsky VV, Petrova GV (2019) Malignant neoplasms in Russia in 2018 (morbidity and mortality) ISBN 978-5-85502-251-3. https://glavonco.ru/cancer_register/%D0%97%D0%B0%D0%B1%D0%BE%D0%BB_2018_%D0%AD%D0%BB%D0%B5%D0%BA%D1%82%D1%80.pdf
7. ICD 10—International classification of diseases 10th revision.—Access mode: https://mkb-10.com/index.php?pid=1346
8. Wang Y, Chang Q, Li Y (2018) Racial differences in urinary bladder cancer in the United States. Sci Rep 8(1):1–8
9. Chen C, Hu L, Chen Y et al (2017) The prognostic value of histological subtype in patients with metastatic bladder cancer. Oncotarget 8(17):28408
10. Yan H, Ying Y, Xie H et al (2018) Secondhand smoking increases bladder cancer risk in nonsmoking population: a meta-analysis. Cancer Manag Res 10:3781
11. Zheng YL, Amr S, Doa'a AS et al (2012) Urinary bladder cancer risk factors in Egypt: a multicenter case–control study. Cancer Epidemiol Prev Biomark 21:537–546
12. Turati F, Bosetti C, Polesel J et al (2017) Family history of cancer and the risk of bladder cancer: a case–control study from Italy. Cancer Epidemiol 48:29–35
13. Ishida K, Hsieh MH (2018) Understanding urogenital schistosomiasis-related bladder cancer: an update. Front Med 5:223
14. Ibragimova MK, Tsyganov MM, Litviakov NV (2018) Human papillomavirus and colorectal cancer. Med Oncol 35:140
15. Ibragimova MK, Kokorina EV, Tsyganov MM et al (2021) Human papillomavirus and ovarian cancer (review of literature and meta-analysis). Infect Genet Evol 95:105086
16. Ibragimova MK, Tsyganov MM, Tarabanovskaya NA et al (2018) Clinical observation of HPV-positive breast tumor. Bull Sib Med 17(1):232–238
17. Tsyganov MM, Pevzner AM, Ibragimova MK et al (2019) Human papillomavirus and lung cancer: an overview and a meta analysis. J Cancer Res Clin Oncol 145(8):1919–1937
18. Walboomers JMM, Jacobs MV, Manos MM et al (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189(1):12–19
19. Widschwendter A, Brunhuber T, Wiedemair A et al (2004) Detection of human papillomavirus DNA in breast cancer of patients with cervical cancer history. J Clin Virol 31:292–297
20. Yao X, Xu Z, Duan C et al (2023) Role of human papillomavirus and associated viruses in bladder cancer: an updated review. J Med Virol 95(9):1–15
21. Shigehara K, Sasagawa T, Namiki M et al (2014) Human papillomavirus infection and pathogenesis in urothelial cells: a mini-review. J Infect Chemother 20(12):741–747
22. Sorlózano A, Moraga AI, Pareja M et al (2009) Detection and genotyping by microarray of human papillomavirus in tissue of bladder and bladder carcinoma biopsy. Bladder Cancer Etymol Diagn Treat 8:1–15
23. Li N, Yang L, Zhang Y et al (2011) Human papillomavirus infection and bladder cancer risk: a meta-analysis. J Infect Dis 204(2):217–223
24. Moher D, Liberati A, Tetzlaff J et al (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8(5):336–341
25. Kim KH, Kim YS (1995) Analysis of p53 tumor suppressor gene mutations and human papillomavirus infection in human bladder cancers. Yonsei Med J 36(4):322–331
26. Smetana Z, Keller T, Leventon-Kriss S et al (1995) Presence of human papilloma virus in transitional cell carcinoma in Jewish population in Israel. Cell Mol Biol (Noisy-le-Grand, France) 41(8):1017–1023
27. LaRue H, Simoneau M, Fradet Y (1995) Human papillomavirus in transitional cell carcinoma of the urinary bladder. Clin Cancer Res 1(4):435–440
28. Lopez-Beltran A, Munoz E (1995) Transitional cell carcinoma of the bladder: low incidence of human papillomavirus DNA detected by the polymerase chain reaction and in situ hybridization. Histopathology 26(6):565–569
29. Gopalkrishna V, Srivastava AN, Hedau S et al (1995) Detection of human papillomavirus DNA sequences in cancer of the urinary bladder by

in situ hybridisation and polymerase chain reaction. Sex Transm Infect 71(4):231–233
30. Tenti P, Zappatore R, Romagnoli S et al (1996) p53 overexpression and human papillomavirus infection in transitional cell carcinoma of the urinary bladder: correlation with histological parameters. J Pathol 178(1):65–70
31. Lopez-Beltran A, Escudero AL, Vicioso L et al (1996) Human papillomavirus DNA as a factor determining the survival of bladder cancer patients. Br J Cancer 73(1):124–127
32. Mvula M, Iwasaka T, Iguchi A et al (1996) Do human papillomaviruses have a role in the pathogenesis of bladder carcinoma? J Urol 155(2):471–474
33. Ludwig M, Köchel HG, Fischer C et al (1996) Human papillomavirus in tissue of bladder and bladder carcinoma specimens. Eur Urol 30:96–102
34. Wang DL, et al. (1996) A preliminary study on the relationship between human papillomavirus infection and bladder cancer. Journal of Chongqing Medical University. 21(10):49–51. https://www.cqvip.com/qk/91955x/1996t10/5218229.html
35. Hui W, Ciling C, Zhenhua G, et al (1996) High risk human papillomavirus and P53 protein expression in bladder cancer. China Oncol 3. https://www.cqvip.com/qk/94871x/199604/2127445.html
36. Zengjun W, Guocai Y, Shanzhang F, et al (1996) A study on the relationship between infection of human papillomavirus and the incidence of bladder carcinoma. Acta Acad Med Nanjing. https://www.cqvip.com/qk/95589a/199605/2117265.html
37. Cooper K, Haffajee Z, Taylor L (1997) Human papillomavirus and schistosomiasis associated bladder cancer. Mol Pathol 50(3):145
38. Chan KW, Wong KY, Srivastava G (1997) Prevalence of six types of human papillomavirus in inverted papilloma and papillary transitional cell carcinoma of the bladder: an evaluation by polymerase chain reaction. J Clin Pathol 50(12):1018–1021
39. Aynaud O, Tranbaloc P, Orth G (1998) Lack of evidence for a role of human papillomaviruses in transitional cell carcinoma of the bladder. J Urol 159(1):86–90
40. Gazzaniga P, Vercillo R, Gradilone A et al (1998) Prevalence of papillomavirus, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus type 2 in urinary bladder cancer. J Med Virol 55(4):262–267
41. Ya LSWHG (1998) Expression of human papillomavirus complex in bladder cancer. Chin J Clin Oncol 08:591–592. https://caod.oriprobe.com/articles/2101835/duo_xing_bie_ren_ru_tou_liu_bing_du_zai_bang_zuo_a.htm
42. Chaomei TWXYL, Wenbin YWQ (1998) Detection of virus genes in carcinoma of bladder by polymerase chain reaction. Acta Acad Med Neimongol 04:25–27. https://caod.oriprobe.com/articles/37154651/ju_he_mei_lian_fan_ying_jian_ce_bang_zuo_ai_zu_zhi.htm
43. Giudici C, Ferrario D, Forlani N et al (1998) Study of human papillomavirus via chemiluminescence technic and polymerase chain reaction in transitional cell carcinoma of the bladder. Pathologica 90(6):776–782
44. Simoneau M, LaRue H, Fradet Y (1999) Low frequency of human papillomavirus infection in initial papillary bladder tumors. Urol Res 27(3):180–184
45. Tekin MJ, Tuncer S, Aki FT et al (1999) Human papillomavirus associated with bladder carcinoma? Analysis by polymerase chain reaction. Int J Urol 6(4):184–186
46. Dinghai W, Xinggao FZL (1999) Human papillomavirus and bladder carcinoma. J Clin Urol 3:119–120. https://qikan.cqvip.com/Qikan/Article/Detail?id=3470087&from=Qikan_Search_Index
47. Chen T, Kong Q, Cao H (2000) The study on relation of human papillomavirus and P53 expression with bladder transitional cell carcinoma. Chin J Exp Clin Virol 14(4):345–348
48. Sur M, Cooper K, Allard U (2001) Investigation of human papillomavirus in transitional cell carcinomas of the urinary bladder in South Africa. Pathology 33(1):17–20
49. Fioriti D, Pietropaolo V, Dal Forno S et al (2003) Urothelial bladder carcinoma and viral infections: different association with human polyomaviruses and papilloma viruses. Int J Immunopathol Pharmacol 16(3):283–288
50. Khaled HM, Bahnassi AA, Zekri ARN et al (2003) Correlation between p53 mutations and HPV in bilharzial bladder cancer. Urol Oncol Semin Orig Investig 21(5):334–341
51. Barghi MR, Hajimohammadmehdiarbab A, Hosseini Moghaddam SMM et al (2005) Correlation between human papillomavirus infection and bladder transitional cell carcinoma. BMC Infect Dis 5(1):1–5
52. Youshya S, Purdie K, Breuer J et al (2005) Does human papillomavirus play a role in the development of bladder transitional cell carcinoma? A comparison of PCR and immunohistochemical analysis. J Clin Pathol 58(2):207–210
53. Moonen PMJ, Bakkers JMJE, Kiemeney LALM et al (2007) Human papilloma virus DNA and p53 mutation analysis on bladder washes in relation to clinical outcome of bladder cancer. Eur Urol 52(2):464–469
54. Badawi H, Ahmed H, Ismail A et al (2008) Role of human papillomavirus types 16, 18, and 52 in recurrent cystitis and urinary bladder cancer among Egyptian patients. Medscape J Med 10(10):232
55. Eslami G, Golshani M, Rakhshon M (2008) The study on relation of human papillomavirus with bladder transitional cell carcinoma. Cancer Ther 6:355–360
56. Shigehara K, Kawaguchi S, Mizokami A et al (2010) Human papillomavirus prevalence in bladder cancer: Molecular and pathological analysis. Cancer Res 70(8 Suppl):Abstract nr 5351
57. Cai T, Mazzoli S, Meacci F et al (2011) Human papillomavirus and non-muscle invasive urothelial bladder cancer: potential relationship from a pilot study. Oncol Rep 25(2):485–489
58. Shigehara K, Sasagawa T, Kawaguchi S et al (2011) Etiologic role of human papillomavirus infection in bladder carcinoma. Cancer 117(10):2067–2076
59. Selma WB, Ziadi S, Gacem RB et al (2010) Investigation of human papillomavirus in bladder cancer in a series of Tunisian patients. Pathol Res Pract 206(11):740–743
60. Yavuzer D, Karadayi N, Salepci T et al (2011) Role of human papillomavirus in the development of urothelial carcinoma. Med Oncol 28(3):919–923
61. Xiao J, Zhu X, Hao GY et al (2011) Association between urothelial carcinoma after renal transplantation and infection by human papillomavirus types 16 and 18. Transpl Proc 43(5):1638–1640
62. Barghi MR, Rahjoo T, Borghei M, et al (2012) Association between the evidence of human papilloma virus infection in bladder transitional cell carcinoma in men and cervical dysplasia in their spouses. Arch Iran Med 15(9)
63. Panagiotakis GI, Papadogianni D, Chatziioannou MN et al (2013) Association of human herpes, papilloma and polyoma virus families with bladder cancer. Tumor Biol 34(1):71–79. https://doi.org/10.1007/s13277-012-0512-2
64. Steinestel J, Cronauer MV, Müller J et al (2013) Overexpression of p16 INK4a in urothelial carcinoma in situ is a marker for MAPK-mediated epithelial-mesenchymal transition but is not related to human papillomavirus infection. PLoS ONE 8(5):e65189
65. Berrada N, Al-Bouzidi A, Ameur A et al (2013) Human papillomavirus detection in Moroccan patients with bladder cancer. J Infect Dev Ctries 7(8):586–592
66. Kim SH, Joung JY, Chung J et al (2014) Detection of human papillomavirus infection and p16 immunohistochemistry expression in bladder cancer with squamous differentiation. PLoS ONE 9(3):e93525
67. Schmid SC, Thümer L, Schuster T et al (2015) Human papilloma virus is not detectable in samples of urothelial bladder cancer in a central European population: a prospective translational study. Infect Agents Cancer 10(1):1–6
68. Pichler R, Borena W, Schäfer G et al (2015) Low prevalence of HPV detection and genotyping in non-muscle invasive bladder cancer using single-step PCR followed by reverse line blot. World J Urol 33(12):2145–2151
69. Mete UK, Shenvi S, Singh MP et al (2018) Human papillomavirus in urothelial carcinoma of bladder: an Indian study. Int J Appl Basic Med Res 8(4):217
70. Badawi H, Abass M, Hamam O, et al (2018) Molecular and in-situ hybridization detection of human papillomavirus genotypes among Egyptian patients with bladder cancer. Int J Pharm Res 10(4):402–405. https://eds.p.ebscohost.com/abstract?site=eds&scope=site&jrnl=09752366&AN=135154619&h=WuBn3EJqkCkXkM0fVBSK8sWMGVzLJJ1pxp7rnNSgINTA3ks8fOOPRl%2fCCSuXSU0T7WRDgYoYVNxgORdZQ8hBWg%3d%3d&crl=c&resultLocal=ErrCrlNoResults&resultNs=Ehost&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d09752366%26AN%3d135154619

71. Llewellyn MA, Gordon NS, Abbotts B et al (2018) Defining the frequency of human papillomavirus and polyomavirus infection in urothelial bladder tumors. Sci Rep 8(1):1–6
72. Kosova IV, Loran OB, Sinyakova LA et al (2018) Immunohistochemical characteristics of bladder cancer in patients with virus-positive tumors. Cancer Urol 14(2):142–154
73. Yıldızhan M, Koçak İ, Kırdar S et al (2020) Detection of human papillomavirus using polymerase chain reaction methods in transitional urothelial bladder cancer. Ann Clin Anal Med 12:353–357
74. Moghadam SO, Mansori K, Nowroozi MR et al (2020) Association of human papilloma virus (HPV) infection with oncological outcomes in urothelial bladder cancer. Infect Agents Cancer 15(1):1–8
75. Yan Y, Zhang H, Jiang C et al (2020) Human papillomavirus prevalence and integration status in tissue samples of bladder cancer in Chinese population. J Infect Dis 224(1):114–122
76. Gordetsky J, Spieker AJ, Pena MCR et al (2020) Squamous cell carcinoma of the bladder is not associated with high-risk HPV. Urology 144:158–163
77. Zykova TA, Shevchenko AN, Khomutenko IA, et al (2020) Studying the interrelation between the HPV infection status and the morphological features of bladder cancer. J Clin Oncol 38(15). https://doi.org/10.1200/JCO.2020.38.15_suppl.e17003
78. Hou L, Hong X, Dai M et al (2017) Association of smoking status with prognosis in bladder cancer: a meta-analysis. Oncotarget 8(1):1278
79. Jørgensen KR, Jensen JB (2020) Human papillomavirus and urinary bladder cancer revisited. APMIS 128(2):72–79
80. Khatami A, Salavatiha Z, Razizadeh MH (2022) Bladder cancer and human papillomavirus association: a systematic review and meta-analysis. Infect Agents Cancer 17(3):1–9
81. Sun J-X, Xu J-Z, Liu C-Q et al (2022) The association between human papillomavirus and bladder cancer: evidence from meta-analysis and two-sample mendelian randomization. J Med Virol 95(1):1–38
82. Reinstatler L, Shee K, Stensland K et al (2019) MP05-12 re-examining an old trend: the association of human papillomavirus and bladder cancer. J Urol 201(Supplement 4):e44–e44

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.