Meta-Analysis of Studies Analyzing the Relationship Between Bladder Cancer and Infection by Human Papillomavirus

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Purpose: Studies have been done of the possibility that infection by human papillomavirus is a risk factor contributing to bladder cancer but no definite conclusions have yet been drawn. We performed a meta-analysis of observational studies published until July 2005 to ascertain the degree of association between bladder cancer and human papillomavirus infection.
Materials and Methods: The MEDLINE database was searched using the key words bladder cancer and virus. Strict criteria were applied to select studies revealing the prevalence in serum of human papillomavirus infection or its direct detection in patients. A total of 44 articles with these methodological criteria were chosen.
Results: In 39 studies the investigators determined the presence of human papillomavirus DNA, and found a prevalence of between 0% and 100% and significant homogeneity analysis ($p < 0.001$). Pooled estimation of the presence of the infection was 16.0% (95% CI 12.8 to 19.1). Pooled OR estimation was 2.3 (95% CI 1.3 to 4.1) with no significant publication bias. In 7 studies human papillomavirus infection was studied by detecting the antigen or antibodies and a prevalence of between 14% and 60% was found with significant homogeneity analysis ($p < 0.001$). Pooled estimation of the prevalence of infection was 32.4% (95% CI 17.0 to 47.8). Pooled OR estimation was 2.9 (95% CI 1.7 to 5.3).
Conclusions: Finding a relationship between bladder cancer and human papillomavirus depends on the method used. In the literature examined there are insufficient cases and samples compared to controls and studies rely on a combination of various microbiological techniques in the same patient and sample, making it difficult to draw any definite conclusion.

Key Words: bladder; bladder neoplasms; papillomavirus, human; chronic disease

Bladder cancer forms a heterogeneous group of carcinomas, including lesions with different pathobiological behaviors. To date mechanisms associated with the initiation and evolution of these tumors together with any possible risk factors involved have been largely unknown.[1] Numerous groups have attempted to ascertain the carcinogenic risks of viruses such as HPV and many have produced contradictory results[2] because they related the virus to different sites in the body. In regard to bladder cancer, few studies to date have related infection with HPV to an increased risk of its development. Any possible relationship is based on the epithelial tropism of HPV and the anatomical proximity of the urogenital zone. Thus, the debate remains open as to whether there is any direct link between chronic HPV infection and bladder cancer or whether it is purely coincidental. Despite all of the research performed to date most studies have arrived at no sufficiently convincing conclusions to be applied in the treatment of bladder cancer and to our knowledge no meta-analysis has been performed to evaluate any such possible relationship. In this context we located and studied international series published until July 2005 of the possible relationship between bladder cancer and HPV. We describe a methodical approach to a meta-analysis of the results. We determined what conclusions may have been reached concerning the relationship between the virus and the cancer in question. It is hoped that such a systematic analysis of the results may afford new conclusions to help direct future research.

MATERIALS AND METHODS

An open search of the MEDLINE database using the key words bladder cancer and virus retrieved 202 articles published before June 2005. Subsequent selection was made of 44 articles published in English, Spanish or French of the relationship between HPV and bladder cancer using a described methodology.[3–46] Clinical cases were excluded. A search of the references of the chosen articles confirmed that no studies had been missed. Because of the wide diversity of the studies, they were stratified according to the laboratory test used.

This meta-analysis has a qualitative and quantitative component. The former is an epidemiological description of the articles with the individual studies considered the research subject, while the latter corresponds to a statistical pooling of results showing OR estimations with a weighting of estimations of individual studies, providing a 95% CI for the OR. Weighting is expressed as the percent weighting of the study compared to the weighting of all articles under consideration. The DerSimonian-Laird method[47] was used to pool values reported in the studies because it provides overall estimations that are least affected by heterogeneity. This heterogeneity was measured using the corresponding

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TABLE 1. *Studies based on HPV DNA*

References	No. Cases (estimated %)/Total No.	No. Controls (%)/Total No. (type)	Tissue	Assay	Genotype Studied (region)	Gene β-Globulin Detection
Agliano et al[3]	11 Type 16, 5 type 18, 7 type 16/18 (50)/46 TCC	0/10 (healthy bladder)	Fixed	Selective PCR + dot blot H	16, 18 (E6)	Yes
Anwar et al[5]	39 (81.3)/46 TCC, 2 SCC	7 (33)/21 (healthy bladder)	Fixed	PCR, dot blot H + SB-H	6, 11, 16, 18, 33 (E6)	Yes
Aynaud et al[4]	0 (0.9)/57 TCC	1—6 (100)/1 (bladder condyloma)	Frozen	SB-H, PCR + dot blot H	6, 11, 16, 18, 31, 33, 35, 39, 42 (L1, E1, E2, E6)	Not indicated
Boucher et al[6]	0 (0.9)/54 TCC, 1 SCC	0/0	Fixed	Dot blot H P32	6, 11, 16 (not indicated)	Not indicated
Bryant et al[8]	12 Type 16/18 (13)/66 deep, 10 superficial + 2 deep/superficial TCC, 3 SCC, 4 Adc, 7 undifferentiated Ca	0/8 (3 dysplasia, 5 benign tumor)	Fixed	H in situ	6b, 11, 16, 18 (not indicated)	Not indicated
Cooper et al[12]	0 (1.9)/25 SCC	0/0	Not indicated	H in situ + PCR	6, 11, 16, 18, 31, 33 (E6)	Yes
Chan et al[9]	13 Type 18 (65)/20 TCC	1—16, 6—18 (70)/10 (inverted papilloma)	Fixed	PCR + dot blot H	6, 11, 16, 18, 31, 33 (E6)	Yes
Chang et al[10]	0 (0.5)/108 TCC	0/0	Fixed	PCR + SB-H	6, 11, 16, 18, 31, 33, 35, 39, 40, 45, 51, 59 (L1)	Yes
Chetsanga et al[11]	1 Type 16 (2.3)/44 TCC	0/0	Frozen	PCR + dot blot H	Generic (L1)	Not indicated
Fioriti et al[13]	1 Type 6 (3.1)/32 not indicated	0/20 (healthy bladder)	Not indicated	H in situ	16, 18, 33 (not indicated)	Not indicated
Furihata et al[14]	28 Types 16, 18, 33 (31.1)/90 TCC	0/0	Fixed	H in situ	6/11, 16/18, 31/33/35 (not indicated)	Not indicated
De Gaetani et al[15]	17 (3 type 6/11, 6 type 16/18, 10 types 31/33/35) (39.5)/43 TCC	0/0	Fixed	PCR + restriction fragment length polymorphism	Generic (L1)	Yes
Gazzaniga et al[16]	8 Type 16, 8 type 18 (45.7)/35 TCC	0/10 (healthy bladder)	Frozen	PCR + dot blot H	16, 18 (not indicated)	Yes
Gopalkrishna et al[17]	3 Type 16 (30)/10 TCC	0/0	Not indicated	H in situ + PCR	16 (upstream regulatory region)	Not indicated
Tekin et al[18]	2 Type 16 (4.8)/42 TCC	0/10 (healthy bladder)	Not indicated	Selective PCR	16, 18 (L1)	Not indicated
Khaled et al[20]	31 Type 16, 9 type 18, 3 type 6/11, 5 type 16/18 (48.5)/99 not indicated	0/0	Frozen	General + selective PCR	6, 11, 16, 18, 33 (L1)	Not indicated
Khaled et al[21]	23 (46)/23 SCC, 22 TCC, 3 Adc, 7 undifferentiated Ca	0/0	Fixed	H in situ	16/18 (not indicated)	Not indicated
Kamel et al[22]	27 (19 type 31, 16 type 18, 13 type 33, 10 type 16, 10 type 11, 13 type 6) (57.4)/40 TCC, 7 SCC	0/0	Fixed	H in situ	6, 11, 16, 18, 31, 33 (not indicated)	Not indicated
Kerley et al[19]	1 Type 11 (4.5)/18 TCC, 3 SCC, 1 Adc	0/5 (healthy bladder)	Fixed	H in situ + selective PCR	6, 11, 16, 18, 31, 33, 35 (not indicated)	Yes
Kitamura et al[23]	1 Type 16 (10)/9 TCC, 1 Adc	0/0	Not indicated	PCR + dot blot H	1, 2, 6, 11, 16, 18 (not indicated)	Not indicated
Knowles et al[24]	TCC, 6 Ca in situ, 2 Adc, 1 SCC, 11 undifferentiated Ca	0/3 (cystitis)	Frozen	PCR + SB-H	6, 8, 11, 16, 18, 33 (L1, E1)	Not indicated
LaRue et al[26]	28 Types 11 + 16 (39.4)/71 not specified	0/8 (healthy bladder)	Frozen	PCR + H in situ	6, 11, 16, 18, 31, 33, 35 (not indicated)	Not indicated
López-Beltrán et al[28]	12 Types 16 + 18 (15.8)/76 TCC	0/0	Fixed	H in situ	6/11, 16/18, 31/33/35 (not indicated)	Not indicated
López-Beltrán et al[29]	7 Types 16 + 18 (9.2)/76 TCC	0/0	Fixed	PCR + SB-H	6, 11, 16, 18 (L1, E5, E6)	Yes
López-Beltrán and Munoz[27]	11 Types 16 + 18 (14.5)/76 TCC	0/0	Fixed	PCR + H in situ	31/33/35 (L1, E5, E6)	Not indicated
Lu et al[30]	0 (1.6)/22 TCC, 4 Adc, 5 SCC	0/0	Fixed	H in situ	16, 18 (not indicated)	Not indicated
Ludwig et al[31]	6 Type 6b (26.1)/21 TCC, 1 Adc, 1 SCC	3—6b (7.3)/ (32 healthy bladder, 9 chronic cystitis)	Not indicated	PCR + restriction fragment length polymorphism	6b, 11, 16, 18 (L1)	Yes
Maloney et al[32]	1 Type 18 (2.4)/22 SCC, 20 TCC	0/0	Not indicated	Selective PCR	6b, 11, 13, 16, 18, 31, 32, 33, 35, 45, 51 (L1, E6)	Not indicated
Mincione et al[34]	1 Type 31–33–51 (5.6)/18 TCC	0/0	Fixed	H in situ	6/11, 16/18, 31/33/51 (not indicated)	Not indicated
Mvula et al[35]	1 Type 16 (2.8)/34 TCC, 2 SCC	0/0	Fixed	Selective PCR	6, 11, 16, 18, 31, 33, 42, 52, 58 (L1, E7)	Not indicated
Noel et al[36]	2 Type 16 (100)/2 TCC	0/2 (healthy bladder)	Fixed	Selective PCR	6b, 11, 16, 18 (E7)	Not indicated
Saltzstein et al[38]	0 (1.5)/33 TCC	0/0	Not indicated	PCR + SB-H	6, 11, 16, 18, 31, 33 (L1, E1)	Not indicated
Shibutani et al[39]	2 Type 6/11, 1 type 16/18, 1 type 31/33 (19)/20 TCC, 1 SCC	2^k (100)/2 (1 dysplasia, 1 inflamed tissue)	Not indicated	SB-H	6/11, 16/18, 31/33 (L1)	Not indicated

TABLE 1 *(continued)*

References	No. Cases (estimated %)/Total No. (type)	No. Controls (%)/Total No. (type)	Tissue	Assay	Genotype Studied (region)	Gene β-Globulin Detection
Simoneau et al[25]	16 (9 type 16, 1 type 11, 4 type 6, 4 type 18) (8.6)/187 TCC	0/0	Frozen	PCR + SB-H/dot blot H	6, 11, 16, 18, 33 (L1)	Not indicated
Smetana et al[40]	20 (33.9)/59 TCC	2 (4.9)/41 (nontumor tissue from case)	Fixed	H in situ + PCR	6/11, 16/18 (E1)	Not indicated
Sur et al[41]	1 (1.6)/64 TCC	0/0	Not indicated	PCR + H in situ	6, 11, 16, 18, 31, 33 (L1)	Yes
Tenti et al[42]	26 Types 16 + 18 (32.9)/79 TCC	0/0	Fixed	PCR + SB-H	6, 11, 16, 18, 33 (E6, E7)	Yes
Yang et al[43]	24 Type 16 (100)/24 not indicated	0/0	Not indicated	MassARRAY®	16, 18 (E7)	Yes
Youshya et al[44]	0 (0.6)/78 TCC	0/0	Fixed	PCR	Generic (L1)	Not indicated
Westenend et al[45]	0 (2.9)/16 SCC	0/0	Fixed	H in situ	6/11, 16/18, 31/33/51 (not indicated)	Not indicated
Wilczynski et al[46]	1 Type 6 (4.5)/22 SCC	0/0	Frozen	PCR + SB-H	6, 11, 16, 18 (L1, E7)	Yes

chi-square test (Q_{exp}). Possible publication biases were examined using Begg's test,[48] which assigns a higher value for lower publication bias. No relationship was considered to exist between exposure to HPV and bladder cancer when the CI included unity.[49] Statistical analysis was performed using STATA® 8.1.

RESULTS

Results are presented by separating the publications into 2 classes according to differences in approach, including 1) those using DNA based studies and 2) those not relying on DNA evidence.

DNA Based Studies

Determining HPV infection. Table 1 lists the names of the authors of 39 studies, material used (mainly transitional cell carcinoma biopsies), methods and results. In most of these cases PCR was used, although only 14 studies (35.9%) used internal genetic extraction and amplification control via β-globulin and only 8 (20.5%) used biopsies of frozen tissue. However, some groups used specific internal amplification controls to increase assay specificity.[10,22,41,43,44] Amplified regions were also different and the genotype detected is reported, mainly types 16 and 18 (fig. 1).

These investigators found a prevalence of between 0% and 100%, although there were few cases at the latter end of the scale. Homogeneity analysis among studies produced a significant result (Q_{exp} 723.3, 38 g. l., $p < 0.001$), thus, showing that not all estimations were similar. The DerSimonian-Laird method[47] indicated that the pooled estimation of the HPV infection prevalence was 16.0% (95% CI 12.8 to 19.1). To rule out any possibility that the apparent significant heterogeneity might have been due to PCR the analysis was repeated, this time distinguishing between the 27 cases that used PCR (15.3%, 95% CI 11.7 to 18.9) and the 12 that did not (18.2%, 95% CI 10.3 to 26.1). This proved that PCR did not give rise to significantly different prevalence values and it did not appear to be the cause of significant heterogeneity among studies.

Determining the pooled estimation of the link between HPV infection and bladder cancer. The pooled estimation between HPV and bladder cancer was determined using the method described, first with those studies presenting

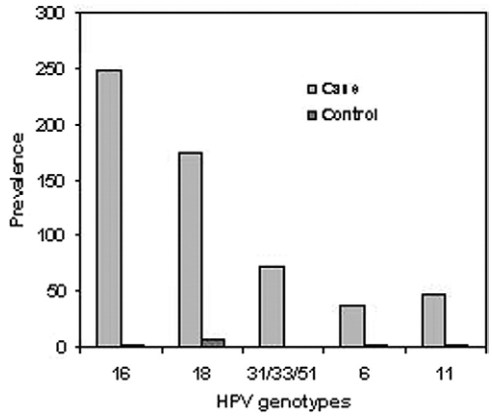

FIG. 1. Prevalence of HPV genotypes in patients with bladder cancer.

definite cases and controls, and then separately with those that did and did not include PCR. A total of 13 studies included descriptions of cases and controls, which in the heterogeneity test showed Q_{exp} 13.2, 12 g. l. (p = 0.356). Thus, there was considerable similarity with little dispersion in the results and no discrepancy among them in regard to the OR. Pooled OR estimation showed a value of 2.3 (95% CI 1.3 to 1.4), indicating a clear association between bladder cancer and HPV exposure, as determined via DNA studies. Figure 2 shows each study together with its estimated OR, its CI range and the weighting assigned to the pooled estimation according to the DerSimonian-Laird method.[47] Begg's test, which was designed to indicate publication bias, proved to be insignificant (p = 0.542).

Analysis of studies using PCR produced a pooled estimation of 2.7 (95% CI 1.5 to 4.6) with no significant difference among studies (Q_{exp} 8.0, 9 g. l., p = 0.531, fig. 3). The estimation of studies that did not use this technique was 1 of 0.7 (95% CI 0.1 to 3.9) with no significant difference among studies (Q_{exp} 2.4, 2 g. l., p = 0.304, fig. 4). These results do not lead to any clear conclusion as to whether the 2 estimations (with and without PCR) are significantly different. However, it could be seen that when PCR was not used, the estimation was considerably lower. The results of Begg's test proved that it was insignificant whether PCR had been used (p = 0.788 and 0.602, respectively). Thus, there was no evidence of publishing bias in these studies.

Studies Not Based on DNA Analysis

Determining the prevalence of viral infection in the cases. Table 2 lists author names, the material used (mainly transitional cell carcinoma), methods and results. Five of the 7 studies detected viral capsid antigen and 2 showed antibodies in serum by Western blotting. The prevalence of infection was between 14% and 60% of cases, although the number of studies involved included few cases. Analysis of homogeneity among studies proved to be significant (Q_{exp} 71.6, 6 g. l., p <0.001), revealing that they did not show similar estimations and there was considerable disparity in results. According to the DerSimonian-Laird method[47] pooled estimation of the viral infection prevalence calculated via the detection of antigens or antibodies was 1 of 32.4% (95% CI 17.0% to 47.8%).

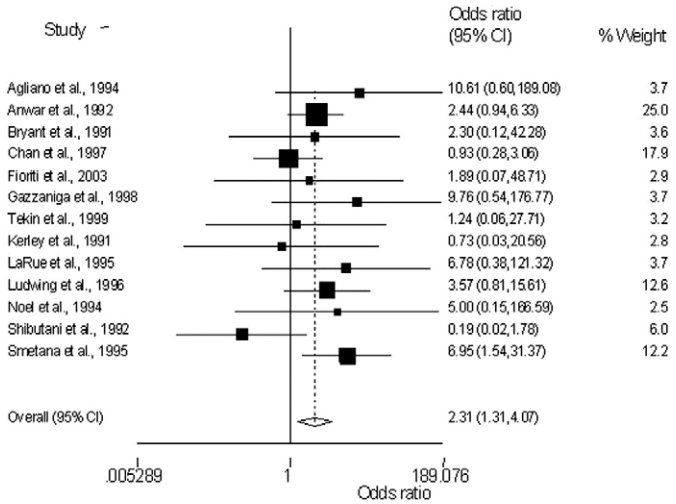

FIG. 2. DNA studies used to find pooled estimation of link between HPV infection and bladder cancer with estimated OR, reliability range and assigned weighting. *Angliano et al., 1994*, Angliano et al.[3] *Anwar et al., 1992*, Anwar et al.[5] *Bryant et al., 1991*, Bryant et al.[8] *Chan et al., 1997*, Chan et al.[9] *Fioriti et al., 2003*, Fioriti et al.[13] *Gazzaniga et al., 1998*, Gazzaniga et al.[16] *Tekin et al., 1999*, Tekin et al.[18] *Kerley et al., 1991*, Kerley et al.[19] *LaRue et al., 1995*, LaRue et al.[26] *Ludwing et al., 1996*, Ludwig et al.[31] *Noel et al., 1994*, Noel et al.[36] *Shibutani et al., 1992*, Shibutani et al.[39] *Smetana et al., 1995*, Smetana et al.[40]

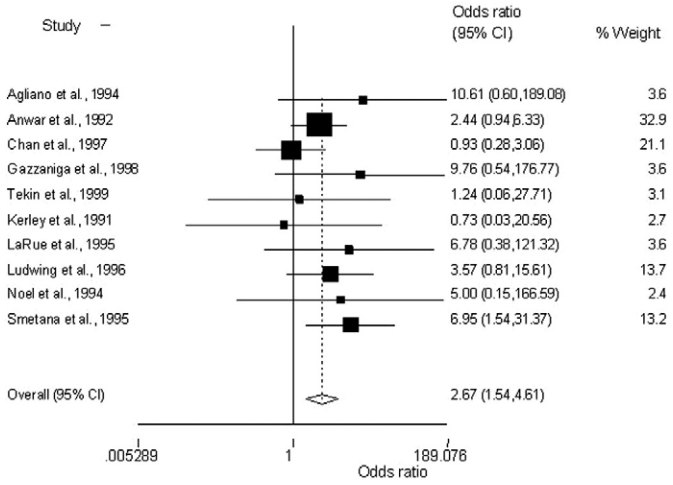

FIG. 3. PCR studies used to find pooled estimation of link between HPV infection and bladder cancer with estimated OR, reliability range and assigned weighting. *Angliano et al., 1994*, Angliano et al.[3] *Anwar et al., 1992*, Anwar et al.[5] *Chan et al., 1997*, Chan et al.[9] *Gazzaniga et al., 1998*, Gazzaniga et al.[16] *Tekin et al., 1999*, Tekin et al.[18] *Kerley et al., 1991*, Kerley et al.[19] *LaRue et al., 1995*, LaRue et al.[26] *Ludwing et al., 1996*, Ludwig et al.[31] *Noel et al., 1994*, Noel et al.[36] *Smetana et al., 1995*, Smetana et al.[40]

Determining the pooled estimation of the link between HPV infection and bladder cancer. Pooled estimation of the link between HPV and bladder cancer was determined according to the method described for all studies that presented defined cases and controls. Three articles described cases and controls that produced a nonsignificant heterogeneity test (Q_{exp} 1.8, 2 g. l., p = 0.409). Thus, there was considerable similarity among studies and no discrepancy among them in regard to OR. The pooled OR estimation resulted in a value of 2.9 (95% CI 1.7 to 5.3). Figure 5 shows each study with its estimated OR and CI, and the weighting given to the pooled estimation.

DISCUSSION

Certain aspects of bladder cancer in its various histological forms are still unknown, such as whether a predetermining genetic factor is involved in its development, although various oncogenes are involved, and what other risk factors might be to blame. This hinders any effort to mount an efficient prevention campaign. In this study we intended to find out more about possible cofactors in the development of the cancer. Thus, we studied HPV, which has been mentioned in the literature as a possible etiological agent.

Q_{exp} values from the analysis of studies that did and did not use DNA, including those using PCR to detect the virus and those using an alternative method, revealed considerable dispersion among the data. Thus, to arrive at an overall OR that might lead to an approximate conclusion we con-

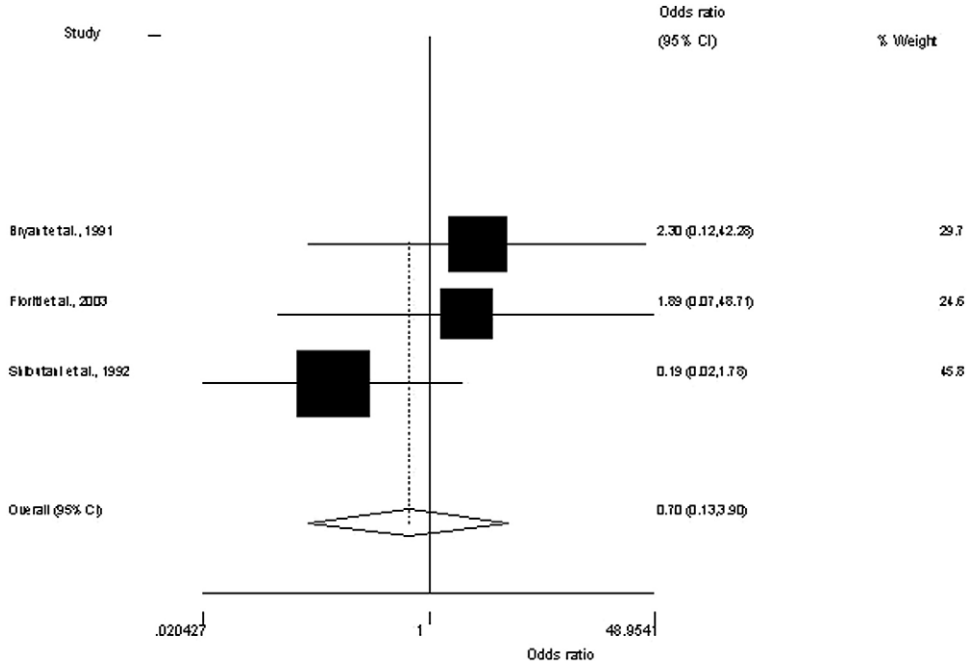

FIG. 4. DNA detection without PCR studies used to find pooled estimation of link between HPV infection and bladder cancer with estimated OR, reliability range and assigned weighting. *Bryant et al., 1991*, Bryant et al.[8] *Fioriti et al., 2000*, Fioriti et al.[13] *Shibutani et al., 1992*, Shibutani et al.[39]

centrated on only 16 studies with a defined control group that showed little dispersion within their results. The result of this analysis seemed to be positive. The 13 studies chosen from those relying on DNA detection revealed a clear link between HPV exposure and bladder cancer.

In studies that did and did not rely on DNA identification the OR estimation was fairly similar, which would indicate a certain stability among techniques and allow us to presume that the findings are consistent. In some cases the level of significance and weighting are not in accordance with each other. As mentioned, this is due to the fact that there is no homogeneity among the parameters analyzed in all studies because each group referred to a different number of cases and controls (none in most articles). This situation was considered by the meta-analysis and it has no bearing on the calculation of the results. It is merely informative.

In the last few years the microbiological tests used to detect HPV infection have seen changes. Today it is most common to use PCR but this should not detract from other techniques that rely on the host response or detect the virus in situ, of which the sensitivity and reliability have been compared. This was done in only a few studies. Thus, in principle the validity of the results is in no doubt. In support of this fact is the satisfactory relationship between the results obtained by Ludwig et al, who used direct and indirect results to detect infection.[31] However, another question is that of explaining the link between infection and cancer. The virus may have been present in the lesion as an instigating factor after being acquired during sexual relations but this does not rule out the fact that it may represent secondary tumor colonization since it forms a normal part of the mucous membranes.

This retrospective study of the published results of HPV involvement in bladder cancer leads to some interesting conclusions. Of the conclusions is that comparisons among studies can be complicated by various factors. 1) The different populations studied may have different risk factors, such as genetics, geography and life-style, of which any might affect carcinoma development in the bladder epithelium. 2) Different researchers often use different techniques with varying specificity and sensitivity. 3) Technical mistakes

TABLE 2. *Studies based on detection of antigen and Abs against virus*

References	No. Cases (estimated %)/Total No.	No. Controls (%)/Total No.	Tissue	Assay (gene)
Bryant et al[7]	7 (14)/16 SCC, 2 superficial + 32 deep TCC	0/0	Fixed	IPO, anti-capsid Ab
López-Beltrán et al[28]	25 (32.9)/76 TCC	0/0	Fixed	IPO, anti-capsid Ab
Roussel et al[37]	1 (16.7)/6 TCC	0/0	Not indicated	IPO, anti-capsid Ab
Smetana et al[40]	19 (17.3)/110 TCC	0/41 (nontumor tissue from cases)	Fixed	IPO, anti-capsid Ab
Youshya et al[44]	47 (60.2)/78 TCC	0/0	Fixed	IPO, anti-capsid Ab
Ludwig et al[31]	1 Ab anti-HPV 16, 1 Ab anti-HPV 6b, 1 Ab anti-HPV 16/18, 2 Abs anti-HPV 18 (21.7)/21 TCC, 1 Adc, 1 SCC	1 Ab anti-HPV 18, 1 Ab anti-HPV 16 (4.9)/41 (32 healthy bladder, 9 chronic systitis)	Serum	Western blot, antigen of types 6b (L1, L2), 16 (L2, E4, E7) y 18 (L2, E7)
Mantovani et al[33]	27 (60)/45 TCC	28 (23.1)/121 (75 healthy bladder, 46 nonneoplasic lesion)	Serum	Enzyme-linked immunosorbent assay + Western blot, genus antigen

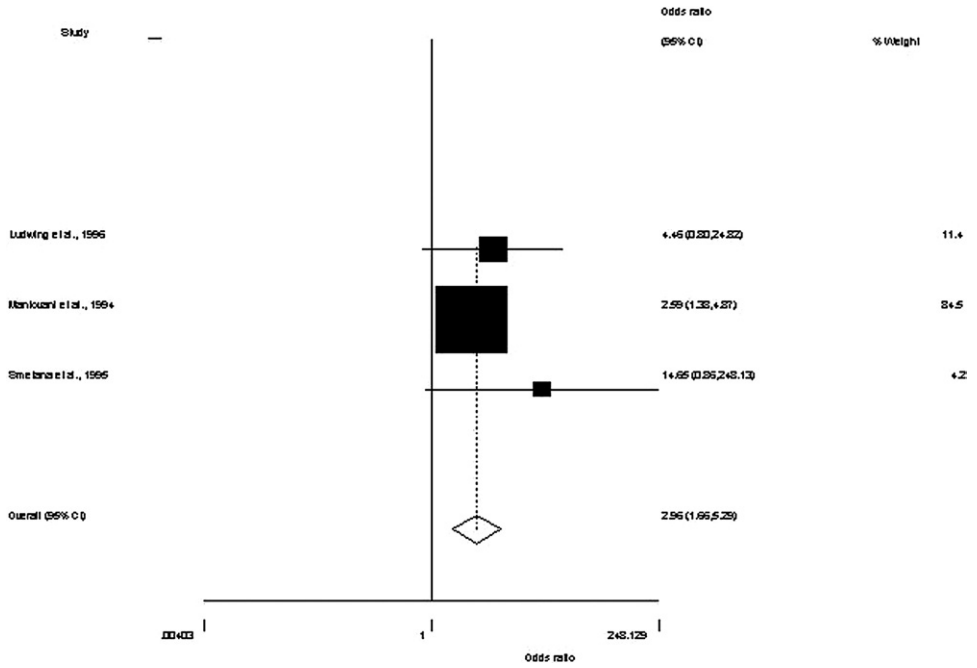

FIG. 5. No detection DNA studies used to find pooled estimation of link between HPV infection and bladder cancer with estimated OR, reliability range and assigned weighting. *Ludwig et al., 1996*, Ludwig et al.[31] *Mantovani et al., 1994*, Mantovani et al.[33] *Smetana et al., 1995*, Smetana et al.[40]

made by the laboratory investigator or even the choice of the right primer could affect the experimental results. Thus, current diagnostic methods such as biopsy specimens may well provide low numbers of HPV genomes and they are often inconclusive for identifying the specific HPV strain, encouraging researchers to further examine universal detection methods using DNA. The most invalid results of our study could be due to a lack of HPV test sensitivity. For this reason the intention of HPV experts and the WHO is to establish international biological standard materials for the therapy and diagnosis of human disease. The availability of international HPV DNA standards would contribute to the field of HPV prevention, diagnosis and treatment.[50,51]

CONCLUSIONS

Before July 2005, 44 studies had analyzed the relationship between HPV and bladder cancer. The methods used were not all the same, although most investigators used PCR. Most of these studies revealed HPV, although to considerably different degrees. Although most of them lacked a defined control group, it is still possible to analyze the pooled OR, given the homogeneous behavior of the studies with well defined cases and controls. This showed a moderate relationship between HPV and bladder cancer. To arrive at a more definitive conclusion would require access to studies including a sufficient number of cases and samples compared to controls that used a combination of various microbiological techniques in a single subject and sample. All of this demands further research into the relationship between HPV and bladder cancer via pathogenic studies of the disease.

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Abbreviations and Acronyms

Adc	=	adenocarcinoma
H	=	hybridization
HPV	=	human papillomavirus
IPO	=	immunoperoxidase
PCR	=	polymerase chain reaction
SB-H	=	Southern blot H
SCC	=	squamous cell carcinoma
TCC	=	transitional cell carcinoma

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EDITORIAL COMMENT

In this meta-analysis of 44 published studies HPV DNA was present in 16% of patients with bladder cancer, while HPV infection detected by antigen or antibody to HPV was present in 32%. The odds of concomitant HPV infection in patients with bladder cancer were higher than those observed in controls. These data suggest an association between HPV infection and the risk of bladder cancer.

These authors draw our attention to these provocative findings. However, these results still do not answer the chicken or egg question. Did the HPV infection predate the cancer and, hence, could it be construed as a causative agent? Or is the infection a harmless secondary colonization? Furthermore, association does not equal causation. Nevertheless, these findings are hypothesis generating and they represent an intriguing area for future research. If further, well controlled studies using standardized HPV detection techniques substantiate the earlier findings, this would provide a novel application for the recently developed anti-HPV vaccine for bladder cancer.[1–3]

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