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Prevalence of Human Papilloma Virus in Patients With Colorectal Cancer: A Systematic Review and Meta-analysis

Masoud Dadashi[1], Shaian Tavakolian[2], Ebrahim Faghihloo[2*]

[1]Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
[2]Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding Author:**
Ebrahim Faghihloo, Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran,
Tel: +98 21 2387, 2556;
Fax: +98 21 2387 647;
Email: faghihloo@sbmu.ac.ir, faghihloo@gmail.com,

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Abstract

Background: Human papillomavirus (HPV) is considered as one of the most common carcinogenic viruses in humans throughout the world and is mostly associated with gynecologic malignancies. However, it is also one of the environmental factors that is involved in colorectal cancer (CRC).

Objective: A meta-analysis was performed to investigate the prevalence of HPV infection in patients suffering from the CRC.

Methods: The frequency of the HPV in patients with CRC was studied from 2001 to 2016. To this end, several databases were reviewed, including PubMed, Web of Science, Embase, Cochrane Library, Google Scholar, Iranmedex, and the Scientific Information Database. Then, the analysis was done by Comprehensive Meta-Analysis (V2.0, Biostat) software. Considering heterogeneity between different studies, the random effect model was used and then the results were checked with Cochran's Q-statistic.

Results: The meta-analysis revealed that the frequency of HPV infection in patients with CRC was 33.7% (a 95% CI of 28.4-39.5). The additional stratified analysis also showed that HPV infection in CRC patients was more widespread in European countries compared to Asian and American countries.

Conclusion: The high rate of HPV infection is a major concern in sexually transmitted diseases around the world, therefore, controlling high-risk behaviors, vaccination, screening, and HPV subtyping can be useful in managing HPV infections.

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Background

Human papillomavirus (HPV) is a small virus with double-stranded DNA that is a member of the Papillomaviridae family, namely, a group with a well-recognized etiological role in cervical and vaginal cancer.[1-3] There is evidence for the presence of more than 100 types of HPV in the medical literature. In addition, 15 types of HPV (16, 18, 35, 31, 39, 51, 45, 56, 52, 66, 59, 69, 68, 82, and 73) are considered to be highly involved in the pathogenesis of genital cancer in women while HPVs responsible for the warts of genitals and skin (HPV 6, 11, 43, 42, 40, 44, 61, 54, 72, 70, and 81) have lower pathogenicity.[4-6] Further, HPV is related to other malignancies including anal, oropharyngeal, penile, vulvar, and HPV-related tumors, which together represent 0.7% of carcinomas in both genera.[7] Viruses are one of the factors that can create a condition inside the body which might ultimately lead to the development of gastrointestinal cancer.[8] Furthermore, HPV is considered as one of the microbial factors that could infect the colon and rectum area. According to some studies,[9-11] this virus usually infects hematogenous anogenital sites and it may spread to the other parts of the body through lymphatic ducts, creating a condition suitable for the development of colorectal cancer (CRC). Global statistics indicate that CRC is one of the most common forms of cancer and it is responsible for a vast majority of cancer-related deaths. Based on estimations, there are 1360602 new cases of CRC and 693 881 CRC-related deaths every year.[12,13] According to the first report in 1990, Kirgan et al[14] showed that there is a potential correlation between HPV infection and CRC. Thus, they evaluated the existence of HPV in 73 archival paraffin-embedded colon cancer tissues and 30 samples of normal colon mucosa (as a control group) by immunohistochemical analysis. According to their results, the HPV antigen was detected in approximately 82% and 23% of colon cancer and normal colon specimens, respectively. In addition, they found a relationship between the presence of HPV in colon cancerous tissues and the CRC. Other studies also addressed the connection between HPV infection and the

development of CRC.[15-19] After 2001, many researchers used the polymerase chain reaction technique to detect the HPV within CRC tissue specimens. Although different methods were used in previous studies, most case-control investigations demonstrated a positive correlation between HPV infection and CRC. This correlation could have many serious effects on health care settings and cancer prevention. Therefore, a systematic review and meta-analysis study was conducted to evaluate the prevalence of HPV in patients with CRC in order to assess the relationship between HPV infection and the risk of CRC.

Methods

Literature Search

A complete database of CRC cases was collected that was positive for HPV infection during 2001-2016. Databases were obtained from PubMed, Web of Science, Embase, Cochrane Library, Google Scholar, Iranmedex, and the Scientific Information Database (SID). Further, only original articles, published in English or Persian, were used that presented data on the prevalence of HPV infection in CRC patients worldwide. The keywords used from Medical Subject Headings or titles or the abstracts with the guide of Boolean operators (and, or) included "Human papillomavirus", "HPV", Prevalence", "Colorectal Cancer", along with "Frequency and Incidence". Moreover, the bibliographies of retrieved articles were checked to obtain any additional useful data. Relevant articles written in the Persian language were searched as well.

Inclusion and Exclusion Criteria

All original articles showing cross-sectional studies on the prevalence of HPV in CRC were considered in this study. Additionally, the articles were selected by searching through the article titles, abstracts, and full texts. The inclusion criteria were using standard methods for the molecular testing of HPV and presenting data on the number of enrolled patients. For safety evaluation, the studies were included if they were conducted on more than 100 subjects. Similarly, review articles, studies drafted in languages other than English or Persian, meta-analyses or systematic reviews, a duplicate publication of the same study, and articles presented in an abstract form were excluded from our study.

Data Extraction and Definitions

Different variables were extracted from the selected studies, including the author's name, study time, settings, as well as the year of publication, the number of investigated patients, the number of HPV isolates, and the source of the isolates. The prevalence of HPV was extracted as well. The data were extracted by two independent investigators. The investigators tried to reach a consensus if there were discrepancies in the extracted data.

Quality Assessment

The included studies were appraised in terms of quality. For this purpose, a quality assessment checklist was used, which was designed by the Joanna Briggs Institute.

Meta-analysis

The analysis was performed by Comprehensive Meta-Analysis (version 2.2, BioStat) software. Depending on statistical heterogeneity between different studies, fixed or random effect models were applied to calculate the summary estimates. Further, statistical heterogeneity was quantified by the I^2 statistic. Finally, Egger's weighted regression methods were used to evaluate the possible publication bias. The *P* value of <0.05 was considered as the statistically significant publication bias.

Results

Characteristics of the Included Studies

Initially, a total of 3061 articles were collected and following removing the duplicates (n = 875), 2076 studies were excluded based on the title and abstract assessment in the secondary screening (Figure 1). Then, 91 out of the remaining 110 studies were excluded upon a full-

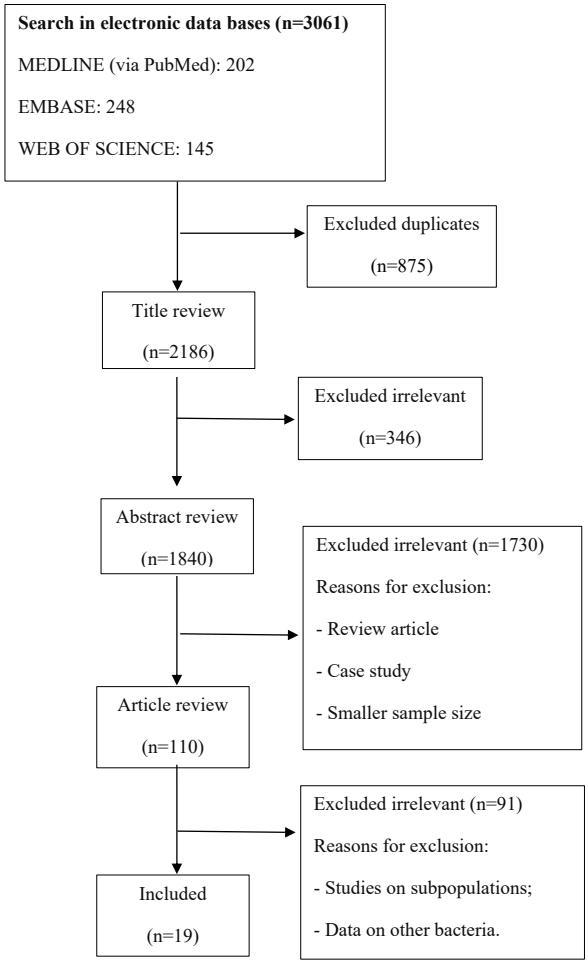

Figure 1. Flow Chart of Study Selection for Inclusion in the Systematic Review.

text search. Thus, 19 eligible studies were chosen for the final analysis. Figure 1 illustrates the reason behind the exclusion of studies based on the evaluation of the title/abstract and full-text articles. Table 1 presents a summary of the characteristics of the included articles. Diagnostic methods for HPV mainly included standard conventional techniques.

The Prevalence of HPV

The HPV prevalence among the populations tested positive for the HPV by molecular testing was 33.7% [a 95% confidence interval (CI) of 28.4-39.5], the related data are provided in Table 2. The heterogeneity test revealed heterogeneities among the studies (I^2= 74.942, P<0.001). Figure 2 displays the forest plot of the meta-analysis of HPV prevalence. As shown in Figure 3, there was no evidence of publication bias (P>0.05 for the Egger's weighted regression analysis). Table 3 shows the stratified analyses conforming to the geographic areas of the included studies.

The Prevalence of HPV-16 and HPV-18

Based on our results, the prevalence of HPV-16 and HPV-18 infections was 19.7% (a 95% CI of 13.0-28.8) and 15.9% (95% CI of 11.0-26.6), respectively (Table 2). The heterogeneity test demonstrated that there were heterogeneities for HPV-16 (I^2 = 83.724, P<0.001) and HPV-18 (I^2 = 65.127, P<0.001) infections, respectively. It was revealed the forest plot of the meta-analysis of HPV-16 and HPV-18 prevalence (Figures 4-7).

Discussion

The HPV infection may lead to the development of tumors in the genital area, especially the lower female genital tract,[20] but its role in gastrointestinal cancers including the CRC requires further investigation.[21] As it is known, the CRC is a multifactorial malignancy thus many factors could be involved in this disease. Genetic variation, inflammatory diseases, diet regimen, and environmental factors such as stress and smoking are among the leading causes of the CRC. Although some studies were unable to detect the HPV in CRC, other studies reported a wide range of HPV infections in CRC patients.[22-25] However, it is unclear how HPV affects tumorigenesis in CRC patients. Our analysis showed that the worldwide prevalence of HPV infections in patients with CRC was 33.7% (a 95% CI of 28.4-39.5). A high prevalence of HPV in the CRC could be the result of a retrograde viral transmission from the urogenital area. Some studies demonstrated that infants and female university students who never experienced penetrative sex were also suffering from HPV infection. This evidence indicates that there could be alternative routes of HPV transmission other than sexual behavior.[26,27]

Table 1. Characteristics of Studies Included in Meta-analysis

First Author	Time of Study	Published Time	Country	Total Number (Inpatients and Outpatients)	CRC	HPV	Diagnostic Methods for HPV	Source of Samples
Yu[29]	2001	2002	China	64	32	7	Nested RT PCR	Colon
Motlagh[30]	2004-2005	2007	Iran	60	60	21	PCR, ICC	Colon
Liu[31]	2007-2010	2010	China	176	96	28	PCR	Colon
Ghabreau[32]	2011	2012	Syria	78	78	42	PCR	Colon
Chen[33]	2000-2005	2012	Taiwan, China	69	69	11	Nested PCR, IHC	Colon
El-Seidi[34]	2011-2012	2014	Egyption	80	40	6	QPCR	Colon
Laskar[35]	2001-2013	2015	India	163	93	34	PCR	Colon, peripheral blood
Li[36]	2005-2007	2015	China	235	95	46	IHC, PCR	Colon
Karbasi[37]	2011-2012	2015	Iran	76	38	13	QPCR	Colon, rectal
Bodaghi*[38]	2004	2005	USA	107	55	23	Nested PCR	Colon
Bodaghi[38]	2004	2005	USA	107	55	28	PCR	Colon
Pérez[39]	2002-2004	2010	Argentina	75	75	33	PCR	Colon
Picanço-Junior[40]	1999-2003	2014	Brazil	144	79	36	PCR	Colon
Soto[41]	2014	2016	Cuba	63	42	15	QPCR	Rectum, rectosigmoid junction, sigmoid colon
Bernabe-Dones[42]	2015	2016	USA	81	45	19	Nested PCR	Colon
Giulian[43]	2007	2008	Italy	66	66	22	Nested PCR	Proximal colon, distal colon, rectum
Moreas[44]	2006-2009	2014	Greece	60	60	16	IHC and CISH	Colon
Lorenzon[45]	2010-2012	2015	Italy	65	65	11	QPCR	Colon
Tanzi[46]	2011-2012	2015	Italy	114	57	9	Nested PCR	Colon, rectum

Note. PCR: Polymerase chain reaction; IHC: Immunohistochemistry; CISH: Chromogenic in situ hybridization; QPCR: Quantitative real time PCR; RT PCR: Reverse transcriptase PCR; CRC: Colorectal cancer; HPV: Human papillomavirus.

Table 2. Meta-analysis of the Prevalence of HPV-16 and HPV-18 Infections in Colorectal Cancerous Samples of Patients in Different Parts of the World

Subgroups	No. of Study	Prevalence of HPV (95% CI)	n/N	Heterogeneity Test, I2 (%)	Heterogeneity Test, *P*-value	Egger's Test, t	Egger's Test, *P* Value
Overall effects	19	33.7 (28.4-39.5)	420/1200	74.942	<0.001	3.997	0.000
HPV-16	17	19.7 (13.0-28.8)	242/1026	83.724	<0.001	4.237	0.000
HPV-18	11	15.9 (11.0-22.6)	103/653	65.177	<0.001	5.430	0.000

Abbreviation: HPV, human papillomavirus.

Table 3. Meta-analysis of the Prevalence of HPV Infections in Colorectal Cancerous Samples of Patients in Different Parts of the World

Country	No. of Study	Prevalence of HPV-18 (95% CI)	n/N	Heterogeneity Test, I2 (%)	Heterogeneity Test, *P* value	Egger's Test, t	Egger's Test, *P* Value
Overall effects	19	33.7 (28.4-39.5)	420/1200	74.942	<0.001	3.997	0.000
Asia (Iran, China, Taiwan, Egypt, India, Syria)	9	32.2 (24.1-41.4)	208/601	75.484	<0.001	2.668	0.031
Europe (Italy, Greece)	6	43.9 (38.8-49.2)	154/351	0.000	<0.001	1.273	0.271
America (USA, Argentina, Cuba, Brazil)	4	23.1 (15.9-32.4)	58/248	57.997	<0.001	6.721	0.021

Abbreviation: HPV, human papillomavirus.

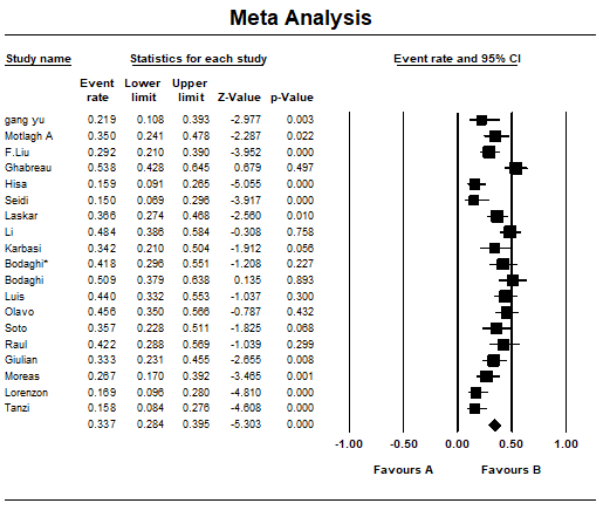

Figure 2. Forest Plot of Meta-analysis on the Prevalence of HPV in CRC.

According to the results of this study, the HPV infection was more common in European researches including Italy and Greece (43.9%; a 95% CI of 38.8-49.2) compared to the other parts of the world. There could be several reasons behind the high prevalence of HPV in Europe. Using advanced devices and methods for HPV detection is one of the reasons that can explain the high prevalence of HPV in these countries. Our study found that high-risk HPV types 16 and 18 (18.0%) are highly prevalent among CRC patients. Given that the development of cervical cancer is caused by E6 and E7 oncoproteins from high-risk HPVs,[28] these viruses have the potential to induce cell proliferation and tumorigenesis in infected colorectal areas.

There were some limitations to this study which must be addressed. First, only published investigations were included in the present study. In addition, heterogeneity

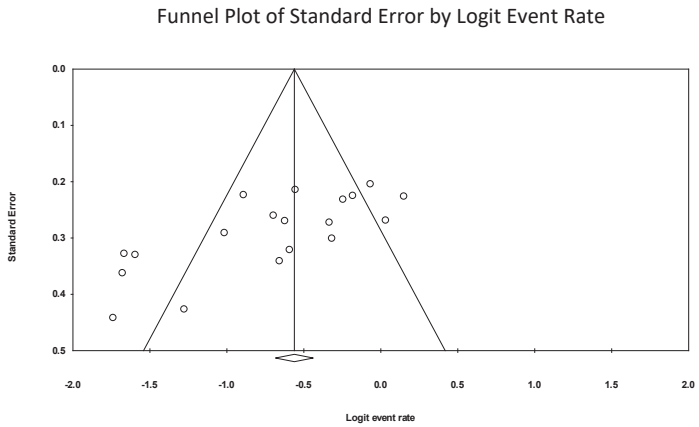

Figure 3. Funnel Plot of Meta-analysis on Prevalence of HPV in CRC.

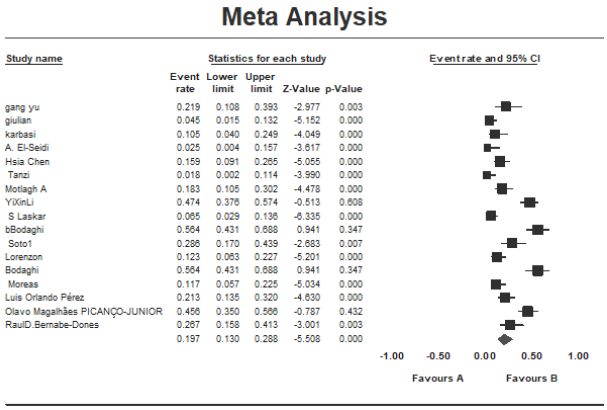

Figure 4. Forest Plot of Meta-analysis on the Prevalence of HPV-16 in CRC.

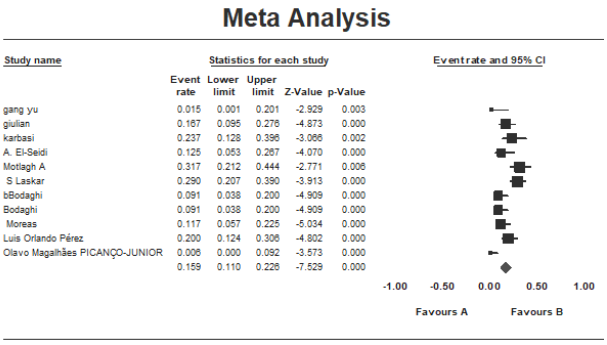

Figure 5. Forest Plot of Meta-analysis on the Prevalence of HPV-18 in CRC.

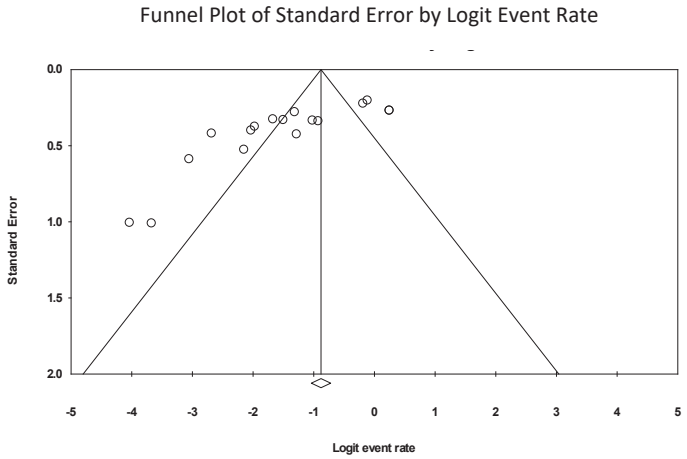

Figure 6. Funnel Plot of Meta-analysis on Prevalence of HPV-16 in CRC.

was extracted from the included articles. Further, our results are not based on the accurate worldwide prevalence of HPV because HPV incidence is not reported from every country around the globe. Similarly, we were unable to determine the risk factors of HPV colonization or infection since we only investigated its prevalence. In conclusion, it seems that there are high rates of HPV infections in CRC patients and these viruses are considered as the causal agents for the CRC. Thus, controlling high-risk behaviors, vaccination, screening and HPV subtyping could be useful for managing HPV infections and possible subsequent malignancies.

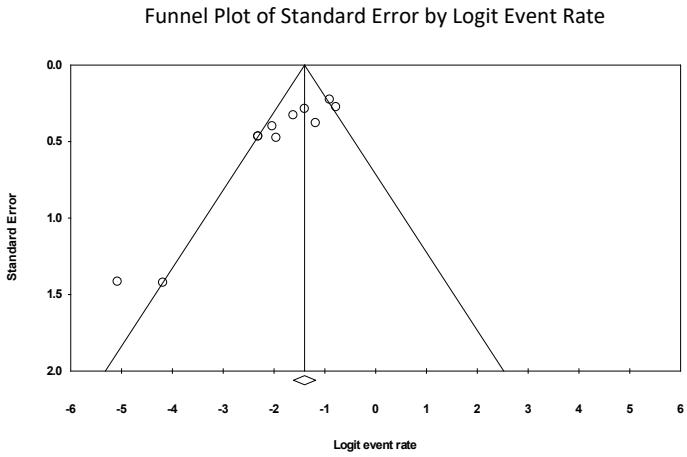

Figure 7. Funnel Plot of Meta-analysis on Prevalence of HPV-18 in CRC.

Authors' Contributions

MD, EF and SHT performed the statistical Analyses. All authors read and approved the final version of the manuscript.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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